Tuberculosis
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CHIVA	Full	17	27	With particularly the young (infants) more commonly presenting with faltering growth, and overall less specific symptoms the statement In section "What are the symptoms of TB" may be worth changing towards -- symptoms of TB may be less specific particularly in high-risk groups such as infants (<12 months). Furthermore in young children TB may present as failure to gain weight and faltering growth across centiles. Different to the adult weight loss.	Thank you for your comment. The text has been amended to: "Because TB can affect many sites in the body, there can be a wide range of symptoms, some of which are not specific and may delay diagnosis. Typical symptoms of pulmonary TB include chronic cough, weight loss, intermittent fever, night sweats and coughing blood. TB in parts other than the lungs has symptoms which depend on the site, and may be accompanied by intermittent fever or weight loss. **In young children, particularly those aged younger than 12 months, a failure to gain weight or grow at a 'normal' rate are more common than weight loss.** TB is a possible diagnosis to be considered in anyone with intermittent fever, weight loss and other unexplained symptoms. Latent tuberculosis without disease, however, has no symptoms."
The Royal College of General Practitioners	Full	General	General	The College welcomes these updated guidelines however, feels there are considerable issues that should be addressed. 1. Overall responsibility and co-ordination of TB services.	Thank you for your comments. 1. The guideline makes clear that the 2 organisations should work in partnership to take responsibility. It is beyond the remit of this

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				Recommendation 181 does not make it clear whether it is PHE or NHS England's overall responsibility for management of Tuberculosis in England. A single TB control board with overall responsibility is required to co-ordinate geographical areas and standardise data collection particularly for patients crossing geographical boundaries and are hard to reach. 2. A single point of contact for GPs is essential. Currently there are at least 4 local services for most GP to contact: 1. Paediatric and children services 2. Adult services 3. Screening services 4. TB prevention clinics See this example from Bristol: http://briscomhealth.org.uk/wp-content/uploads/2015/02/TB-Care-Pathway-2-TB-Screening-in-Primary-Care.pdf	guideline to determine who, if either, should have overall responsibility for TB prevention and control activities as both have a key role to play. 2. Due to different local arrangements for how TB services are commissioned and provided it would be difficult to specify a single point of contact. Recommendation 1.1.1.2 does recommend a role for multidisciplinary TB teams to provide local referral pathways, including details of who to refer and how.

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				3. Tuberculin skin testing requires 2 hospital clinic appoints which are likely to be difficult for hard to reach groups. Have alternatives been valuated such as follow up by mobile phone with a standard paper measure? 4. The role of the GP The guidelines do not recognise that TB often co-exists with other conditions other than HIV such as diabetes and pregnancy. Considerable GP input may be required to managing these co-existing conditions.	3. Although it is agreed that this may be a useful area for review, it was not one identified in the course of scoping and therefore has not been addressed within this guidance. 4. The guidance attempted to address the co-management of TB and these comorbidities or coexisting conditions in the following review questions (see chapter 4.9 of the full guideline document): *In people co-infected with drug susceptible, active TB and HIV receiving drug treatment for both infections, what are the key pharmacological considerations that should be taken into account when selecting a treatment regimen for treating active or latent TB?* *How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB? In this review, the key*

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					comorbidities or co-existing conditions identified were HIV, liver disease, renal disease, diabetes, substance misuse, vision impairment / eye disease and pregnancy / breastfeeding. These reviews were conducted in recognition of the fact that TB often co-exists with other conditions other than HIV, such as those noted by the stakeholder. Following consideration of these reviews, the Lack of evidence available meant that the Committee did not feel able to make specific recommendations for the comanagement of these conditions. Instead, they discussed who should be involved in management decisions and decided that clinicians work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or coexisting condition. The GP may be involved in care, but it was concluded that with the specialist multidisciplinary team with appropriate experience was the element that needed stating to ensure good management of both conditions.
Royal College of Paediatrics and Child Health	Full	General	General	The areas that will be most difficult to implement and have biggest impact on practice are: • using only TST as first line test for latent TB in children	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.

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				• change in TST cutoff to 5mm irrespective of BCG status • testing for hepatitis B and C prior to treatment for latent TB • the proposed management of TB contact in children aged 4 weeks to 2 years differs from common practice in most large centres and from WHO recommendations, and the evidence base for this is not clear The recommendation to perform NAAT on one sample from each site in the diagnosis of active TB in children will have an impact on service but is welcome; guidance on laboratory standards for this may be necessary.	
Royal College of Paediatrics and Child Health	Full	General	General	The document is long and unwieldy and not user-friendly. Consideration should be given to producing a separate section with all the guidance on paediatric TB	Thank you for your comment. It has been shared with the NICE editorial team, who have worked with the Guideline Development Group (GDG) and the development team to produce: • more user-friendly, navigable versions of the current documents (the Full and Short versions of the guideline) – this has included adding shorter, section-level content lists at the start of each section (hyperlinking, for example, to all paediatric chapters in that section), as well as ensuring that links to glossary terms and references are clear, to help readers move

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					around the guideline and quickly find what they are looking for; • the NICE pathway – an online resource for healthcare professionals to use on a day-to-day basis, which presents recommendations from a guideline (as well as linking them to relevant guidelines in a set of interactive topic-based diagrams; and • the 'Information for the Public' (formerly called 'Understanding NICE guidance') – a summary of the guideline recommendations in everyday language that is aimed at patients, their families and carers, and the wider public.
Royal College of Paediatrics and Child Health	Full	General	General	Throughout the document there is inconsistency in sometimes referring to pulmonary TB and sometimes to smear-positive pulmonary TB. In paediatric practice contact with smear positive and smear negative pulmonary TB is often managed in the same way. For simplicity pulmonary TB could be term used throughout for child contacts.	Thank you for highlighting this. The terminology has now been made consistent across the recommendations such that: • smear status is given for recommendations in which the evidence base supported such a differentiation; and • where smear status *is* specified, it is always described as 'smear-positive/-negative' rather than 'sputum-smear-positive/-negative' as this was considered to be more common terminology by the GDG.

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	General	General	Treatment of monoresistance is poorly supported by the evidence. Before rifampicin was introduced, the gold standard for treatment was 2SHE9Z)/10HE. This has been included in a number of SCTs which are mentioned in Appendix D8. There is no evidence to support the use of 2HZE/16HE. This was a factual error that has persisted through several editions of the guidelines and must be corrected according to the available evidence.	The GDG discussed the use of streptomycin-based regimen, but concluded that it was no longer part of current practice. The GDG agree that there is no evidence to support the use of 2HZE/16HE and so it has not been recommended by this guidance. For all monoresistances – except for rifampicin monoresistance, which in clinical practice is considered a proxy to multidrug resistant tuberculosis and which should be managed as such – the GDG recommend rifampicin-based regimens. Rifampicin is considered to be the most potent first-line antituberculosis drug, and the GDG decided that its inclusion in the treatment of all rifampicin-susceptible disease – throughout both the initial and continuation phases – was essential to a successful therapeutic regimen and therefore to be best practice.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	General	General	Re-introduction of drugs after TB treatment includes the only RCT (Sharma et al) in Appendix D9, but this evidence has not been included in the recommendations. There is a concern that the gradual introduction of drugs with lower doses will lead to drug-resistance, as noted by Mitchison 1998. If there is an evidence base, why does opinion persist?	The GDG reviewed the evidence from Sharma et al, which is included in the description of the evidence base. For example, the evidence statement reads, "Very low quality evidence from 2 randomised controlled trials in 220 people with active tuberculosis who had experienced drug-induced hepatotoxicity showed sequential reintroduction of antituberculosis drugs to be associated with a lower recurrence of drug-

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					induced hepatotoxicity than simultaneous reintroduction, though the effect was not statistically significant (OR (95% CI) = 0.44 (0.18 to 1.03)).” This pooled evidence from both available RCTs and found sequential reintroduction of drugs to be associated with a better outcome (that is, a lower incidence of hepatotoxicity), though the small number of events and patients involved meant that the effect estimate did not reach statistical significance. However, the GDG combined this evidence with their own experience of managing treatment interruptions, and concluded that sequential reintroduction should be used over simultaneous reintroduction in people who have experienced drug-induced hepatotoxicity. Hepatotoxicity may be caused by many drugs, therefore sequential reintroduction can help to pinpoint which drugs are causing the problem. This rationale is stated within the Evidence to Recommendations table for this recommendation. The GDG also discussed the Mitchison paper highlighted by the stakeholder. However, as a theoretical exploration of the mechanisms by which drug resistance might arise, the GDG did not feel it provided a strong enough evidence base upon which to change the current recommendation.

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	General	General	Other oddities: 1. Nursing care is assumed to not include an holistic approach (use of enhanced case management as though this differs from ordinary patient-responsive care) 2. ADA should not be mentioned and has no role in the diagnosis of TB (see WHO reviews)	Thank you for your comments 1. For the purposes of this guideline the GDG use the term "enhanced case management" as relating to the need to engage with wider networks including the social care housing and voluntary sector. In some cases the glossary item details the broader health and psycho-social care aspects of this approach in relation to people with TB and their broader support needs 2. As per the NICE guidelines manual (2012), the evidence for ADA was reviewed objectively, and given consideration equal to that given for other tests and – where the GDG concluded that the evidence was strong enough – recommendations were made on its use. Although the World Health Organisation has similar methods to those used by NICE, and it is likely that similar evidence was reviewed, decisions made both within the reviewing and by the NICE committee may be different to decisions made by the WHO. The decision-making by the WHO committee reflect the fact that the World Health Organisation considered the use of such tests internationally, across a broader range of settings with more diverse resource and staffing availability, as well as different training capacities, whereas NICE

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					considers their use solely for use in England and Wales. Where recommended, NICE recommends the use of ADAs as one part of a battery of investigations, and never as a standalone test that would be interpreted in isolation from the other tests recommended. The rationales for ADAs given in the guideline are as follows: Pleural TB Considerable evidence (65 evaluations) investigating the use of ADAs in the diagnosis of pleural tuberculosis was identified. Although the group noted the low quality of the evidence, as well as the between-study variation in reference standard used and the estimates of effect for both sensitivity and specificity, they also noted that when the estimates were pooled the test performed well. The GDG was generally unfamiliar with this test and had very little experience of its use in practice, but they could not ignore the volume of evidence and the accuracy achieved by the test. They noted that most of the study's conducted the test using Giusti's method, and that practice should reflect this. They also noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability is consistently met. The GDG did, however, note that adenosine

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					deaminase is not a tuberculosis-specific marker, rather it is a general marker for immune reactions occurring within lymphocytes and its presence could also be suggestive of other infections. It is particularly important that other conditions, such as sarcoidosis (which in addition to being associated with raised adenosine deaminase levels has a similar clinical and radiological profile), be ruled out. Therefore the GDG were not comfortable in recommending its use in the absence of other tests, nor did they feel that its use should necessarily be routine. CNS TB The GDG also noted that ADAs performed well in the diagnosis of tuberculous meningitis, with a threshold for test interpretation of 4 U/l achieving good sensitivity. The GDG concluded that this test may be particularly useful, therefore in confirming negative results provided by other tests. It is important to avoid false negative results in the diagnosis of CNS tuberculosis given the severe consequences of missing a diagnosis. GI TB Having considered the evidence for the use of ADAs, the GDG concluded that the high pooled sensitivity 94.9% (95% CI 89.7 to 97.5%) and specificity 96.2% (95% CI 93.9 to 97.7%) was good grounds on which to recommend the use of

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					ADAs in the diagnosis of gastrointestinal tuberculosis, although the evidence base included a number of case-control studies. The GDG noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability was consistently met and that practice should reflect this. Pericardial TB On reviewing the evidence for ADAs, the GDG noted that at 88% (95% CI 82 to 91%) the pooled sensitivity across the 5 studies was considerably above the threshold for acceptability. The GDG concluded that this was sufficient justification for adding this test to the diagnostic pathway for pericardial tuberculosis as well.
				3. TB7.7 is not in the RD1 sequence, is currently included in QuantiFERON Gold and Gold in Tube, but not in QuantifFERON Platinum nor the TB.SPOT.TB test. 4. Rifampicin is NOT known to be teratogenic (large surveys from pregnancies occurring due its interaction with the oral contraceptive pill).	3. Thank you for highlighting this. It has now been corrected in all relevant sections of the guideline. 4. Thank you for your comment. The text now states: "According to the SPCs, the use of rifampicin in pregnant women in the third trimester is associated with an elevated risk of neonatal bleeding, and very high doses of rifampicin in first trimester have been associated with malformations of the foetus in animal studies. However, the GDG were aware of no human studies that suggest that rifampicin is teratogenic,

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					nor are any cited in the SPCs, so they did not consider a recommendation against the use of rifampicin in pregnant women to be appropriate."
British Thoracic Society	Full	general	general	In general, recommendations should be graded by the quality of evidence that supports the recommendation.	Thank you for your comment. Recommendations are developed using a range of evidence. This is used to explore the trade-off between potential benefits and potential harms of interventions, diagnostic tools or prognostic factors, and is interpreted and judged based on the quality of the evidence available as well as the GDG's own knowledge and experience. The group also take account of a range of other issues (including any ethical concerns, social value judgements, equity considerations and inequalities in outcomes, particularly impacts on people sharing the characteristics protected by equality legislation) and policy imperatives. The GDG must use its judgement to decide what the evidence means in the context of the guideline (see the Evidence to Recommendations sections in the full guideline) and decide what recommendations can be made to practitioners, commissioners of services and others. Some recommendations can be made with more certainty than others. For some interventions, the group is confident that – given the information it has looked at (the quality of the evidence, but also the estimates of effect, ethical concerns,

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					social value judgements, equity considerations and inequalities in outcomes) – most patients would choose the intervention. It is this certainty that determines the strength of the recommendation, which is in turn reflected in the wording of the recommendation as follows: *Interventions that must (or must not) be used* We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening. *Interventions that should (or should not) be used – a 'strong' recommendation* We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients. *Interventions that could be used* We use 'consider' when we are confident that an intervention will do more good than harm for most

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					patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.
British Thoracic Society	Full	general	general	Previous recommendations should be open for comment if there is new evidence	These recommendations are from CG117 and did not fall within the scope of this update.
British Thoracic Society	Full	general	general	There are many repetitions in advice which could be readily collated. The full version of the guideline is unwieldy. The structure is not easily appreciated from scrolling up and down the enormously long contents pages. To avoid printing it all out, a short description of how it is set out might have been helpful. The document length will also mean that the recommendations may not be implemented or not noted. In view of the classification of "must", "offer" and "consider", a document with the "must" recommendations would be a useful summary, ensuring that the evidence is good. The list of recommendations begins with some very soft measures that really come under the GMC guidance on good clinical practice, rather than	Thank you for your comment. It has been shared with the NICE editorial team, who have worked with the GDG and the development team to produce: • more user-friendly, navigable versions of the current documents (the Full and Short versions of the guideline) – this has included adding shorter, section-level content lists at the start of each topic section (hyperlinking, for example, to all paediatric content in that section), as well as ensuring that links to glossary terms and references are clear, to help readers move around the guideline and quickly find what they are looking for; • the NICE pathway – an online resource for

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				being specific for TB. In keeping with this, there should be a clear distinction made between evidence-based medicine and political policy (e.g. recommendations 184 onwards).	healthcare professionals to use on a day-to-day basis, which presents recommendations from a guideline (as well as linking them to recommendations from a guideline relevant in a set of interactive topic-based diagrams; and • the 'Information for the Public' (formerly called 'Understanding NICE guidance') – a summary of the guideline recommendations in everyday language that is aimed at patients, their families and carers, and the wider public. The GDG editors and the development team have also worked to limit any repetition of recommendations, inserting cross reference where necessary. Thank you for your comment. The GDG considered the evidence in the light of current policy decisions and whilst some recommendations do pertain to a strategic approach the GDG considered an over-arching strategic multi-sector approach was the most appropriate means with which to deliver TB services to meet the needs of the whole population in particular those who are disproportionately affected by TB. This strategic approach also enables action by those who commission services, despite some of the inherent uncertainties in the evidence reviewed.

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British Thoracic Society	Full	General	General	Desirable elements missing within the short guidance which would be useful as a guide to non specialists are: • The investigations which should be done routinely prior to starting TB treatment • How we should monitor for drug toxicity	Thank you for your comment. The investigations that should be routinely carried prior to starting TB treatment are specified: • for treatment of active TB, clinicians should refer to the relevant sections of the British National Formulary or the British National Formulary for Children • for treatment of latent TB, in the following recommendations: *"Base the choice of regimen on the person's clinical circumstances. Offer:* *• 3 months of isoniazid (with pyridoxine) and rifampicin to people aged younger than 35 years if hepatotoxicity is a concern;* ***this would include both liver function (including transaminase) test results and assessment of risk factors*** *• 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant."* *"****Offer testing for HIV before starting treatment for latent TB.*** *See NICE guidelines on increasing the uptake of HIV testing among black Africans in England and increasing the uptake of HIV testing among men who have sex with men."*

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					*"**Offer testing for hepatitis B and C before starting treatment for latent TB in adults.** See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults."* *"**Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people.** See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults."* Treatment monitoring is specified: • for treatment of active TB, clinicians should refer to the relevant sections of the British National Formulary or the British National Formulary for Children • for treatment of latent TB, in the following recommendation: "Manage treatment with caution, ensuring careful monitoring of liver function, in: • people with non-severe liver disease • people with abnormal liver function (including

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					abnormal transaminase levels) before starting treatment for latent TB infection • people who misuse alcohol or drugs." Pretreatment testing and within treatment monitoring were specified for the treatment of latent TB because of the finer distinctions in the trade-off of benefits and harms when deciding whether or not to undergo treatment – that is, people with latent infection are not yet symptomatic and may never become so. For this reason, the tests specified were felt to be necessary in maximising the gains of treatment whilst minimising any potential impact on patient health or quality of life through the incidence of adverse events. This is important in the treatment of active disease as well, but the potential consequences of not treating someone with active disease can be so severe that these tests would not necessarily impact treatment decisions in the same way. Guidance has been provided, where possible, on how these tests should be performed (for example, in referring to other NICE guidance). However, it is not within the scope of this guideline to define what constitutes 'normal' or 'appropriate' liver function – this is an issue that goes beyond TB. Following review of the SPCs for the 4 main antituberculosis drugs, the

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					following text has been added to the Evidence to Recommendations table: "… liver function should be assessed before treatment is initiated, as specified in the British National Formulary. Isoniazid, especially if given with rifampicin, may induce abnormalities in liver function, particularly in patients with pre-existing liver disorders, the elderly, the very young and the malnourished. The Summary of Product Characteristics … recommend that transaminase measurements – especially glutamic pyruvic transaminase and glutamic oxaloacetic transaminase – be obtained at baseline. Furthermore, those with abnormal liver function before treatment initiation should undergo more cautious management of their regimen, including careful clinical monitoring – the Summary of Product Characteristics for isoniazid and rifampicin recommend that this be undertaken monthly. They did not feel that it was strong enough to recommend that people with abnormal liver function not be eligible for treatment."
British Thoracic Society	Full	General	General	Missing references include Cochrane reviews (preventive treatment and management of spinal TB)	Thank you for your comment. The two reviews do not meet our inclusion criteria as explained in detail below:

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					Jutte PC, Van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. Cochrane Database Syst Rev 2006 (1):CD004532 The inclusion and exclusion criteria for this systematic review differed from those in our review*:* • The Cochrane review included only RCTs*,* whereas the NICE review included RCTs, quasi-RCTs, non-randomised controlled trials, cohort studies, case series. • The Cochrane review included only studies with at least one year follow-up*,* whereas the NICE review had no restriction on the length of follow-up. • The Cochrane review included studies using regimens containing any combination of antituberculosis drugs, whereas the NICE review included only studies using regimens containing drugs licensed in the UK, preferably the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol). • The Cochrane review included only studies treating active disease of the thoracic and/or lumbar spine, whereas the NICE review included studies treating active disease of any part of the

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					spine. Despite these differences, the references in the Cochrane review were reviewed and considered for inclusion in our review. *Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2010 (1):CD000171 - Gray DM, Zar H, Cotton M. Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006418* There are a large number of reviews on this topic each containing a large number of references. To ensure no studies were missed in the NICE review, and to ensure that all information needed to enable the planned network meta-analyses was available to the NICE analysts, it was decided that single review would be included in preference others. Instead, the references lists of each individual review were screened and considered for inclusion in our review. Data was then extracted from those studies that matched our inclusion and exclusion criteria.

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British Thoracic Society	Full	General	General	Recommendations for treatment for ophthalmic TB is missing	Thank you for your comment. Ophthalmic TB is covered in the following recommendations; For diagnosis, follow the recommendation below (that is, refer the patient with suspected ophthalmic TB to an expert due to its rarity): "Refer to an expert for sites not listed here, including TB of the eye and other rare sites of disease." For treatment, follow the recommendations below: "For people with active TB without central nervous system involvement, offer: • isoniazid (with pyridoxine), rifampicin, pyrazinamide and ethambutol for 2 months, then • isoniazid (with pyridoxine) and rifampicin for a further 4 months. Modify the treatment regimen according to drug susceptibility testing." "For people with active TB of the central nervous system, offer: • isoniazid (with pyridoxine), rifampicin, pyrazinamide and ethambutol for 2 months, then • isoniazid (with pyridoxine) and rifampicin for a further 10 months.

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					Modify the treatment regimen according to drug susceptibility testing." "Use fixed-dose combination tablets as part of any TB treatment regimen." "Do not offer anti-TB treatment dosing regimens of fewer than 3 times per week." "Consider a daily dosing schedule as first choice in people with active extrapulmonary TB." "Consider 3 times weekly dosing for people with active TB only if: • a risk assessment identifies a need for directly observed therapy and enhanced case management and • daily directly observed therapy is not possible." "If the person has a comorbidity or coexisting condition such as: • HIV, or • severe liver disease, for example, Child-Pugh level B or C, or • stage 4 or 5 chronic kidney disease (a glomerular filtration rate of <30 ml/minute/1.73m2), or • diabetes, or • eye disease or impaired vision, or

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					• pregnancy or breastfeeding, or • a history of alcohol or substance misuse work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or coexisting condition." "For people with HIV and active TB without central nervous system involvement, do not routinely extend treatment beyond 6 months." "For people with HIV and active TB with central nervous system involvement, do not routinely extend treatment beyond 12 months." "Take into account drug-to-drug interactions when co-prescribing antiretroviral and anti-TB drugs."
British Thoracic Society	Full	General	General	Despite intrathoracic mediastinal adenopathy representing 10% of TB presentations this is not addressed in the extra-pulmonary section tables	Thank you for your comment. For people with intrathoracic mediastinal adenopathy, the recommendations should be followed for lymph node TB. This has now been stated in the relevant recommendations: "Use the site-specific investigations listed in table 4 to diagnose and assess lymph node TB (including intrathoracic mediastinal adenopathy)."
British Thoracic	Full	General	General	Other anomalies:	Thank you for your comments, responses to specific comments are as follows:

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Society				1. Nursing care is assumed to not include an holistic approach (use of enhanced case management as though this differs from ordinary patient-responsive care) 2. ADA should not be mentioned and has no role in the diagnosis of TB (see WHO reviews)	1. For the purposes of this guideline the GDG use the term "enhanced case management" as relating to the need to engage with wider networks including the social care housing and voluntary sector. In some cases the glossary item details the broader health and psycho-social care aspects of this approach in relation to people with TB and their broader support needs. 2. As per the NICE guidelines manual, the evidence for ADA was reviewed objectively, and given consideration equal to that available for other tests and – where the GDG concluded that the evidence was strong enough – recommendations were made on its use. Although the World Health Organisation has similar methods to those used by NICE, and it is likely that similar evidence was reviewed, decisions made both within the reviewing and by the NICE GDG may be different for decision made by the WHO. The decision-making by the WHO committee reflect the fact that the World Health Organisation considered the use of such tests internationally, across a broader range of settings with more diverse resource and staffing availability, as well as different training capacities, whereas NICE considers their use solely for use in England and Wales. Where recommended, NICE recommends

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					the use of ADAs as one part of a battery of investigations, and never as a standalone test that would be interpreted in isolation from the other tests recommended. The rationales for ADAs given in the guideline are as follows: Pleural TB Considerable evidence (65 evaluations) investigating the use of ADAs in the diagnosis of pleural tuberculosis was identified. Although the group noted the low quality of the evidence, as well as the between-study variation in reference standard used and the estimates of effect for both sensitivity and specificity, they also noted that when the estimates were pooled the test performed well. The GDG was generally unfamiliar with this test and had very little experience of its use in practice, but they could not ignore the volume of evidence and the accuracy achieved by the test. They noted that most of the study's conducted the test using Giusti's method, and that practice should reflect this. They also noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability is consistently met. The GDG did, however, note that adenosine deaminase is not a tuberculosis-specific marker,

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					rather it is a general marker for immune reactions occurring within lymphocytes and its presence could also be suggestive of other infections. It is particularly important that other conditions, such as sarcoidosis (which in addition to being associated with raised adenosine deaminase levels has a similar clinical and radiological profile), be ruled out. Therefore the group were not comfortable in recommending its use in the absence of other tests, nor did they feel that its use should necessarily be routine. CNS TB The group also noted that ADAs performed well in the diagnosis of tuberculous meningitis, with a threshold for test interpretation of 4 U/l achieving good sensitivity. The GDG concluded that this test may be particularly useful, therefore in confirming negative results provided by other tests. It is important to avoid false negative results in the diagnosis of CNS tuberculosis given the severe consequences of missing a diagnosis. GI TB Having considered the evidence for the use of ADAs, the GDG concluded that the high pooled sensitivity 94.9% (95% CI 89.7 to 97.5%) and specificity 96.2% (95% CI 93.9 to 97.7%) was good grounds on which to recommend the use of

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					ADAs in the diagnosis of gastrointestinal tuberculosis, although the evidence base included a number of case-control studies. The GDG noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability was consistently met and that practice should reflect this. Pericardial TB On reviewing the evidence for ADAs, the GDG noted that at 88% (95% CI 82 to 91%) the pooled sensitivity across the 5 studies was considerably above the threshold for acceptability. The GDG concluded that this was sufficient justification for adding this test to the diagnostic pathway for pericardial tuberculosis as well.
				3. TB7.7 is not in the RD1 sequence, is currently included in QuantiFERON Gold and Gold in Tube, but not in QuantifFERON Platinum nor the TB.SPOT.TB test. 4. Rifampicin is NOT known to be teratogenic (large surveys from pregnancies occurring due its interaction with the oral contraceptive pill).	3. Thank you for highlighting this. It has now been corrected in all relevant sections of the guideline. 4. Thank you for your comment. The text now states: "According to the SPCs, the use of rifampicin in pregnant women in the third trimester is associated with an elevated risk of neonatal bleeding, and very high doses of rifampicin in first trimester have been associated with malformations of the foetus in animal studies. However, the GDG were aware of no human studies that suggest that rifampicin is teratogenic,

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					nor are any cited in the SPCs, so they did not consider a recommendation against the use of rifampicin in pregnant women to be appropriate."
CHIVA	Full	General	General	There is throughout the NICE guidance inconsistencies in referring to pulmonary TB and sometimes to smear-positive pulmonary TB. This adds to a document that is very long and could be structured clearer. As paediatricians a summary for paediatrics will make the document clearer for those working with children.	Thank you for highlighting this. The terminology has now been made consistent across the recommendations such that smear status is always described as 'smear-positive/-negative' rather than 'sputum-smear-positive/-negative' as this was considered to be more common terminology by the GDG.
CHIVA	Full	General	General	Areas that will impact particularly on the children's care are: -TST cutoff reduced to 5mm irrespective of BCG status -only TST as first line test for latent TB in children - TB contact management in children aged 4 weeks to 2 years in this guidance differs from practice in most large children services. It also differs from the WHO recommendations. A clearer statement in regards to the evidence should be given. -Latent TB and testing for hepatitis B and C prior to start of treatment for latent TB - To perform NAAT on one sample from each site	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.

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				in the diagnosis of active TB in children, a proposal we support.	
British Thoracic Society	Full	General	General	Gastrointestinal tuberculosis . Table for diagnosis of GI TB add actual biopsies via US or CT and also EUS.	Thank you for your comment. Biopsy is included in the recommendations for GI TB. The GDG did not consider it appropriate to specify how the biopsy should be obtained
British Thoracic Society	Full	General	General	Evidence for ADA is low since most studies observational .	Thank you for your comment. This is reflected to the 'very low' grading given to all evidence for ADA.
British Thoracic Society	Full	General	General	There is evidence that tests including NAAT should be used in combination.	Thank you for your comment. This is reflected in the fact that for no site of disease is a single test alone recommended for the diagnosis of active TB. Instead, the GDG selected multiple tests that should be used in combination to diagnose TB, coming together to give an overall 'diagnostic picture' that can be interpreted by clinicians. In this way the poor sensitivity and/or specificity inherent to many TB diagnostics can mitigated.
British Thoracic Society	Full	General	General	ADA testing is not available in most trusts.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
NHS National	Full	General	General	In chapter 6 there are multiple instances of 'infectious' control measures, this should be	Thank you for highlighting this. It has now been corrected.

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Services Scotland				'infection' control measures	
NHS National Services Scotland	Full	General	General	There is no mention of standard infection control precautions in the infection control recommendations. These are fundamental and should be mentioned. These would ideally be placed at the start of the chapter; these will also reduce the risk from patients who are infectious but not symptomatic, which is discussed as an issue by the authors.	Thank you for your comment. The following introductory text has now been added to the 'NICE version' (the list of recommendations only): "In addition to the recommendations listed here, see NICE guidelines on the prevention and control of healthcare-associated infections in primary and community care (CG139 and PH36)."
Birmingham & Solihull TB Service	Full	General	General	The areas that will be most difficult to implement and have biggest impact on practice are: -using only TST as first line test for latent TB in children -change in TST cut off to 5mm irrespective of BCG status -testing for hepatitis B and C prior to treatment for latent TB -the proposed management of TB contact in children aged 4 weeks to 2 years differs from common practice in most large centres and from WHO recommendations, and the evidence base for this is not clear	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.

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				-the recommendation to perform NAAT on one sample from each site in the diagnosis of active TB in children will have an impact on service but is welcome; guidance on laboratory standards for this may be necessary	
NHS England	Full	General	General	We note that there are 311 recommendations and that all of the documentation regarding this consultation is very long and that not many people will read it and therefore use it.	Thank you for your comment. It has been shared with the NICE editorial team, who have worked with the GDG and the development team to produce: • more user-friendly, navigable versions of the current documents (the Full and Short versions of the guideline) – this has included adding shorter, section-level content lists at the start of each topic section (hyperlinking, for example, to all paediatric content in that section), as well as ensuring that links to glossary terms and references are clear, to help readers move around the guideline and quickly find what they are looking for; • the NICE pathway – an online resource for healthcare professionals to use on a day-to-day basis, which presents recommendations from a guideline (as well as linking them to recommendations from a guideline relevant in a set of interactive topic-based diagrams; and • the 'Information for the Public' (formerly called 'Understanding NICE guidance') – a summary of

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					the guideline recommendations in everyday language that is aimed at patients, their families and carers, and the wider public.
NHS England	Full	General	General	The document refers to 'high risk' populations. The document does not make clear if this is 40/100,000, 150/100,000 or other. It does refer to 500/100,000 in the BCG section.	Thank you for your comment. Unlike 'high incidence countries', 'high risk populations' are not defined numerically, rather they are defined by their associated risk factors. There are three ways in which populations may be considered 'high risk' in this guidance. One population referred to as 'high risk' are those at high risk of TB – that is, those at high risk of becoming infected with TB. Those at high risk of becoming infected with TB are those described in section 1.2.1 to 1.2.3 of the 'short version' of the guideline: • contacts of people with infectious disease • new entrants from high incidence countries • people who are immunocompromised • healthcare workers in contact with TB patients or clinical materials • people from underserved groups, including people who are homeless, people who misuse substances, prisoners and other detainees and vulnerable migrants. A second population referred to as high risk are those at high risk of progressing to active disease

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					once. These are specified in recommendation 1.2.4.1 as people who: • are HIV positive; • are children younger than 5 years; • have excessive alcohol intake; • are injecting drug users; • have had solid organ transplantation; • have a haematological malignancy; • are having chemotherapy; • have had a jejunoileal bypass; • have diabetes; • have chronic renal failure or are receiving haemodialysis; • have had a gastrectomy; • are having anti-tumour necrosis factor-alpha treatment or other biologic agents; or • have silicosis. The third 'high risk' population are those at high risk of having multidrug-resistant TB , defined in recommendation 1.4.1.1 as: • a history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment • contact with a known case of multidrug-resistant

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					TB • birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug-resistant.
NHS England	Full	General	General	We welcome the emphasis on rapid access to diagnostics and TB services.	Thank you for your comment.
NHS England	Full	General	General	The phrase 'under-served and high risk groups' is used frequently through both documents and implies that the under-served TB population is of greater number and incidence compared to high risk populations. We would recommend that the wording in the phrase is changed to 'high risk and under-served groups' to reflect the numbers of TB patients and actual incidence. We recognise that the workload impact on services can be disproportionate to the numbers from each group but the phraseology should reflect the higher burden of TB.	Thank you for your comment, the order in which these groups are mentioned is not intended to reflect the burden of disease. However, as under-served groups form part of the broader term (as high risk groups who may have needs over and above other high risk groups) this order is considered appropriate. Having considered moving the order as suggested we feel this changes the meaning of the recommendations and would subsequently read as though under-served groups were not part of those classed as high-risk which by definition in this guideline they are. There was some consideration about whether under-served could be subsumed within a broader high-risk group category but the GDG considered that this would not reflect the fact that in the majority of cases where underserved

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					groups are mentioned these recommendations are incorporated from PH37 which specifically used a validated under-served groups filter when identifying the evidence and the broader category has only been added by extrapolation on the consensus discussions of the committee thus we feel the distinction needs to remain.
Health Protection Scotland	Full	General	General	In chapter 6 there are multiple instances of 'infectious' control measures, this should be 'infection' control measures.	Thank you for highlighting this. It has now been corrected.
Health Protection Scotland	Full	General	General	There is no mention of standard infection control precautions in the infection control recommendations. These are fundamental and should be mentioned. These would ideally be placed at the start of the chapter; these will also reduce the risk from patients who are infectious but not symptomatic, which is discussed as an issue by the authors.	Thank you for your comment. The following introductory text has now been added to the 'NICE version' (the list of recommendations only): "In addition to the recommendations listed here, see NICE guidelines on the prevention and control of healthcare-associated infections in primary and community care (CG139 and PH36)."
Royal College of Nursing	Full	General	General	The Royal College of Nursing welcomes proposals to update this guideline. The RCN invited members from its Public Health Forum, who have an interest in or cared for people with tuberculosis to review and comment on the draft guideline. The comments below are based on feedback from our members.	Thank you for your comment.

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Public Health England	Full	General	General	The shift to reducing size of Mantoux to 5 mm to indicate 'abnormality (infection)' will lead to a large increase in numbers of people on IPT – it seems this aims to bring UKL into line with others internationally and is evidence based – but there will be a good degree of impact on services as a result of this	Thank you for this comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). However, your response has been passed on to the NICE implementation support team to inform their support activities for this guideline.
Public Health England	Full	General	General	On the topic of accommodation, recommendations do not reflect that a strategic approach needs to be taken ie, that the TB Control Board and commissioners should understand needs and commission appropriately. The recommendations place responsibility for accommodation with the MDTB teams. Responsibility should lie with both. There is already legislation that requires local housing authorities to understand the housing needs of their population, and homelessness, and to have a statutory duty to have a homelessness strategy	Thank you for your comment, the housing recommendation in question has been updated following the consultation and now reads as follows; Public Health England, working with the Local Government Association and their special interest groups, should consider working with national housing organisations such as the Chartered Institute of Housing, Homeless Link, Sitra and the National Housing Federation to raise the profile of TB. This is to ensure people with TB are

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				therefore you would not be suggesting anything new if you make it clear that accommodation is something that requires a strategic approach. Suggestions below for improvements to wording reflect this position.	considered a priority for housing. .
London TB workforce Group	Full	General	General	Not user friendly, not an easy task scrutinising through the various amendments. We would welcome a concise final version.	Thank you for your comment. It has been shared with the NICE editorial team, who have worked with the GDG and the development team to produce: • more user-friendly, navigable versions of the current documents (the Full and Short versions of the guideline) – this has included adding shorter, section-level content lists at the start of each topic section (hyperlinking, for example, to all paediatric content in that section), as well as ensuring that links to glossary terms and references are clear, to help readers move around the guideline and quickly find what they are looking for; • the NICE pathway – an online resource for healthcare professionals to use on a day-to-day basis, which presents recommendations from a guideline (as well as linking them to recommendations from a guideline relevant in a set of interactive topic-based diagrams; and • the 'Information for the Public' (formerly called 'Understanding NICE guidance') – a summary of the guideline recommendations in everyday

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					language that is aimed at patients, their families and carers, and the wider public.
Calderdale and Huddersfeld FT]	Full	General	General	The threshold for "High-incidence countries" is not stipulated. Old guidelines advised to screen those from countries with a TB incidence of 40/100,00 pa but the Collaborative TB Strategy advises to screen from Sub-Saharan Africa and countries of 150/100,000 pa. Could NICE advise what the threshold is now?	Thank you for your comment. This is specified in the glossary as "A high-incidence country or area has more than 40 cases of TB per 100,000 people per year."
Calderdale and Huddersfeld FT]	Full	General	General	The other anomaly between the TB Strategy and NICE is: the TB Strategy says to screen 16-35year olds by IGRA (with no advice on the screening of other age groups), yet NICE advises to screen ALL with Mantoux tests.	Thank you for this comment. The GDG was aware of this apparent conflict. However, the group emphasised the different context in which the recommendations apply: where the Collaborative TB Strategy for England envisages a 'co-ordinated, local screening programme', the recommendations in this guideline are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document, The Collaborative TB Strategy for England's rationale for concentrating on those aged 16–35 is not related to anticipated effectiveness or cost effectiveness, but to target resources at people at greatest risk ('because the highest burden of TB disease and the largest proportion of new entrants from high incidence countries are aged between 16 and 35 years'). The choice of test (TST -v- IGRA) may also be

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					influenced by setting: the analyses on which the recommendations in this guideline are based assumed relatively high TST read-rates, which is appropriate for the case-finding context. This may not hold in a screening situation, where there may be reason to prefer a test that can be accomplished in a single interaction. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7).
Calderdale and Huddersfeld FT]	Full	General	General	Concerns for increased costs are: 1. Most contact screening and some new entrant screening advises 2-stage testing, depending on results. This would incur increased costs for community Services/Primary Care	Thank you for your comments, we have response to each specific comment as follows: 1. Thank you for this comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be

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					expensive to implement across the whole population' (chapter 7). However, your comment has been passed on to the NICE implementation support team to inform their support activities for this guideline. Furthermore, whilst this analysis was concerned with opportunistic, rather than structured screening programmes, the results show that for newly arrived migrants from high-prevalence countries, TST (≥5 mm) dominated the TST (≥5 mm) positive followed by QFT-GIT and T-SPOT.TB-alone strategies, represented good value for money in comparison with QFT-GIT alone (generating extra QALYs at a cost of around £1500 each), and had a 47% probability of being the optimal option if QALYs are valued at £20,000. The TST (≥5 mm) negative followed by QFT-GIT strategy generated most QALYs, but the small marginal benefit over TST (≥5 mm) alone was associated with an ICER of £58,720 per QALY.
				2. There will be considerable increase in individuals eligible for CPX if we include those up to the age of 65 years, for Primary and Secondary Care providers	2. Thank you for this comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an

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				3. Patients are to be offered testing for HIV and hepatitis B and C before starting treatment for LTBI with careful monitoring of liver function throughout treatment, with those cost implications	intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). However, your comment has been passed on to the NICE implementation support team to inform their support activities for this guideline. 3. This was discussed with the GDG and the recommendation has been amended as follows: *Offer testing for HIV before starting treatment for latent TB. See NICE guidelines on increasing the uptake of HIV testing among black Africans in England and increasing the uptake of HIV testing among men who have sex with men.* *Offer testing for hepatitis B and C before starting treatment for latent TB in adults. Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults.* New text in the Evidence to Recommendations table The group noted the increased risk of

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					hepatotoxicity during treatment during latent tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore concluded that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment and that treatment could be carefully managed and monitored if undertaken. **They concluded that the reduced risk of hepatitis B or C coinfection in children, and the impact this would have on the cost-effectiveness of testing, meant that only a weak recommendation for testing could be made.** They also stated that health economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing those at increased risk of coinfection would have been useful to their decision-making.
				4. Advice to offer BCG vaccine, up to the age of 35 years, for PTB contacts and new entrants from sub-Saharan Africa and countries and other countries with a TB incidence of 150/100,000 pa	4. Thank you for your comment, These recommendations are from CG117 and do not fall

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				or greater, will result in a need for increased HIV testing prior to vaccination and increased number of BCGs to be given	within the scope of the update.
British Infection Association	Full	General	General	Change to the size on Mantoux test regarded as positive to 5mm or larger whatever the BCG status Concerns that this will over estimate the number of people with LTBI	Thank you for your comment. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses.
British	Full	General	General	Increasing the age of latent TB treatment to 65	Thank you for your comment. Our systematic

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Infection Association				years. Concerns regarding the quality of safety data around this and what plans are there for researching any increase in drug toxicities and adverse events.	review, network meta-analysis, and original economic analysis suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a much greater relative risk of death from TB in those people who progress to active disease at older age. Additional analysis has been undertaken which examines the trade-off between risk and benefit further; these analyses suggest that, for all ages of people diagnosed with LTBI, the potential risks of treatment are very much smaller than the potential benefits. For more detail, please see 'Deaths prevented and caused by drug treatment of LTBI' in section 7.2.4 of the full guideline and accompanying discussion in the LETR table [7.2.6].
British Infection Association	Full	General	General	Contact tracing to be reduced to only contacts of those with pulmonary TB Concerns that an undiagnosed index case in the household maybe missed, particularly important when the patient is a child who has been diagnosed- usually there is a smear positive adult to find.	Thank you for your comment. The Committee discussed this concern but concluded that, due to the resource implications of contact-tracing and the relatively few cases identified by tracing contacts of people with non-infectious extrapulmonary TB, contact-tracing should be limited to those index cases who are infectious (those with pulmonary TB).
British Infection Association	Full	General	General	In section 1.2.2.1 managing latent TB infection- large, very inclusive list of people who it is suggested should have longer term follow up (3	Thank you for your comment. This recommendation was produced by consensus and was not underpinned by an evidence review.

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				and 12 months) if treatment for LTBI not given. Would like to know the evidence for this as concerns regarding workforce implications.	It is intended to safeguard patients who chose not to undergo treatment against the risk of developing active TB. Having defined monitoring timepoints at 3 and 12 months helps to remove the barriers to monitoring that may arise if the recommendation were to wait until the patient becomes symptomatic and must re-engage with TB services on their own.
British Infection Association	Full	General	General	Section 1.3.1.8. Are they really recommending rapid diagnostic nucleic acid amplification tests on all children's samples?	Thank you for your comment. The recommendation is to perform NAATs once on each sample type (unless more are considered necessary). For example, if 1 spontaneous sample and 2 gastric lavages are collected, then NAATs should be performed on the spontaneous sample and on 1 of the gastric lavages. This example is now provided in the Evidence to Recommendations table.
British Infection Association	Full	General	General	Section 1.3.2.6 Test people with disseminated (including miliary) TB for central nervous system involvement. Would value a definition of disseminated. Many increase the CNS radiological burden and lumber puncture rate.	Thank you for your comment. A definition of disseminated TB has been included in the glossary as follows: "Blood-borne spread of TB which may or may not be accompanied by chest X-ray or high resolution CT changes." Any investigation for CNS involvement should be left to the discretion of the treating TB specialist.

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British Infection Association	Full	General	General	Table 13. We would suggest a recommendation to consider Moxifloxacin in monoresistant patients.	Thank you for your comment. The GDG discussed this option. However, because no evidence was identified for moxifloxacin-containing regimens, they did not feel able to make a recommendation for their use when compared to other interventions which had an evidence base to support their use.
British Infection Association	Full	General	General	We would value more clear guidance on the infection control aspects of MDRTB and the follow up of contacts	Thank you for your comment. There are 8 infection control recommendations in section 1.5.3 that are solely concerned with MDR-TB. Contact-tracing should be as for drug susceptible disease. Contact-tracing for index cases with MDR-TB with should be as for drug susceptible disease, though it is considered more urgent. The LTBI treatment regimen may be designed based on the resistance pattern of the isolate from the index case, though chemoprophylaxis is not always given. Patients should be referred to a specialist or, as a minimum, their management should be discussed with the specialist advisory services through the regional multidrug-resistant TB network. The Committee were prevented from writing further MDR-specific recommendations by both the rarity and case-specific nature of MDR management, as well as a paucity of evidence.

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Oxford Immunotec	Full	General	General	The cost effectiveness model contains many statements highlighting the limitations of the review. Keeping these limitations in mind, are the results of this review sufficiently robust to be used to change national guidelines? Here are some examples: o For immunocompromised people most of the evidence was insufficient and inconsistent (page 32) o Amongst recently arrived people from countries with a high TB burden, there was no significant difference in the performance of IGRAs compared to TST in identifying LTBI (page 32) o The evidence was inconclusive in large part due to unexplained heterogeneity, poor reporting, missing data, and great uncertainty around the effect estimates for the association between test results and the constructs of validity for LTBI (page 32) o Other factors that may have contributed to this variability are study setting, type of population, type of test, prior BCG vaccination, and the limitations of screening tests (inter-/intra-rate variability in interpretation of test results, boosting, conversion, reversion, different cut-offs for test positivity, assay manufacturing, pre-analytical processing, and/or incubation delay).	Thank you for your comment. The economic analysis included a full probabilistic sensitivity analysis, in which the full range of uncertainty in the distributions of parameters derived from the clinical systematic review was fed into the model to give probabalistic estimates of cost-effectiveness which reflect the parameter uncertainty present in a transparent way. The limitations of the clinical evidence base are discussed at length in the clinical review. With regard to BCG status as an example, the precise relationship between BCG status and diagnostic accuracy could not be determined, and the GDG considered this in their deliberations along with the other benefits and limitations of the evidence and methodologies used. However, the GDG did note that studies that reported data on this factor suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted the important fact that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of

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				Apart from these issues, various sources of methodological bias may have independently distorted the review findings. For example, the study findings may have been biased due to lack of blinding, selection bias, partial verification bias due to incomplete outcome data assessment, and incorporation bias. (page 32) o Findings should be viewed by clinicians and policy makers cautiously because of the limited evidence, the lack of a gold standard diagnostic test and the assumptions made (page 33) o The forest plots of sensitivities and specificities were generated and due to high unexplained heterogeneity (not explained by IGRA type and TST threshold, similar diagnostic methods of active TB), no meta analysis could be performed (page 100 referring to the analysis for children). o The absence of any clear pattern in the distribution of sensitivity and specificity values reflect underlying between-study differences in study populations/conditions, settings, and variation in exposure definitions and measurement. In light of the observed heterogeneity, no meta-analysis was undertaken (page 211)	5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses. It could be inferred that the overall impact of BCG status on the accuracy of these results for decision making purposes is likely to be small. For these reasons, the GDG chose not to recommend that a different TST threshold (or a different test) should be adopted in people with a history of BCG, as some other guidelines (including previous versions of NICE guidance) do. The GDG emphasised the importance of clarity regarding the application of these recommendations to case finding in high risk groups as opposed to blanket screening.

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Oxford Immunotec	Full	General	General	The following publications should also be considered in the review as they investigate the predictive value of the T-SPOT.TB test: Jonnalagadda S, Lohman B, Brown E, Wamalwa D, Maleche E, Obimbo, Majiwa M, Farquhar C, Otieno P, Ngacha DM, Stewart GJ. Latent Tuberculosis Detection by Interferon γ Release Assay during Pregnancy Predicts Active Tuberculosis and Mortality in Human Immunodeficiency Virus Type 1-Infected Women and Their Children. J Infect Dis. 2010 Dec 15;202(12):1826-1835. Leung CC, Yam WC, Ho PL, Yew WW, Chan CK, Law WS, Lee SN, Chang KC, Tai LB, Tam CM. T-Spot.TB outperforms tuberculin skin test in predicting development of active tuberculosis among household contacts. Respirology. 2015 Apr;20(3):496-503.	Thank you for your comment and for providing these references. These studies would not have met the inclusion criteria for this review for the following reasons. The study by Jonnalagadda and colleagues has not compared IGRA vs TST. The study by Leung et al provides evidence on LTBI that progresses to active TB among household contacts, and this population was outside the remit of our review.
Oxford Immunotec	Full	General	General	The above comments suggest that there are some major weaknesses in the economic model review. These can be highlighted as follows: 1. The derivation of the key parameters of sensitivity and specificity are not clearly described The 95% credible intervals for sensitivity (and to a lesser extent specificity) are very large	Thank you for your comments. Responses to each specific comment are as follows: 1. The derivation of all parameters included in the model is described in Appendix H of the full guideline. The full distributions of these parameter estimates are incorporated into the probabilistic cost-effectiveness model which therefore allows

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					explicit consideration of these uncertainties.
				2. Definitions of sensitivity and specificity while theoretically acceptable are difficult to use pragmatically due to the large number of subjects that would have to be screened, the length of follow-up and the necessity to not treat infected subjects for LTBI. None of the studies cited followed these requirements. However, it should be noted that the PREDICT study being carried out in the UK uses precisely this methodology and should be reporting its results in the near future and will shed much needed light on these issues	2. As we were only able to consider published evidence in our review, the PREDICT study was not available at the time of writing this guideline.
				3. Some of the assumptions used in the model (accuracy of x-ray and sputum tests, conversion rates from LTBI to active disease) do not reflect reality	3. The parameters in question were derived from a thoroughgoing systematic review of the evidence and were implemented in a model which underwent a full probabilistic sensitivity analysis.
				4. The key cost data for the QFT and T-SPOT.TB tests is from a single, but different, organisation for each test and is at least 7 years old. How representative can this be for a cost effectiveness model in 2015?	4. The economic analysis is informed by a decision analytical model whereby information used to parameterise the model are obtained from various sources. It is unlikely in modelling to have all cost data, for example, from the same source. The source of the cost data appeared to be transparent on how they have been derived. Pooran et al. (2010) stated what these costs comprised. On this basis we inflated these costs using the Hospital and Community Health Services (HCHS) pay and price index. In some

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					instances, authors are not clear/transparent on how costs are derived.
Oxford Immunotec	Full	General	General	The authors of the model highlight many of these deficiencies and in particular on page 33 state "findings should be viewed by clinicians and policy makers cautiously because of the limited evidence, the lack of a gold standard diagnostic test and the assumptions made. If the authors themselves advise policy makers to be cautious how can they be used as the basis for new national guidelines? Perhaps updating the IGRA section of the guidelines should wait for the outcome of the PREDICT study.	As we were only able to consider published evidence in our review, the PREDICT study was not available at the time of writing this guideline The Surveillance team have been informed of the PREDICT study.
Royal College of Paediatrics and Child Health	Full	General	16	The word TB should be explained on page 16 that it means tuberculosis	Thank you for highlighting this. It has now been added.
Royal College of Paediatrics and Child Health	Full	General	17 20	The very young is not appropriate term, it should be infants and young children	Thank you for highlighting this. It has now been corrected.
Homerton Hospital	Full	General	18	As the positive test is now 5 mm instead of 15 mm, many more will have a chest x-ray. The	Thank you for your comment. The Developer is uncertain they have fully understood the points it

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NHS Foundation Trust (HHFT)				need to repeat these tests will become more difficult to recommend (booster effect; waning DTH with age etc.).	contains, but has addressed the points identified: *Lowering of TST threshold from 15 mm to 5 mm* The model for children suggested that TST ≥5 mm, being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the

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					most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).change in threshold *The impact of lowering the threshold on the number of chest X-rays that will need to be performed (and in turn the associated impact on resources this might have)* With regards the increased number of chest X-rays that will be performed to rule out active disease in those with a positive TST, it should be noted that this cost was taken into account in the economic analyses conducted (see the results above). We have also passed your comment to the NICE implementation support team to inform their support activities for this guideline. It should also be noted that the guidance for managing people with latent TB who are at increased risk of going on to develop active TB but who choose not to undergo treatment for latent TB has changed. Chest X-rays are no longer recommended after 3 and 12 months due to a lack of clinical- and cost-effectiveness

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					evidence, which may mitigate the increase in X-rays that might occur due to the change in the threshold for TST interpretation. *Booster effect of BCG* Although BCG vaccination with booster shots after infancy has been associated with compromised TST specificity (that is, increased false-positives, which might in turn unnecessarily increase the demand for chest X-rays), this is not recommended by this guideline or by the Green Book. *Booster effect of TST on IGRA* As stated in the Evidence to Recommendations, the GDG noted that Mantoux testing can interfere with the results of IGRA testing, and therefore result in false-positive diagnosis. It has therefore been recommended that in the case of two-step testing the tests should be performed relatively close together (6 weeks). *Delayed hypersensitivity reactions due to previous exposure to TB* No guidance (due to a lack of evidence) has been made with regards avoiding false positive results that might arise due to delayed hypersensitivity reactions following previous exposure to TB.

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British Thoracic Society	Full	General	18	As the positive test is now 5 mm instead of 15 mm, many more will have a chest x-ray. The need to repeat these tests will become more difficult to recommend (booster effect; waning DTH with age etc.).	Thank you for your comment. The Developer is uncertain they have fully understood the points it contains, but has addressed the points identified: *Lowering of TST threshold from 15 mm to 5 mm* The model for children suggested that TST ≥5 mm, being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied

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					on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).change in threshold *The impact of lowering the threshold on the number of chest X-rays that will need to be performed (and in turn the associated impact on resources this might have)* With regards the increased number of chest X-rays that will be performed to rule out active disease in those with a positive TST, it should be noted that this cost was taken into account in the economic analyses conducted (see the results above). We have also passed your comment to the NICE implementation support team to inform their support activities for this guideline. It should also be noted that the guidance for managing people with latent TB who are at increased risk of going on to develop active TB but who choose not to undergo treatment for latent TB has changed. Chest X-rays are no

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					longer recommended after 3 and 12 months due to a lack of clinical- and cost-effectiveness evidence, which may mitigate the increase in X-rays that might occur due to the change in the threshold for TST interpretation. *Booster effect of BCG* Although BCG vaccination with booster shots after infancy has been associated with compromised TST specificity (that is, increased false-positives, which might in turn unnecessarily increase the demand for chest X-rays), this is not recommended by this guideline or by the Green Book. *Booster effect of TST on IGRA* As stated in the Evidence to Recommendations, the GDG noted that Mantoux testing can interfere with the results of IGRA testing, and therefore result in false-positive diagnosis. It has therefore been recommended that in the case of two-step testing the tests should be performed relatively close together (6 weeks). *Delayed hypersensitivity reactions due to previous exposure to TB* No guidance (due to a lack of evidence) has been made with regards avoiding false positive results that might arise due to delayed hypersensitivity

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					reactions following previous exposure to TB.
Royal College of Paediatrics and Child Health	Full	General	26 10	Not clear who to refer to for deciding strategy	Thank you for your comment. The recommendation has been amended to say: "Refer children younger than 2 years and in close contact with people with smear-negative pulmonary TB to a specialist to determine what testing strategy for latent TB would be most appropriate. **This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician.**"
CHIVA	Full	General	132	4th paragraph The statement 'However, the immune system has begun to develop in these children and has now reached a level that enables the use of tests for latent TB.' makes little sense. Any major difference between a 4-week old infant vs a 2-week old neonate?	Thank you for your comment. The text has now been amended to: "However, the immune system has begun to develop in these children and has now theoretically reached a level that enables the use of tests for latent TB."
CHIVA	Full	General	132	5th paragraph Indicating that children over 2 years have a similar immune response to adults is not in line with Connell TG et al. Indeterminate interferon-gamma release assay results in children. Pediatr	Thank you for your comment. It has been shared with the GDG for their consideration. However, Connell (2010) did not meet the inclusion criteria for the relevant review because it wasn't a full report of a peer-reviewed study (it was published only as a letter), and Tebruegge (2014) did not meet the inclusion criteria because it did not

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				Infect Dis J. 2010 Mar;29(3):285-6. And Tebruegge et al. Extremes of age are associated with indeterminate QuantiFERON-TB gold assay results. J Clin Microbiol. 2014 Jul;52(7):2694-7.	compare the accuracy of IGRAs with TSTs in head to head comparison (only QFT-GIT was studied). The GDG did not judge this evidence to provide a strong enough basis from which to change the rationale for their recommendations, nor change the recommendations themselves.
Royal College of Paediatrics and Child Health	Full	General	132	5th paragraph The statement: 'Over the age of 2 years, the group felt that diagnosis of latent TB and the actions associated with it should be as for adults. This is because the immune system has now sufficiently developed to reduce the risk of both infection and progression to active disease, as well as to provide a sufficient immune response to allow the tests to function.' is not entirely accurate. There is ample evidence to suggest that IGRA perform less well in children > 2 years of age compared to adults. See: 1. Tebruegge et al. Extremes of age are associated with indeterminate QuantiFERON-TB gold assay results. J Clin Microbiol. 2014 Jul;52(7):2694-7. Connell TG et al. Indeterminate interferon-gamma release assay results in children. Pediatr Infect Dis J. 2010 Mar;29(3):285-6.	Thank you for your comment. It has been shared with the GDG for their consideration. However, Connell (2010) did not meet the inclusion criteria for the relevant review because it wasn't a full report of a peer-reviewed study (it was published only as a letter), and Tebruegge (2014) did not meet the inclusion criteria because it did not compare the accuracy of IGRAs with TSTs in head to head comparison (only QFT-GIT was studied). The GDG did not judge this evidence to provide a strong enough basis from which to change the rationale for their recommendations, nor change the recommendations themselves.

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CHIVA	Full		132	The document states that Mantoux testing can interfere with the results of IGRA testing, and therefore result in false-positive diagnosis.' This statement is incorrect. Published data suggest that TSTs do not impact on IGRA results. Ritz N. Absence of interferon-gamma release assay conversion following tuberculin skin testing. Int J Tuberc Lung Dis. 2011Jun;15(6):767-9.	Thank you for your comment. Although this evidence *suggests* that Mantoux testing does not result in conversion of subsequent IGRA testing in the absence of concomitant TB exposure, it is a single study of 16 individuals. The GDG were mindful that further evidence is required to remove the need for caution in using the 2-step approach.
Royal College of Paediatrics and Child Health	Full	General	132	3rd paragraph refers sequentially to neonates having an "immune system not yet developed", "underdeveloped immune system" and "lack of an immune system" – the last statement goes too far!	Thank you for your comment. "The lack of immune system in neonates..." has now been amended to: "The developing immune system in neonates..."
Royal College of Paediatrics and Child Health	Full	General	132	4th paragraph The statement 'However, the immune system has begun to develop in these children and has now reached a level that enables the use of tests for latent TB.' makes little sense. Does the GDG really believe that the immune system is significantly more mature in a 4-week old infant compared with a 2-week old neonate? We suggest to re-phrase this sentence at least.	Thank you for highlighting this. The text has now been amended to: "However, the immune system has begun to develop in these children and has now theoretically reached a level that enables the use of tests for latent TB."
Royal College of	Full	General	132	The statement 'The GDG noted that Mantoux testing can interfere with the results of IGRA	Thank you for your comment. The study did not meet the inclusion criteria for the review as the

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Paediatrics and Child Health				testing, and therefore result in false-positive diagnosis.' is incorrect. In fact, the published data regarding whether or not TST influence IGRA results are conflicting. The following study provides compelling data to suggest that TSTs do not impact on IGRA results (and discusses the limitations of previous studies in detail): Ritz N. Absence of interferon-gamma release assay conversion following tuberculin skin testing. Int J Tuberc Lung Dis. 2011 Jun;15(6):767-9.	population consisted of healthy people with low risk of TB exposure. Furthermore, although this evidence suggests that Mantoux testing does not result in conversion of subsequent IGRA testing in the absence of concomitant TB exposure, it is a single study of 16 individuals. Further evidence is required to remove the need for caution in using the 2-step approach.
CHIVA	Full	General	132	neonates having "lack of an immune system" – an overstatement. 3rd paragraph	Thank you for highlighting this. "The lack of immune system in neonates..." has now been amended to: "The developing immune system in neonates..."
CHIVA	Full	General	142 51	There is no evidence that exposure to NTM causes false-positive TST results. See Tebruegge M et al. Discordance between TSTs and IFN-gamma release assays: the role of NTM and the relevance of mycobacterial sensitins. Eur Respir J. 2010 Jul;36(1):214-5. This sentence needs to be re-worded.	Thank you for your comment. Tebruegge (2010) did not meet the inclusion criteria for any of the reviews conducted (the paper is a short narrative review presented in a letter, rather than a full report of a peer-reviewed study). However, your comment was shared with the Guideline Committee, who agreed that this information supported the removal of the statement.
Royal College of Paediatrics and Child	Full		142	While NTM disease can produce 'false' positive TST results, there is no evidence that exposure to NTM alone causes false-positive TST results. This sentence needs to be re-worded. See	Thank you for your comment. Tebruegge (2010) did not meet the inclusion criteria for any of the reviews conducted (the paper is a short narrative review presented in a letter, rather than a full

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Health			51	Tebruegge M et al. Discordance between TSTs and IFN-gamma release assays: the role of NTM and the relevance of mycobacterial sensitins. Eur Respir J. 2010 Jul;36(1):214-5.	report of a peer-reviewed study). However, your comment was shared with the Guideline Committee, who agreed that this information supported the removal of the statement.
CHIVA	Full	General	254	"ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately." Also note INT J TUBERC LUNG DIS 10(12) :1318-1330 2006 Ethambutol Dosage for the Treatment of Children: Literature review and Recommendations . Donald PR et al. with only 2 of 3871 children (0.05%) receiving Ethambutol doses of 15-30 m/kg was Ethambutol stopped due to possible ocular toxicity; They therefore concluded that children of all ages can be given Ethambutol in daily doses of 20mg/kg (range 15-25 mglkg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern. Also the Royal College of Ophthalmologists suggest that children don't need any special precautions when using ethambutol (RCOphth Document reference: 2010/PROF/121) Furthermore the recommendation to give ethambutol to everyone with active TB is not	Thank you for your comment. Donald (2006) and the Royal College of Ophthalmologists document were not directly relevant to any of the reviews conducted for this guidance – the data presented did not consider the use of ethambutol in children *with eye disease or visual impairment*, rather they was concerned with the use of ethambutol in any child with TB (furthermore, these documents were narrative rather than a systematic reviews). However, the Committee discussed this statement and agreed that the word 'caution' was too strong. They concluded that it was important that clinicians are aware of the minimal risk of visual changes associated with ethambutol in order to watch for them. Their intention was not to encourage clinicians to avoid using ethambutol in children under 5. The text has been amended to: "Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug. **In very young children who are not yet able to report symptomatic visual changes accurately, ethambutol can still be**

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				followed.	**used though clinicians should be alert for signs of visual change.**"
Royal College of Paediatrics and Child Health	Full	General	254	"ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately." This contradicts the recommendation to give ethambutol to everyone with active TB. The Royal College of Ophthalmologists suggest that children don't need any special precautions when using ethambutol (RCOphth Document reference: 2010/PROF/121) Also note INT J TUBERC LUNG DIS 10(12) :1318-1330 2006 Ethambutol Dosage for the Treatment of Children: Literature review and Recommendations . Donald PR et al. This reported that in only 2 of 3871 children (0.05%) receiving Ethambutol doses of 15-30 m/kg was Ethambutol stopped due to possible ocular toxicity; They therefore concluded that children of all ages can be given Ethambutol in daily doses of 20mg/kg (range 15-25 mglkg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern.	Thank you for your comment. Donald (2006) and the Royal College of Ophthalmologists document were not directly relevant to any of the reviews conducted for this guidance – the data presented did not consider the use of ethambutol in children *with eye disease or visual impairment*, rather they was concerned with the use of ethambutol in any child with TB (furthermore, these documents were narrative rather than a systematic reviews). However, the Committee discussed this statement and agreed that the word 'caution' was too strong. They concluded that it was important that clinicians are aware of the minimal risk of visual changes associated with ethambutol in order to watch for them. Their intention was not to encourage clinicians to avoid using ethambutol in children under 5. The text has been amended to: "Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug. **In very young children who are not yet able to report symptomatic visual changes accurately, ethambutol can still be used though clinicians should be alert for signs of visual change.**"

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Birmingham & Solihull TB Service	Full	General	254	"Ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately." This contradicts the recommendation to give Ethambutol to everyone with active TB. The Royal College of Ophthalmologists suggest that children don't need any special precautions when using Ethambutol (RCOphth Document reference: 2010/PROF/121) Also note INT J TUBERC LUNG DIS 10(12) :1318-1330 2006 Ethambutol Dosage for the Treatment of Children: Literature review and Recommendations . Donald PR et al. This reported that in only 2 of 3871 children (0.05%) receiving Ethambutol doses of 15-30 m/kg was Ethambutol stopped due to possible ocular toxicity; They therefore concluded that children of all ages can be given Ethambutol in daily doses of 20mg/kg (range 15-25 mg/kg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern.	Thank you for your comment. Donald (2006) and the Royal College of Ophthalmologists document were not directly relevant to any of the reviews conducted for this guidance – the data presented did not consider the use of ethambutol in children *with eye disease or visual impairment*, rather they was concerned with the use of ethambutol in any child with TB (furthermore, these documents were narrative rather than a systematic reviews). However, the Committee discussed this statement and agreed that the word 'caution' was too strong. They concluded that it was important that clinicians are aware of the minimal risk of visual changes associated with ethambutol in order to watch for them. Their intention was not to encourage clinicians to avoid using ethambutol in children under 5. The text has been amended to: "Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug. **In very young children who are not yet able to report symptomatic visual changes accurately, ethambutol can still be used though clinicians should be alert for signs of visual change.**"
Royal College of	Full	1.1	17-18	In section on diagnosis, putting histology and radiology into same sentence ends up with a	Thank you for your comment. The text has now

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Paediatrics and Child Health				grammatically incorrect and meaningless sentence. Also NAATs should logically be discussed straight after culture as both are microbiological confirmation of diagnosis, before discussing TST and IGRAs.	been amended to: "TB is diagnosed in a number of ways. Tissue samples from biopsies may show changes that suggest TB, as do certain X-ray changes, particularly on chest X- rays. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. Newer rapid molecular diagnostics – nucleic acid amplification tests (NAATs) – that are able to detect small amounts of genetic material from the mycobacterium by repeatedly amplifying target sequences are also available. Mantoux tests and interferon gamma-release assays (IGRAs) can show if someone has been exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGRAs involve taking a blood sample, which is processed at a laboratory."
Royal College of Paediatrics and Child	Full	1.1	16	What is meant by TB is "now" a notifiable disease? It has been notifiable since 1912 (A Newsholme, Notification of Tuberculosis in Great Britain, A Historical Note, BMJ 1934, July 14,	Thank you for your comment. The introductory text in both the Full and Short versions of the guideline has now been amended.

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Health				pp75-76). Indeed the word "now" is overused throughout the opening paragraphs.	
Royal College of Paediatrics and Child Health	Full	1.1	16 24	In introduction it says that 'TB is caused by M.tuberculosis'. In line with the rest of the document, suggest to change to: TB is caused by M.tb *complex, including other mycobacteria: M. bovis, M. africanum; most cases are caused by M.tb.*	Thank you for highlighting this. The introductory text in both the Full and Short versions of the guideline has now been amended to: "TB is a curable disease caused by a bacterium called Mycobacterium tuberculosis ('M. tuberculosis' or 'M.Tb')**, or other bacterium in the M. tuberculosis complex (that is, M. bovis or M. africanum).**"
CHIVA	Full	1.1	16	TB has been notifiable for more than 100 years. There is no need for wording in the introduction - TB is "now" a notifiable disease?	Thank you for your comment. The introductory text in both the Full and Short versions of the guideline has now been amended.
Royal College of Paediatrics and Child Health	Full	1.1	17	In section "What are the symptoms of TB" it may be worth stating that the symptoms of TB may be less specific particularly in high-risk groups such as infants (<12 months) Also in young children TB may present as failure to gain weight and faltering growth across centiles rather than actual weight loss.	Thank you for your comment. The text has been amended to: "Because TB can affect many sites in the body, there can be a wide range of symptoms, some of which are not specific and may delay diagnosis. Typical symptoms of pulmonary TB include chronic cough, weight loss, intermittent fever, night sweats and coughing blood. TB in parts other than the lungs has symptoms which depend

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					on the site, and may be accompanied by intermittent fever or weight loss. In young children, particularly those aged younger than 12 months, a failure to gain weight or grow at a 'normal' rate are more common than weight loss, as such. **TB is a possible diagnosis to be considered in anyone with intermittent fever, weight loss and other unexplained symptoms. Latent tuberculosis without disease, however, has no symptoms.**"
CHIVA	Full	1.1	17 18	NAATs should be discussed after cultures as both are microbiological confirmation of diagnosis. TST and IGRAs should follow thereafter.	Thank you for your comment. The text has been amended to: "TB is diagnosed in a number of ways. Tissue samples from biopsies may show changes that suggest TB, as do certain X-ray changes, particularly on chest X- rays. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. Newer rapid molecular diagnostics – nucleic acid amplification tests (NAATs) – that are able to detect small amounts of genetic material from the mycobacterium by repeatedly amplifying target sequences are also available. Mantoux test and interferon gamma-release assays (IGRAs) can show if someone has been

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					exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGRAs involve taking a blood sample, which is processed at a laboratory."
Birmingham & Solihull TB Service	Full	1.1	17	In section "What are the symptoms of TB" it may be worth stating that the symptoms of TB may be less specific particularly in high-risk groups such as infants (<12 months) Also in young children TB may present as failure to gain weight and faltering growth across centiles rather than actual weight loss	Thank you for your comment. The text has been amended to: "Because TB can affect many sites in the body, there can be a wide range of symptoms, some of which are not specific and may delay diagnosis. **Typical symptoms of pulmonary TB include chronic cough, weight loss, intermittent fever, night sweats and coughing blood. TB in parts other than the lungs has symptoms which depend on the site, and may be accompanied by intermittent fever or weight loss.** In young children, particularly those aged younger than 12 months, a failure to gain weight or grow at a 'normal' rate are more common than weight loss, as such. **TB is a possible diagnosis to be considered in anyone with intermittent fever, weight loss and other unexplained symptoms. Latent tuberculosis without disease, however, has no symptoms.**"

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Royal College of Paediatrics and Child Health	Full	1.1	18 24	'Treatment should be continued for 6 months'. Suggest to change to: Treatment should be continued for *at least* 6 m.	Thank you for your comment. The GDG discussed this concern, but concluded that regimens of longer than 6 months were not justified by either the evidence (of which none was identified in this population) or in their clinical experience. 6 months of isoniazid is recommended in neonates. For children and young people over the age of 4 weeks, either of the recommended regimens (6 months of isoniazid or 3 months of isoniazid and rifampicin) may be used, though selection should be based on the parameters outlined in the recommendation below: "Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin to people aged younger than 35 years if hepatotoxicity is a concern; this would include both liver function (including transaminase) test results and assessment of risk factors • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant." The following text has now been added to the Evidence to Recommendations table: "Given that there was a lack of evidence

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					regarding which regimens should be used for chemoprophylaxis and the treatment of latent TB in children, the recommendations were predominantly based on paediatric expert opinion. Isoniazid should be started on its own in neonates and started in the absence of evidence of infection as a precaution. It was decided that to add rifampicin would be inappropriately exposing non-infected neonates to drugs. For children older than 4 weeks the choice should be isoniazid for 6 months or isoniazid and rifampicin for 3 months. While one is waiting for the second TST isoniazid alone is justified to avoid unnecessary exposure to a second drug in uninfected children."
NA	Full	1.2.1.1	1.2.1.1.	Question One-This is a huge change in our TB Team. Previously we were only classifying a strongly positive Mantoux reaction as 14 mm +, and also we weren't doing any Mantoux testing on over-35 year olds, but only a CXR.	Thank you for your comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). However, your comment has been shared with the NICE implementation support team to inform their support activities for

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					this guideline.
NA	Full	1.2.1.11	1.2.1.11	Question 1: This recommendation will be a challenging change in practice because we have been confidently using Igras in our New Arrival clinics for over 2 years now. This has meant that the there is less room for false positives from a Mantoux, as the Igra carries a far higher sensitivity/ specifity level. Also, the client has only had to attend 1 appointment and not 2 …….	Thank you for your comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). However, your comment has been shared with the NICE implementation support team to inform their support activities for this guideline.
Royal College of Paediatrics and Child Health	Full	1.5	General	No guidance on visual toxicity monitoring is provided if ethambutol is used. It is only mentioned in the Evidence to Recommendations in the section 4.9.6.5 (page 254) 'People with tuberculosis and impaired vision or eye disease' that 'the use of ethambutol is associated with a range of visual disturbances, including loss of acuity, restriction of visual fields, red-green colour blindness and optic neuritis.	Thank you for your comment. The GDG discussed the available information, as well as their knowledge and experience, but did not feel it was a strong enough basis upon which to provide recommendations. For this reason they recommended that people with TB and eye disease or impaired vision should be managed in conjunction with a specialist multidisciplinary team with experience of managing TB and eye disease or impaired vision.

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				Care is therefore advised when ethambutol is prescribed to those with visual defects. Ocular examinations including acuity, colour discrimination and visual field are recommended before starting treatment and periodically during treatment, especially if high doses are used.'	
Royal College of Paediatrics and Child Health	Full	1.5	General	Pyridoxine is mentioned in different Evidence to Recommendations sections, but no guidance is provided which groups of adults and children treated with isoniazid should receive pyridoxine.	Thank you for your comment, The GDG added the following text to each recommendation in which isoniazid has been recommended: (… isoniazid (with pyridoxine)…) Additional text in the Evidence to Recommendations table: "The GDG noted the widespread use of pyridoxine in the evidence base for all isoniazid-containing regimens. It is administered as prophylaxis against peripheral neuropathy, and it is unclear what the incidence of this adverse event would have been if pyridoxine had not been co-administered. Co-administration of pyridoxine is also recommended in the BNF. The group therefore concluded that this should be reflected in their recommendations."
CHIVA	Full	1.5	general	A clear guidance as to which children or adults should receive Pyridoxine if treated with isoniazid.	Thank you for your comment. The GDG added the following text to each recommendation in which isoniazid has been recommended:

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					(… isoniazid (with pyridoxine)…) Additional text in the Evidence to Recommendations table: "The GDG noted the widespread use of pyridoxine in the evidence base for all isoniazid-containing regimens. It is administered as prophylaxis against peripheral neuropathy, and it is unclear what the incidence of this adverse event would have been if pyridoxine had not been co-administered. Co-administration of pyridoxine is also recommended in the BNF. The group therefore concluded that this should be reflected in their recommendations."
Royal College of Paediatrics and Child Health	Full	1.6	69	The research recommendation on identifying effective strategies to enhance uptake of latent TB diagnosis and completion of treatment is welcome and important as this is the major reason for failure of the current system	Thank you for your comment.
Royal College of Paediatrics and Child Health	Full	1.6	69	The research recommendation on universal v targeted use of NAAT is less relevant to children as Recommendation 35 stipulates universal use of NAAT in children already. The research recommendation on establishing whether NAAT should be done locally or centrally is even more relevant to children as this guideline	Thank you for your comment.

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				is recommending universal use of NAAT in all children with suspected TB. In which laboratories this should be done is thus already an important issue in children.	
CHIVA	Full	1.6	69	Recommendation on identifying effective strategies to enhance uptake of latent TB diagnosis and completion of treatment is welcome and important.	Thank you for your comment.
CHIVA	Full	1.6	69	The research recommendation on establishing whether NAAT should be done locally or centrally is even more relevant to children as this guideline is recommending universal use of NAAT in all children with suspected TB. In which laboratories this should be done is thus already an important issue in children	Thank you for your comment.
Birmingham & Solihull TB Service	Full	1.6	69	The research recommendation on identifying effective strategies to enhance uptake of latent TB diagnosis and completion of treatment is welcome and important as this is the major reason for failure of the current system	Thank you for your comment.
Birmingham & Solihull TB Service	Full	1.6	69	The research recommendation on universal v targeted use of NAAT is less relevant to children as Recommendation 35 stipulates universal use of NAAT in children already	Thank you for your comment.

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				The research recommendation on establishing whether NAAT should be done locally or centrally is even more relevant to children as this guideline is recommending universal use of NAAT in all children with suspected TB. In which laboratories this should be done is thus already an important issue in children	
Royal College of Paediatrics and Child Health	Full	3	157	Given the advice to perform NAAT in all children, advice may need already to be given in this guideline on where this should be done. One contributor commented on a case where sending a sample to a commercial lab for NAAT rather than NHS reference lab resulted in possible delay of assessment for resistance.	Thank you for your comment. It is hoped that including this topic as a research recommendation will encourage studies in this area, which will in turn be available when the guidance is reviewed.
Royal College of Paediatrics and Child Health	Full	3.1.1	105	There is no data to suggest that 'the majority will clear the infection' (versus containing the infection). This cannot be proven with currently available methods.	Thank you for your comment. The text has been amended to: "Of those who are infected, many will clear the infection."
Royal College of Paediatrics and Child Health	Full	3.1.4	138	Position of title "people who are immune compromised" needs reformatting as it looks as though it refers to recommendation 14 about new entrants rather than the recommendations below.	Thank you for your comment. The title has now been repositioned.

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CHIVA	Full	3.1.4.10	137	Repeat testing with TST and IGRA 6 weeks after an initial negative test is an advantage, and may be appropriate also in contacts of smear-negative disease The use of repeat testing means that there need be no concern about doing a test early and worrying about a false negative test as done too early	Thank you for your comment. With regards extending repeat testing to contacts of people with smear-negative disease, the lack of evidence on this meant that the GDG did not feel able to make such a recommendation. As stated in the Evidence to Recommendations table, diagnosis of latent infection in these individuals can be complex, and should be considered by an expert on a case-by-case basis. This is reflected in the recommendation below: "Refer children younger than 2 years and in close contact with people with smear-negative pulmonary or laryngeal TB to a specialist to determine what testing strategy for latent TB should be done. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician." The use of one-step or two-step testing will therefore be at the discretion of the specialist managing the case.
Royal College of Paediatrics and Child	Full	3.1.4.10	137	The use of repeat testing with TST and IGRA 6 weeks after an initial negative test is welcome, and may be appropriate also in contacts of smear-negative disease.	Thank you for your comment. With regards extending repeat testing to contacts of people with smear-negative disease, the lack of evidence on this meant that the GDG did not

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Health				The use of repeat testing means that there need be no concern about doing a test early and worrying about a false negative test as done too early.	feel able to make such a recommendation. As stated in the Evidence to Recommendations table, diagnosis of latent infection in these individuals can be complex, and should be considered by an expert on a case-by-case basis. This is reflected in the recommendation below: "Refer children younger than 2 years and in close contact with people with smear-negative pulmonary or laryngeal TB to a specialist to determine what testing strategy for latent TB should be done. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician." The use of one-step or two-step testing will therefore be at the discretion of the specialist managing the case.
Birmingham & Solihull TB Service	Full	3.1.4.10	137	The use of Mantoux as first line to screen for latent TB in new immigrant population is at odds with recent PHE guidance around developing services for screening new migrants.	Thank you for your comment. Although the scope and methodology for the Public Health England guidance overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the PHE guidance centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries

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					who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
CHIVA	Full	3.1.4.14	138	PHE guidance around developing services for screening new migrants will be affected with the change to Mantoux as first line TB screen for new immigrant population.	Thank you for your comment. Although the scope and methodology for the Public Health England guidance overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the PHE guidance centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					health economic modelling that underpinned these, are focused on different areas.
Royal College of Paediatrics and Child Health	Full	3.1.4.14	138	The use of Mantoux as first line to screen for latent TB in new immigrant population is at odds with recent PHE guidance around developing services for screening new migrants.	Thank you for your comment. Although the scope and methodology for the Public Health England guidance overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the PHE guidance centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
Birmingham & Solihull TB Service	Full	3.1.4.14	138	The use of Mantoux as first line to screen for latent TB in new immigrant population is at odds with recent PHE guidance around developing services for screening new migrants.	Thank you for your comment. Although the scope and methodology for the Public Health England guidance overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the PHE

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					guidance centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
CHIVA	Full	3.1.4.15 6	138	There needs also to be consideration of TB screening in children who may become immune-compromised eg prior to anti-TNF therapy or transplantation	Thank you for your comment. The recommendation has been amended to "If latent TB is suspected in children and young people who are **anticipated to be or are currently** immunocompromised (for example, if they are from a high incidence country or have been in close contact with people with suspected infectious or confirmed pulmonary or laryngeal TB), refer to a TB specialist. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."

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CHIVA	Full	3.1.4.15	138	If latent TB is suspected in an immunecompromised child must mean if such a child has had contact; it may therefore be clearer to say that immunecompromised children should be referred for specialist assessment after contact.	Thank you for your comment. The recommendation has been amended to "If latent TB is suspected in children and young people who are **anticipated to be or are currently** immunocompromised (for example, if they are from a high incidence country or have been in close contact with people with suspected infectious or confirmed pulmonary or laryngeal TB), refer to a TB specialist. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	3.1.4.15	138	If latent TB is suspected in an immunecompromised child must mean if such a child has had contact; it may therefore be clearer to say that immunecompromised children should be referred for specialist assessment after contact.	Thank you for your comment. The recommendation has been amended to "If latent TB is suspected in children and young people who are anticipated to be or are currently immunocompromised (for example, if they are from a high incidence country or have been in close contact with people with suspected infectious or confirmed pulmonary or laryngeal TB), refer to a TB specialist. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
CHIVA	Full	3.1.4.15	138	It is not appropriate for children to be managed by adult physicians.	Thank you for your comment. The following clarification has been added to the

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				It should read 'paediatric TB specialist'.	recommendations: "This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	3.1.4.15	138	This should read 'paediatric TB specialist'. It is not appropriate for children to be managed by adult physicians.	Thank you for your comment. The following clarification has been added to the recommendations: "This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	3.1.4.15 6	138	There needs also to be consideration of TB screening in children who may become immune-compromised eg prior to anti-TNF therapy or transplantation.	Thank you for your comment. The recommendation has been amended to "If latent TB is suspected in children and young people who are **anticipated to be or are currently** immunocompromised (for example, if they are from a high incidence country or have been in close contact with people with suspected infectious or confirmed pulmonary or laryngeal TB), refer to a TB specialist. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics	Full	3.1.3.3	127	This modelling really makes little sense. No country uses TST > 5 mm as a cut-off (except for immunocompromised patients). It does not matter	Thank you for your comment. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-

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and Child Health			13	what this artificial model suggests – it is certain that lowering the cut-off to 5 mm would produce a large proportion of false-positive results (especially in BCG-vaccinated individuals – which is precisely why 10 mm should be used instead).	positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses. Given the lack of existing substantive evidence on which to recommend a 6 mm induration cutoff , the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the

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					group noted that reliably measuring the difference between 5 mm and 6 mm in practice was extremely difficult. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied

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					on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).
CHIVA	Full	3.1.3.3	127 13	The change of TST > 5 mm as a cut-off (except for immunocompromised patients) is really difficult to understand. The drop to >5mm will lead to a large proportion of false-positive results. This would in particular affect BCG-vaccinated individuals. Therefore we would suggest to use 10 mm instead.	Thank you for your comment. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to

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					be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses. Given the lack of existing substantive evidence on which to recommend a 6 mm induration cutoff , the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the group noted that reliably measuring the difference between 5 mm and 6 mm in practice was extremely difficult. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared

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					with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).
CHIVA	Full	3.1.4.4	136	The recommendation to use only TST in children	Thank you for your comments. The Guidelines

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				unless in a large-scale outbreak or TST unavailable is clearly based on the preceding cost analysis. This will have service implications, not least such as during recent shortages of tuberculin. Is it necessary to be this prescriptive about which test to use? In particular when it might affect organising an effective service which maximises engagement and adherence. IGRA should be an option in older children as for adults.	Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7).
Royal College of Paediatrics and Child Health	Full	3.1.4.4	136	The recommendation to use only TST in children unless in a large-scale outbreak or TST unavailable is clearly based on the preceding cost analysis. This will have service implications, not least such as during recent shortages of tuberculin. In older children (over 2 years or over 5 years) it has become common practice in many centres only to use IGRA, and this may be reasonable. The research section (see above) states that engagement with latent TB detection and treatment services is essential; it is likely that whether a TST or IGRA is used has a marginal effect on diagnosis rates compared to engagement and adherence. It therefore seems inappropriate to be this prescriptive about which test to use, when the	Thank you for your comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). It was not possible to further subdivide the age ranges of high risk subgroups on the basis of the evidence considered.

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				effect of this is trivial compared to organising an effective service which maximises engagement and adherence. There seems to be no reason for not recommending considering IGRA in older children as for adults. One of the justifications for this later in the document is that children would need to be referred to a hospital to have blood tests done whereas in fact for older children community teams could be trained to take bloods from at least school aged children . An option to consider IFN gamma testing should also be considered at least for older children	
Birmingham & Solihull TB Service	Full	3.1.4.4	136	The recommendation to use only TST in children unless in a large-scale outbreak or TST unavailable is clearly based on the preceding cost analysis. This will have service implications, not least such as during recent shortages of tuberculin. In older children (over 2 years or over 5 years) it has become common practice in many centres only to use IGRA, and this may be reasonable. The research section (see above) states that engagement with latent TB detection and treatment services is essential; it is likely that whether a TST or IGRA is used has a marginal effect on diagnosis rates compared to engagement and adherence. It therefore seems inappropriate to be this prescriptive about which test to use, when the effect of this is trivial	Thank you for your comment. The management of large incidents and screening of LTBI patients in any context other than the opportunistic screening of a patient presenting to a physician is outside the scope of this modelling work, which did not consider different service delivery modalities. In addition, it was not possible to further subdivide the sub-populations (older children for example) given the resource constraints and the limitations of the evidence which are detailed in Appendix H. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing

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				compared to organising an effective service which maximises engagement and adherence. There seems to be no reason for not recommending considering IGRA in older children as for adults. One of the justifications for this later in the document is that children would need to be referred to a hospital to have blood tests done whereas in fact for older children community teams could be trained to take bloods from at least school aged children . An option to consider IFN gamma testing should also be considered at least for older children	should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA

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					alone).
CHIVA	Full	3.1.4.5	136	In neonates it should highlight that an assessment needs to take place urgently in view of the risk of progression in this age-group Is the statement here If a neonate has been in close contact with people with pulmonary TB WHO HAVE not had at least 2 weeks of anti-TB treatment: And not as stated If a neonate has been in close contact with people with pulmonary TB and has not had at least 2 weeks of anti-TB treatment	Thank you for your comment. The text has now been amended to "If a neonate has been in close contact with people with pulmonary or laryngeal TB and has not had at least 2 weeks of anti-TB treatment…"
CHIVA	Full	3.1.4.5	136	All infants should be assessed for active TB independent of results of TST in view of the risk of progression to active TB in this age group and the lack of sensitivity of TST.	Thank you for your comment. The text has now been amended so that *all* children under 2 years who are close contacts of people with suspected/confirmed pulmonary or laryngeal TB will undergo assessment for active TB.
CHIVA	Full	3.1.4.5	136	IGRA are unreliable in neonates, and likely add very little in this context. We suggest to change to 'if immune-based testing (ie TST +/- IGRA) is negative then stop isoniazid and give BCG'. This will allow clinicians to perform TST alone or TST and IGRA sequentially.	Thank you for your comment. The GDG judged the wording to be clearer and produces less ambiguity with regards to the steps involved.

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CHIVA	Full	3.1.4.5	136	"if the test for active TB is negative, continue isoniazid treatment for a total of 6 months" This could say; if the ASSESSMENT for active TB is negative, continue isoniazid treatment for a total of 6 months	Thank you for your comment. This part of the recommendation has now been amended to "…if this assessment for active TB is negative, …"
Royal College of Paediatrics and Child Health	Full	3.1.4.5	136	If a neonate has been in close contact with people with pulmonary TB and has not had at least 2 weeks of anti-TB treatment: Should this read; If a neonate has been in close contact with people with pulmonary TB WHO HAVE not had at least 2 weeks of anti-TB treatment: There should be some indication that this assessment needs to take place urgently after contact given the risk of progression in this age-group.	Thank you for your comment. This part of the recommendation has now been amended to "If a neonate has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment…"
Royal College of Paediatrics and Child Health	Full	3.1.4.5	136	"If the Mantoux test is positive (5 mm or larger, regardless of BCG history), reassess for active TB (see section 1.3.1)". – given the risk of progression to active TB in this age group and the lack of sensitivity of TST, ALL children should be reassessed for active TB irrespective of TST	Thank you for your suggestion. The recommendations have now been amended to: "If a neonate has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks

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				result.	of anti-TB treatment: • Assess for active TB. • Start isoniazid (with pyridoxine). • Carry out a Mantoux test after 6 weeks of treatment. • If the Mantoux test is inconclusive, refer the person to a TB specialist. • If the Mantoux test is positive (5 mm or larger, regardless of BCG history), **reassess for active TB**; if this assessment is negative, continue isoniazid (with pyridoxine) for a total of 6 months. • If the Mantoux test is negative, **reassess for active TB** and consider an interferon-gamma release assay …" "If a child aged between 4 weeks and 2 years has been in close contact with people with smear-positive pulmonary or laryngeal TB: • Assess for active TB. • Start treatment for latent TB and carry out a Mantoux test. • If the Mantoux test is inconclusive, refer the person to a TB specialist. • If the Mantoux test is positive (5 mm or larger,

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					regardless of BCG history), **reassess for active TB**; if this assessment is negative, complete treatment for latent TB. • If the Mantoux test is negative, continue treatment for latent TB, **reassess for active TB after 6 weeks** and repeat the Mantoux test…"
Royal College of Paediatrics and Child Health	Full	3.1.4.5	136	This section does not make sense. It states that an IGRA should be 'considered' if the TST is negative – and then stop INH if both TST and IGRA are negative. This implies that an IGRA has to be done to arrive at this point. IGRA are unreliable in neonates, and likely add very little in this context. We suggest to change 'if both are negative' to 'if immune-based testing (ie TST +/- IGRA) is negative then stop isoniazid and give BCG'. This will allow clinicians to perform TST alone or TST and IGRA sequentially.	Thank you for your comment. The GDG considered current wording to be clearer and produces less ambiguity with regards to the steps involved.
Royal College of Paediatrics and Child Health	Full	3.1.4.5	136	"if the test for active TB is negative, continue isoniazid treatment for a total of 6 months" There is no "test" for active TB – This could say; if the ASSESSMENT for active TB is negative, continue isoniazid treatment for a total of 6 months.	Thank you for your comment. This part of the recommendation has now been amended to "…if this assessment for active TB is negative…"

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Birmingham & Solihull TB Service	Full	3.1.4.5	136	If a neonate has been in close contact with people with pulmonary TB and has not had at least 2 weeks of anti-TB treatment: Should this read; If a neonate has been in close contact with people with pulmonary TB WHO HAVE not had at least 2 weeks of anti-TB treatment: There should be some indication that this assessment needs to take place urgently after contact given the risk of progression in this age-group	Thank you for your comment. This part of the recommendation has now been amended to "If a neonate has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment…"
Birmingham & Solihull TB Service	Full	3.1.4.5	136	"If the Mantoux test is positive (5 mm or larger, regardless of BCG history), reassess for active TB (see section 1.3.1)". – given the risk of progression to active TB in this age group and the lack of sensitivity of TST, ALL children should be reassessed for active TB irrespective of TST result	Thank you for your comment. It is intended that the sensitivity of a 1-step Mantoux test will be raised with the addition of a 2nd Mantoux and/or IGRA.
CHIVA	Full	3.1.4.6	137	ALL children aged 4 weeks to 2 years who have had significant TB contact should be assessed clinically for active TB as mentioned above due to a high risk of progression. TST is NOT a sensitive enough indicator to exclude TB without a urgent assessment.	Thank you for your comment. The recommendations have now been amended to "If a child aged between 4 weeks and 2 years has been in close contact with people with smear-positive pulmonary or laryngeal TB:

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					• **Assess for active TB**. • Start treatment for latent TB and carry out a Mantoux test. • If the Mantoux test is inconclusive, refer the person to a TB specialist. • If the Mantoux test is positive (5 mm or larger, regardless of BCG history), **reassess for active TB**; if this assessment is negative, complete treatment for latent TB. • If the Mantoux test is negative, continue treatment for latent TB, **reassess for active TB** after 6 weeks and repeat the Mantoux test…"
CHIVA	Full	3.1.4.6	137	The recommendation for children aged 4 weeks to 2 years is to assess for active TB and treat if found to have active TB; if no evidence of active TB and TST positive, treat for latent TB; if no evidence of active TB and TST negative, give prophylactic isoniazid and retest later, if positive and no evidence of active TB, treat for latent TB; if repeat TST negative and no evidence of active TB stop prophylaxis. It is important for the committee to be aware that, in line with WHO recommendations (which extend this policy to age 5 years) the most common practice amongst UK paediatric TB experts is to	Thank you for your comment. The Committee discussed this concern but decided that, although a single TST is not sufficiently sensitive to allow chemoprophylaxis to be stopped, the use of an additional Mantoux test and an interferon gamma release assay raises the overall sensitivity of the diagnostic pathway to a point at which a negative result on all 3 tests is sufficient to allow chemoprophylaxis to be stopped. This reduces unnecessary exposure of non-infected young children to drugs. With regards the chemoprophylactic regimen prescribed in these children, the Committee

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				start children of this age who are contacts and have no evidence of active TB on full latent TB treatment (usually 3 months of isoniazid and rifampicin) and to complete the course, irrespective of the initial TST result and without repeating the TST after 6 weeks. This is based on the high risk of rapidly progressive disease in this age group, and the lack of sensitivity of TST. Is there a compelling evidence base on which to recommend the different and more complex strategy recommended here?	concluded that regimens of longer than 6 months were not justified by either the evidence (of which none was identified in this population) or in their clinical experience. 6 months of isoniazid is recommended in neonates. For children and young people over the age of 4 weeks, either of the recommended regimens (6 months of isoniazid or 3 months of isoniazid and rifampicin) may be used, though selection should be based on the parameters outlined in the recommendation below: "Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin to people aged younger than 35 years if hepatotoxicity is a concern; this would include both liver function (including transaminase) tests and assessment of risk factors • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant." The following text has now been added to the Evidence to Recommendations table: "Given that there was a lack of evidence regarding which regimens should be used for chemoprophylaxis and the treatment of latent TB

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					in children, the recommendations were predominantly based on paediatric expert opinion. Isoniazid should be started on its own in neonates and started in the absence of evidence of infection as a precaution. It was decided that to add rifampicin would be inappropriately exposing non-infected neonates to drugs. For children older than 4 weeks the choice should be isoniazid for 6 months or isoniazid and rifampicin for 3 months. While one is waiting for the second TST isoniazid alone is justified to avoid unnecessary exposure to a second drug in uninfected children."
Royal College of Paediatrics and Child Health	Full	3.1.4.6	137	As above, ALL children aged 4 weeks to 2 years who have had significant TB contact should be assessed clinically for active TB, as a positive TST is NOT a sensitive enough indicator, and the risk of progression to active TB is high in this age-group. It should be stated that this assessment needs to take place urgently.	Thank you for your comment. The recommendations have now been amended so that all children under the age of 2 undergo an assessment for active TB before testing for latent infection as follows: "If a child aged between 4 weeks and 2 years has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment: • Assess for active TB…""
Royal College of Paediatrics and Child	Full	3.1.4.6	137	The recommendation for children aged 4 weeks to 2 years is to assess for active TB and treat if found to have active TB; if no evidence of active TB and TST positive, treat for latent TB; if no	Thank you for your comment. The Committee discussed this concern but decided that, although a single TST is not sufficiently sensitive to allow chemoprophylaxis to be stopped, the use of an

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Health				evidence of active TB and TST negative, give prophylactic isoniazid and retest later, if positive and no evidence of active TB, treat for latent TB; if repeat TST negative and no evidence of active TB stop prophylaxis. It is important for the committee to be aware that, in line with WHO recommendations (which extend this policy to age 5 years) the most common practice amongst UK paediatric TB experts is to start children of this age who are contacts and have no evidence of active TB on full latent TB treatment (usually 3 months of isoniazid and rifampicin) and to complete the course, irrespective of the initial TST result and without repeating the TST after 6 weeks. This is based on the high risk of rapidly progressive disease in this age group, and the lack of sensitivity of TST. Is there a compelling evidence base on which to recommend the different and more complex strategy recommended here?	additional Mantoux test and an interferon gamma release assay raises the overall sensitivity of the diagnostic pathway to a point at which a negative result on all 3 tests is sufficient to allow chemoprophylaxis to be stopped. This reduces unnecessary exposure of non-infected young children to drugs. With regards the chemoprophylactic regimen prescribed in these children, the Committee concluded that regimens of longer than 6 months were not justified by either the evidence (of which none was identified in this population) or in their clinical experience. 6 months of isoniazid is recommended in neonates. For children and young people over the age of 4 weeks, either of the recommended regimens (6 months of isoniazid or 3 months of isoniazid and rifampicin) may be used, though selection should be based on the parameters outlined in the recommendation below: "Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin to people aged younger than 35 years if hepatotoxicity is a concern; this would include both liver function (including transaminase) tests and assessment of risk factors • 6 months of isoniazid (with pyridoxine) if

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					interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant." The following text has now been added to the Evidence to Recommendations table: "Given that there was a lack of evidence regarding which regimens should be used for chemoprophylaxis and the treatment of latent TB in children, the recommendations were predominantly based on paediatric expert opinion. Isoniazid should be started on its own in neonates and started in the absence of evidence of infection as a precaution. It was decided that to add rifampicin would be inappropriately exposing non-infected neonates to drugs. For children older than 4 weeks the choice should be isoniazid for 6 months or isoniazid and rifampicin for 3 months. While one is waiting for the second TST isoniazid alone is justified to avoid unnecessary exposure to a second drug in uninfected children."
Birmingham & Solihull TB Service	Full	3.1.4.6	137	As above, ALL children aged 4 weeks to 2 years who have had significant TB contact should be assessed clinically for active TB, as a positive TST is NOT a sensitive enough indicator, and the risk of progression to active TB is high in this age-group It should be stated that this assessment needs to	Thank you for your comment. The recommendations have now been amended so that all children under the age of 2 undergo an assessment for active TB before testing for latent infection as follows: "If a child aged between 4 weeks and 2 years has been in close contact with people with smear-

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				take place urgently	positive pulmonary or laryngeal TB: • **Assess for active TB**. • Start treatment for latent TB and carry out a Mantoux test. • If the Mantoux test is inconclusive, refer the person to a TB specialist. • If the Mantoux test is positive (5 mm or larger, regardless of BCG history), **reassess for active TB**; if this assessment is negative, complete treatment for latent TB. • If the Mantoux test is negative, continue treatment for latent TB, **reassess for active TB** after 6 weeks and repeat the Mantoux test…"
Birmingham & Solihull TB Service	Full	3.1.4.6	137	The recommendation for children aged 4 weeks to 2 years is to assess for active TB and treat if found to have active TB; if no evidence of active TB and TST positive, treat for latent TB; if no evidence of active TB and TST negative, give prophylactic isoniazid and retest later, if positive and no evidence of active TB, treat for latent TB; if repeat TST negative and no evidence of active TB stop prophylaxis. It is important for the committee to be aware that, in line with WHO recommendations (which extend this policy to age 5 years) the most common	Thank you for your comment. The Committee discussed this concern but decided that, although a single TST is not sufficiently sensitive to allow chemoprophylaxis to be stopped, the use of an additional Mantoux test and an interferon gamma release assay raises the overall sensitivity of the diagnostic pathway to a point at which a negative result on all 3 tests is sufficient to allow chemoprophylaxis to be stopped. This reduces unnecessary exposure of non-infected young children to drugs. With regards the chemoprophylactic regimen prescribed in these children, the Committee

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				practice amongst UK paediatric TB experts is to start children of this age who are contacts and have no evidence of active TB on full latent TB treatment (usually 3 months of isoniazid and rifampicin) and to complete the course, irrespective of the initial TST result and without repeating the TST after 6 weeks. This is based on the high risk of rapidly progressive disease in this age group, and the lack of sensitivity of TST. Is there a compelling evidence base on which to recommend the different and more complex strategy recommended here?	concluded that regimens of longer than 6 months were not justified by either the evidence (of which none was identified in this population) or in their clinical experience. 6 months of isoniazid is recommended in neonates. For children and young people over the age of 4 weeks, either of the recommended regimens (6 months of isoniazid or 3 months of isoniazid and rifampicin) may be used, though selection should be based on the parameters outlined in the recommendation below: "Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin to people aged younger than 35 years if hepatotoxicity is a concern; this would include both liver function (including transaminase) tests and assessment of risk factors • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant." The following text has now been added to the Evidence to Recommendations table: "Given that there was a lack of evidence regarding which regimens should be used for chemoprophylaxis and the treatment of latent TB

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					in children, the recommendations were predominantly based on paediatric expert opinion. Isoniazid should be started on its own in neonates and started in the absence of evidence of infection as a precaution. It was decided that to add rifampicin would be inappropriately exposing non-infected neonates to drugs. For children older than 4 weeks the choice should be isoniazid for 6 months or isoniazid and rifampicin for 3 months. While one is waiting for the second TST isoniazid alone is justified to avoid unnecessary exposure to a second drug in uninfected children."
CHIVA	Full	3.1.4.7	137	Recommendations 5 and 6 It is unclear what 'specialist' means here – does it mean a consultant in paediatric respiratory medicine or paediatric infectious diseases who has sufficient experience in this area?	Thank you for your comment. The following clarification has been added: " This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	3.1.4.7	137	It is unclear what 'specialist' means here – does it mean a consultant in paediatric respiratory medicine or paediatric infectious diseases who has sufficient experience in this area?	Thank you for your comment. The following clarification has been added: "This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
CHIVA	Full	3.1.4.7	137	Recommendations 5 and 6 Same recommendations refer to contacts of	Thank you for your comment. These recommendations refer to contacts of people with smear-positive disease. There was a lack of

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				"pulmonary TB" aged < 2 years suggesting the recommendations are irrespective of sputum smear status; why this separate recommendation on contacts of smear-negative TB which in fact recommends nothing other than to seek expert advice?	evidence on the diagnosis of latent infection in child contacts of people with smear-negative disease. As stated in the Evidence to Recommendations table, diagnosis of latent infection in these individuals can be complex, and should be considered by an expert on a case-by-case basis. This is reflected in the recommendation below: "Refer children younger than 2 years and in close contact with people with smear-negative pulmonary or laryngeal TB to a specialist to determine what testing strategy for latent TB should be done. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	3.1.4.7	137	Recommendations 5 and 6 refer to contacts of "pulmonary TB" aged < 2 years suggesting the recommendations are irrespective of sputum smear status; why this separate recommendation on contacts of smear-negative TB which in fact recommends nothing other than to seek expert advice?	Thank you for your comment. These recommendations refer to contacts of people with smear-positive disease. There was a lack of evidence on the diagnosis of latent infection in child contacts of people with smear-negative disease. As stated in the Evidence to Recommendations table, diagnosis of latent infection in these individuals can be complex, and should be considered by an expert on a case-by-case basis. This is reflected in the recommendation below:

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					"Refer children younger than 2 years and in close contact with people with smear-negative pulmonary or laryngeal TB to a specialist to determine what testing strategy for latent TB should be done. This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
CHIVA	Full	3.1.4.8	137	As noted above, using only TST is significantly different from current practice in many units	Thank you for your comment. Although current practice may influence the Committee's decision-making, the role of NICE guidance is to ensure that current practice is based upon the best available evidence. Clinical and cost-effectiveness analyses of this evidence shape the guidance, and the guidance in turn shapes current practice, although it is acknowledged that changes to current practice can be challenging. The comment has been shared with the NICE implementation support team to inform their support activities for this guideline.
Royal College of Paediatrics and Child Health	Full	3.1.4.8	137	As noted above, using only TST is significantly different from current practice in many units.	Thank you for your comment. Although current practice may influence the Committee's decision-making, the role of NICE guidance is to ensure that current practice is based upon the best available evidence. Clinical and cost-effectiveness analyses of this evidence shape the guidance, and the guidance in turn shapes

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					current practice, although it is acknowledged that changes to current practice can be challenging. Therefore, your response has been passed to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Paediatrics and Child Health	Full	3.1.4.8	137	The common age of transition from paediatric to adult services is 16 not 18, and it may be more appropriate to group recommendations as 2-15 and 16 and above rather than 2-17.	Thank you for your comment. However, the age cut-offs used in the recommendations reflect those used in the update reviews, which were in turn determined by those used in CG117. The upper age limit of 17 reflects the upper limit used within the updated reviews for the diagnosis of latent TB in children.
CHIVA	Full	3.1.4.8	137	The common age of transition from paediatric to adult services is 16 not 18, and it may be more appropriate to group recommendations as 2-15 and 16 and above rather than 2-17	Thank you for your comment. However, the age cut-offs used in the recommendations reflect those used in the update reviews, which were in turn determined by those used in CG117. The upper age limit of 17 reflects the upper limit used within the updated reviews for the diagnosis of latent TB in children.
Royal College of Paediatrics and Child Health	Full	3.1.4.8	137	It is also unclear what a "close" contact is.	Thank you for your comment. The glossary definition for 'contacts' has been amended as follows: "A person who has spent time with someone with infectious TB. Close contacts are people for whom this exposure has been more prolonged,

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					frequent, or intense. For example, these could include 'household contacts' – those who share a bedroom, kitchen, bathroom or sitting room with the index case. Close contacts may also include boyfriends or girlfriends and frequent visitors to the home of the index case. Occasionally, a workplace associate may be judged to have had contact equivalent to that of household contacts." The definition allows a certain amount of judgement on behalf of those undertaking the contact-tracing. This may be useful in cases, for example, where the index case is judged to be particularly infectious, or any contacts are known to possess features that put them at high risk of going on to develop active TB, both of which may lead the person undertaking the contact-tracing to employ a more permissive definition of 'close'.
CHIVA	Full	3.1.4.8	137	It is also unclear what a "close" contact is	Thank you for your comment. The glossary definition for 'contacts' has been amended as follows: "A person who has spent time with someone with infectious TB. 'Close contacts' are people for whom this exposure has been more prolonged, frequent, or intense. For example, these could include 'household contacts' – those who share a bedroom, kitchen, bathroom or sitting room with the index case. Close contacts may also include

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					boyfriends or girlfriends and frequent visitors to the home of the index case. Occasionally, a workplace associate may be judged to have had contact equivalent to that of household contacts, though exposure is generally considered equivalent to that of a 'social contact' (that is, not prolonged, frequent, or intense)." The definition allows a certain amount of judgement on behalf of those undertaking the contact-tracing. This may be useful in cases, for example, where the index case is judged to be particularly infectious, or any contacts are known to possess features that put them at high risk of going on to develop active TB, both of which may lead the person undertaking the contact-tracing to employ a more permissive definition of 'close'.
CHIVA	Full	3.3.7.31	155	Take a posterior-anterior chest X-ray; This only applies to Adults as Children will mostly have AP CXR.	Thank you for your comment. The GDG discussed the available options and concluded that it was better not to specify the type of chest X-ray. In practice, clinicians would order a "chest X-ray", leaving the radiologist to determine the type.
Royal College of Paediatrics and Child	Full	3.3.7.31	155	Take a posterior-anterior chest X-ray; do further diagnostic investigations (as detailed below and summarised in table 1) if chest X-ray appearances suggest TB.	Thank you for your comment. The GDG discussed the available options and concluded that it was better not to specify the type of chest X-ray. In practice, clinicians would order a "chest X-ray", leaving the radiologist to determine the

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Health				This only applies to Adults as Children will mostly have AP CXR.	type.
Royal College of Paediatrics and Child Health	Full	3.3.7.35	155	The recommendation to perform NAAT routinely on one sample from each site in children is welcome. It may be necessary to comment on whether this should be done locally or in reference laboratory.	Thank you for your comment. This was not covered within the evidence reviews for the current guidance. However, it is hoped that including this topic as a research recommendation will encourage studies in this area, which will in turn be available when the guidance is reviewed.
CHIVA	Full	3.3.7.35	156 1	In children and young people aged 15 years or younger with suspected ~~pulmonary~~ TB (pulmonary or extrapulmonary), offer rapid diagnostic nucleic acid amplification tests.. (for example, spontaneous sputum, induced sputum, ~~or~~ gastric lavage, CSF, pleural fluid, ascetic fluid, tissue biopsy, FNA, etc)	Thank you for your comment. The evidence reviews did not find NAATs to be effective diagnostics for every site of disease. With regards extrapulmonary TB, the GDG concluded that the evidence supported their use on CSF, pericardial fluid and lymph node biopsy and aspirate. The limited evidence available for the different age subgroups (adults compared with children and young people) meant that the GDG did not feel able to make age-specific recommendations for the diagnosis of extrapulmonary TB.
Royal College of Paediatrics and Child Health	Full	3.3.7.35	156	In children and young people aged 15 years or younger with suspected ~~pulmonary~~ TB (pulmonary or extrapulmonary), offer rapid diagnostic nucleic acid amplification tests.. (for example, spontaneous sputum, induced sputum, ~~or~~ gastric lavage, CSF, pleural fluid, ascetic fluid,	Thank you for your comment. However, the evidence reviews did not find NAATs to be effective diagnostics for every site of disease. With regards extrapulmonary TB, the GDG concluded that the evidence supported their use on CSF, pericardial fluid and lymph node biopsy

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				tissue biopsy, FNA, etc).	and aspirate. The limited evidence available for the different age subgroups (adults compared with children and young people) meant that the GDG did not feel able to make age-specific recommendations for the diagnosis of extrapulmonary TB.
CHIVA	Full	3.3.7.37	157	Should the person advising be a paediatrician or can advice be from an adult physician? Ideally management of paediatric TB should be led by a paediatrician with appropriate TB experience.	Thank you for your comment. The following clarification has been added: "This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	3.3.7.37	157	Should the person advising be a paediatrician or can advise be from an adult physician? Ideally management of paediatric TB should be led by a paediatrician with appropriate TB experience. Paediatricians managing TB should be linked into a paediatric TB network.	Thank you for your comment. The following clarification has been added: "This should be a paediatrician with experience and training in TB, or a general paediatrician with advice from a specialised clinician."
Royal College of Paediatrics and Child Health	Full	4.4 4.5	General	No guidance on when treatment (intensive treatment phase, overall duration) should be extended.	Thank you for your comment. However, the data available did not show significant benefits from regimens of longer duration (that is, longer than 6 months for people with TB without CNS involvement, and longer than 12 months in people with TB with CNS involvement) for any of the groups examined. Furthermore, there was a range of issues affecting the quality of the

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					evidence, such that the GDG did not feel able to make any recommendations with regards to when treatment should be extended. For the full explanation of the GDG's decision-making, please see the following Evidence to Recommendations sections in the full guideline: 4.4.6, 4.5.5 and 4.7.6.
CHIVA	Full	4.4 4.5	general	More guidance is needed when a longer treatment course might be required.	Thank you for your comment. However, the data available did not show significant benefits from regimens of longer duration (that is, longer than 6 months for people with TB without CNS involvement, and longer than 12 months in people with TB with CNS involvement) for any of the groups examined. Furthermore, there was a range of issues affecting the quality of the evidence, such that the GDG did not feel able to make any recommendations with regards to when treatment should be extended. For the full explanation of the GDG's decision-making, please see the following Evidence to Recommendations sections in the full guideline: 4.4.6, 4.5.5 and 4.7.6.
CHIVA	Full	3.1.4.9	137	As noted above, changing the TST cutoff to 5 mm will significantly increase the number of children treated for latent TB; presumably this has been accounted for in the economic assessment. There	Thank you for your comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in

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				is also a risk of treating children who do not have latent TB, especially those with TST 5-10mm, in whom a confirmatory IGRA may be helpful The use of WHO limits (using a 10 mm cut-off, as used by most countries) would be more appropriate. However, in immunocompromised/immunosuppressive patients 5 mm may be considered as positive. Again, the terminology used here is poorly chosen. Children (2-17 years) should be treated for LTBI is the TST is positive (ie this should not only be 'considered').	relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). The strength of the recommendation has been changed to "offer". The GDG concluded, on balance, that the risk of treating false-positive children had to be considered in the context of their much higher risk of progression to active TB.
Royal College of Paediatrics and Child Health	Full	3.1.4.9	137	As noted above, changing the TST cutoff to 5 mm will significantly increase the number of children treated for latent TB; presumably this has been accounted for in the economic assessment. There is also a risk of treating children who do not have latent TB, especially those with TST 5-10mm, in whom a confirmatory IGRA may be helpful The use of WHO limits (using a 10 mm cut-off, as used by most countries) would be more appropriate. However, in immunocompromised/immunosuppressive	Thank you for your comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole

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				patients 5 mm may be considered as positive. Again, the terminology used here is poorly chosen. Children (2-17 years) should be treated for LTBI is the TST is positive (ie this should not only be 'considered').	population' (chapter 7). The strength of the recommendation has been changed to "offer". The GDG concluded, on balance, that the risk of treating false-positive children had to be considered in the context of their much higher risk of progression to active TB.
Royal College of Paediatrics and Child Health	Full	3.7.7.44	179	For this (and other sites) it is not clear whether every investigation in the table should be performed on each patient, and some statement to this effect may be necessary.	Thank you for your comment. The column headed 'Imaging' represents imaging that should be considered for each person with disease suspected at the site listed under the column headed 'Suspected site of disease', and 'Routine tests' are tests that should be carried out on the sample listed in the 'Specimen' column (again, on each patient with disease suspected at the site listed). The column headed 'Additional test on primary specimen (if it would alter management)' denotes tests that should be carried out if the routine tests have not enabled the clinician to make a sufficiently confident diagnosis. Given the relatively poor diagnostic test accuracy of many TB tests on one or more measure, the aim of the collections of diagnostic tests provided in the tables is to enable the clinician to build up a diagnosis holistically, across a number of tests. The column headed 'Additional test on primary specimen (if it would alter

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					management)' are tests that *may* be required if the diagnosis is not clear from the routine tests and imaging described in the other columns.
CHIVA	Full	3.7.7.45	180	Assessment for CNS TB in a child should include also dilated fundoscopy , this is not an investigation and should be stated	Thank you for your comment. However, the GDG discussed the possibility of including dilated fundoscopy in the diagnostic pathway for CNS TB, and although they agreed that it is part of the general assessment for a child with suspected CNS disease, it is not a diagnostic for TB itself. This means that it falls outside of the scope of this guidance.
Royal College of Paediatrics and Child Health	Full	3.7.7.45	180	Assessment for CNS TB (certainly in a child) should include dilated fundoscopy – although not an investigation this should be stated.	Thank you for your comment. However, the GDG discussed the possibility of including dilated fundoscopy in the diagnostic pathway for CNS TB, and although they agreed that it is part of the general assessment for a child with suspected CNS disease, it is not a diagnostic for TB itself. This means that it falls outside of the scope of this guidance.
Royal College of Paediatrics and Child Health	Full	3.7.7.47	180	Is the table meant to imply that imaging is always indicated for lymph node TB? Presumably not, but the tables give no indication of the utility of the investigations and whether or not they should be done on each patient.	Thank you for your comment. The tables indicate the possible imaging for each site – it is not necessary to carry out CXR and CT scans for all pulmonary cases, for example. However, it is good practice to assess for pulmonary involvement in lymph node TB to check for the potential for infectivity, and for miliary TB with the

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					consequent requirements for screening for CNS disease. Peripheral lymph nodes may not require imaging but intrathoracic lymph nodes do.
CHIVA	Full	4.9	236	Table 19 on co-administration of anti-HIV and anti-TB drugs – advice is given on increase dose of efavirenz if co-administered with rifampicin; this contradicts HIV- guidelines which state that no adjustment is necessary with currently used EFV dose (600 mg) (WHO 2013, DHHS 2014). Recent studies in HIV-infected patients with TB have not shown a significant effect of rifampicin on efavirenz exposure (JAMA 2008;300:530-539; Antivir Ther 2009;14:687-695; Antimicrob Agents Chemother 2009; 53(3):863-868; AIDS 2006; 20(1):131-132). Tables 18 and 19 recommend against co-administration of rifampicin and protease inhibitors. For HIV-infected patients with a resistant virus the choice is limited; this is especially relevant for children, in whom the dose of rifabutin co-administered with boosted protease inhibitors is not known. In practice the boosted protease inhibitors are co-administered with rifampicin with therapeutic drug monitoring and relevant dose adjustment. This should be noted in the guidelines that although co-administration is not generally recommended, it can be considered	Thank you for your comment. The GDG sought to summarise key pharmacological considerations raised within the BNF and SPCs of antiretroviral and first-line antituberculosis drugs with regards to drug interactions and overlapping toxicity profiles in people receiving treatment for both HIV and tuberculosis in Tables 18 and 19. Table 18 is a summary of potential issues that can arise in the co-administration of the drugs described, and Table 19 provides information on why these issues occur, as well as more detail on the action required. They do not represent NICE recommendations as such, except in that NICE guidelines are developed upon the assumption that prescribers will use the BNF and a medicine's SPC to inform their decision-making. The labelling in the table has been amended to make this clearer: 'Recommended action' amended to 'Action suggested in BNF/SPC'. Additionally, the concerns noted have now been included within the Evidence to Recommendations table: "Non-nucleoside reverse transcriptase inhibitors are mostly free of clinically significant interactions

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				by a specialist MDT if there is limited choice of ART. It should be stated that rifamycins remain one of the most potent TB drug class and should be included in the TB regimen unless they are contraindicated.	with rifampicin and rifabutin, During consultation, it was noted by a number of stakeholders that the suggested action within the SPCs to increase dose of efavirenz if co-administered with rifampicin contradicts current best practice, as stated within the World Health Organization's HIV guidance. Following publication of a number of studies in HIV-infected patients with TB that did not show a significant effect of rifampicin on efavirenz exposure, this guidance states that no adjustment is necessary for efavirenz dosing (600 mg) (WHO, 2013)."
Royal College of Paediatrics and Child Health	Full	4.9	236	Tables 18 and 19 recommend against co-administration of rifampicin and protease inhibitors. For HIV-infected patients with a resistant virus the choice is limited; this is especially relevant for children, in whom the dose of rifabutin co-administered with boosted protease inhibitors is not known. In practice the boosted protease inhibitors are co-administered with rifampicin with therapeutic drug monitoring and relevant dose adjustment. This should be noted in the guidelines that although co-administration is not generally recommended, it can be considered by a specialist MDT if there is limited choice of ART. Table 19 on co-administration of anti-HIV and anti-TB drugs – advice is given on increase dose	Thank you for your comment. The GDG sought to summarise key pharmacological considerations raised within the BNF and SPCs of antiretroviral and first-line antituberculosis drugs with regards to drug interactions and overlapping toxicity profiles in people receiving treatment for both HIV and tuberculosis in Tables 18 and 19. Table 18 is a summary of potential issues that can arise in the co-administration of the drugs described, and Table 19 provides information on why these issues occur, as well as more detail on the action required. They do not represent NICE recommendations as such, except in that NICE guidelines are developed upon the assumption that prescribers will use the BNF and a medicine's SPC to inform their decision-making.

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				of efavirenz if co-administered with rifampicin; this contradicts HIV- guidelines which state that no adjustment is necessary with currently used EFV dose (600 mg) (WHO 2013, DHHS 2014). Recent studies in HIV-infected patients with TB have not shown a significant effect of rifampicin on efavirenz exposure (JAMA 2008;300:530-539; Antivir Ther 2009;14:687-695; Antimicrob Agents Chemother 2009; 53(3):863-868; AIDS 2006; 20(1):131-132). It should be stated that rifamycins remain one of the most potent TB drug class and should be included in the TB regimen unless they are contraindicated.	The labelling in the table has been amended to make this clearer: 'Recommended action' amended to 'Action suggested in BNF/SPC'. Additionally, the concerns noted have now been included within the Evidence to Recommendations table: "Non-nucleoside reverse transcriptase inhibitors are mostly free of clinically significant interactions with rifampicin and rifabutin, During consultation, it was noted by a number of stakeholders that the suggested action within the SPCs to increase dose of efavirenz if co-administered with rifampicin contradicts current best practice, as stated within the World Health Organization's HIV guidance. Following publication of a number of studies in HIV-infected patients with TB that did not show a significant effect of rifampicin on efavirenz exposure, this guidance states that no adjustment is necessary for efavirenz dosing (600 mg) (WHO, 2013)."
CHIVA	Full	3.7.7.51	180 8	Molecular tests should be performed on bone biopsies and joint fluid. There is evidence to suggest that PCR has greater yield than culture in bone and joint TB.	Thank you for your comment. However, no evidence meeting the inclusion criteria specified within the review protocols was identified for the use of NAATs on bone biopsies or joint fluid. The Committee therefore did not feel able to recommend these tests on these specimens, particularly given the concerns raised by

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					stakeholders elsewhere with regards to the resource implications of increasing the recommended applications for NAATs.
Royal College of Paediatrics and Child Health	Full	3.7.7.51	P 180	There is evidence to suggest that PCR has greater yield than culture in bone and joint TB. Therefore, molecular tests should be performed on bone biopsies and joint fluid.	Thank you for your comment. However, no evidence meeting the inclusion criteria specified within the review protocols was identified for the use of NAATs on bone biopsies or joint fluid. The GDG therefore did not feel able to recommend these tests on these specimens, particularly given the concerns raised by stakeholders elsewhere with regards to the resource implications of increasing the recommended applications for NAATs.
CHIVA	Full	4.6.7.65	208	65. Test people with disseminated (including miliary) TB for central nervous system involvement. More specific guidance should be provided, i.e offer MRI Brain + consider LP.	Thank you for your comment. The GDG stated that any investigation for CNS involvement should be left to the discretion of the treating TB specialist.
Royal College of Paediatrics and Child Health	Full	4.6.7.65	208	65. Test people with disseminated (including miliary) TB for central nervous system involvement. More specific guidance should be provided, i.e offer MRI Brain + consider LP.	Thank you for your comment. The GDG stated that any investigation for CNS involvement should be left to the discretion of the treating TB specialist.

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	6	1	In general, recommendations should be graded by the quality of evidence that supports the recommendation.	Thank you for your comment. Recommendations are developed using a range of evidence. This is used to explore the trade-off between potential benefits and potential harms of interventions, diagnostic tools or prognostic factors, and is interpreted and judged based on the quality of the evidence available, as well as the GDG's own knowledge and experience. The group also take account of a range of other issues (including any ethical concerns, social value judgements, equity considerations and inequalities in outcomes, particularly impacts on people sharing the characteristics protected by equality legislation) and policy imperatives. The GDG must use its judgement to decide what the evidence means in the context of the guideline (see the Evidence to Recommendations sections in the full guideline) and decide what recommendations can be made to practitioners, commissioners of services and others. Some recommendations can be made with more certainty than others. For some interventions, the group is confident that – given the information it has looked at (the quality of the evidence, but also the estimates of effect, ethical concerns, social value judgements, equity considerations and inequalities in outcomes) – most patients would choose the intervention. It is this certainty that determines the strength of the

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					recommendation, which is in turn reflected in the wording of the recommendation as follows: *Interventions that must (or must not) be used* We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening. *Interventions that should (or should not) be used – a 'strong' recommendation* We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients. *Interventions that could be used* We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the

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					patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.
CHIVA	Full	4.7.7.69	221	*'At the start of an anti-TB treatment regimen, offer children and young people with active TB of the ……..An example of a suitable regimen is oral prednisolone, starting at a dose of 4 mg/kg of body weight/day. [new 2015]'* Dosing seems very high- especially for older children with a near adult weight. Also, it remains uncertain whether 2mg/kg is as effective as 4mg/kg prednisolone in children with TB meningitis, as highlighted in Prasad and Singh's Cochrane Review on this topic (Corticosteroids for managing tuberculous meningitis).	Thank you for your comment. The GDG discussed the dosing of corticosteroids in light of this comment and agreed that dosing should be in line with the British National Formulary for Children. The following text has been added to the Evidence to Recommendations table: "The group concluded that the doses of corticosteroids previously recommended for adults were still appropriate, as was a gradual withdrawal of the corticosteroids in both adults and children. The GDG considered this to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions. The previous dosing recommended for children were judged to be too high, especially for older children with a near adult weight. Prescribing for children should be in line with the British National Formulary for Children."
Royal College of	Full	4.7.7.69	221	*'At the start of an anti-TB treatment regimen, offer children and young people with active TB of the*	Thank you for your comment. The GDG discussed the dosing of corticosteroids in light of

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Paediatrics and Child Health				*central nervous system dexamethasone or prednisolone. This should initially be at a high dose with gradual withdrawal over 4–8 weeks. An example of a suitable regimen is oral prednisolone, starting at a dose of 4 mg/kg of body weight/day. [new 2015]'* This dosing seems very high- especially for e.g. 14 yr old weighing 50kg- max dose should be stated (adult dosing is dexamethasone) Also, it remains uncertain whether 2mg/kg is as effective as 4mg/kg prednisolone in children with TB meningitis, as highlighted in Prasad and Singh's Cochrane Review on this topic (Corticosteroids for managing tuberculous meningitis).	this comment and agreed that dosing should be in line with the British National Formulary for Children. The following text has been added to the Evidence to Recommendations table: "The group concluded that the doses of corticosteroids previously recommended for adults were still appropriate, as was a gradual withdrawal of the corticosteroids in both adults and children. The GDG considered this to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions. The previous dosing recommended for children were judged to be too high, especially for older children with a near adult weight. Prescribing for children should be in line with the British National Formulary for Children."
Birmingham & Solihull TB Service	Full	4.7.7.69	221	'At the start of an anti-TB treatment regimen, offer children and young people with active TB of the central nervous system dexamethasone or prednisolone. This should initially be at a high dose with gradual withdrawal over 4–8 weeks. An example of a suitable regimen is oral prednisolone, starting at a dose of 4 mg/kg of body weight/day. [new 2015]' This dosing seems very high- especially for eg 14	Thank you for your comment. The GDG discussed the dosing of corticosteroids in light of this comment and agreed that dosing should be in line with the British National Formulary for Children. The following text has been added to the Evidence to Recommendations table: "The group concluded that the doses of

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				yr old weighing 50kg- max dose should be stated (adult dosing is dexamethasone) Also, it remains uncertain whether 2mg/kg is as effective as 4mg/kg prednisolone in children with TB meningitis, as highlighted in Prasad and Singh's Cochrane Review on this topic (Corticosteroids for managing tuberculous meningitis).	corticosteroids previously recommended for adults were still appropriate, as was a gradual withdrawal of the corticosteroids in both adults and children. The GDG considered this to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions. The previous dosing recommended for children were judged to be too high, especially for older children with a near adult weight. Prescribing for children should be in line with the British National Formulary for Children."
CHIVA	Full	6.1.7.102	292	*"Do not admit people with suspected infectious or confirmed 1 pulmonary TB to a ward containing immunocompromised 2 patients, such as transplant recipients, people with HIV and those 3 on anti-tumour necrosis factor alpha or other biologics, unless 4 they can be cared for in a negative-pressure room on the same 5 ward. [new 2015]"* This has implications for most paediatric units- negative pressure rooms not common. Common to have oncology patients in ward (in side rooms).	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Paediatrics	Full	6.1.7.102	292	*"Do not admit people with suspected infectious or confirmed 1 pulmonary TB to a ward containing immunocompromised 2 patients, such as*	Thank you for your response. We have passed it to the NICE implementation support team to

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and Child Health				*transplant recipients, people with HIV and those 3 on anti-tumour necrosis factor alpha or other biologics, unless 4 they can be cared for in a negative-pressure room on the same 5 ward. [new 2015]"* This has implications for most paediatric units- negative pressure rooms not common. Common to have oncology patients in ward (in side rooms).	inform their support activities for this guideline.
Royal College of Paediatrics and Child Health	Full	6.1.7.104	292	In people who may have TB, only carry out aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment in an appropriately engineered and ventilated area (ideally a negative pressure room). [new 2015].' No definition what is appropriately engineered and ventilated area if not a negative pressure room. Most children who undergo induced sputum are TB culture negative. Restriction of the procedure to a negative pressure room is not be feasible. More guidance on alternative to a negative pressure room should be given.	Thank you for your comment. This guideline considers two levels of respiratory isolation as defined by NHS Estates: • negative-pressure rooms, which have air pressure continuously or automatically measured, as defined by NHS Property Services; • single rooms that are not negative pressure but are vented to the outside of the building The GDG considered that robust infection control guidelines and standards for respiratory isolation are already in place and that negative pressure was the ideal for such procedures. See https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/148503/HBN_04-01_Supp_1_Final.pdf for further information.

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CHIVA	Full	5.5.7.95	286 20	Certain forms of INH-resistant MTB (due to inhA mutations) can be treated effectively with high-dose INH. INH is however not effective in INH-resistance caused by katG mutations. This should be included in the table.	Thank you for your comment. However, no evidence for this was presented to the GDG. Therefore, they were not able to make the suggested recommendation.
Royal College of Paediatrics and Child Health	Full	5.5.7.95	286	Certain forms of INH-resistant MTB (due to inhA mutations) can be treated effectively with high-dose INH. INH is however not effective in INH-resistance caused by katG mutations. This should be included in the table.	Thank you for your comment. However, no evidence for this was presented to the GDG. Therefore, they were not able to make the suggested recommendation.
CHIVA	Full	7.1.5 7.2.7	306 322	Although it is specified in the Evidence to Recommendations that 'liver function should be assessed before treatment is initiated, as specified in the British National Formulary'. No specific guidance for baseline LFTs is provided for patients with latent or active TB.	Thank you for your comment. Although investigation of liver function is important before undertaking treatment, it is not within the scope of this guideline to define what constitutes 'normal' or 'appropriate' liver function – this is an issue that goes beyond TB. However, following review of the SPCs for isoniazid and rifampicin, the following text has been added to the Evidence to Recommendations table: "The group concluded that the evidence overall, in conjunction with their own clinical experience, supported their recommendation that liver function should be assessed before treatment is initiated, as specified in the British National

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Formulary. **Isoniazid, especially if given with rifampicin, may induce abnormalities in liver function, particularly in patients with pre-existing liver disorders, the elderly, the very young and the malnourished. The Summary of Product Characteristics for isoniazid and rifampicin (the drugs recommended by this guideline for the treatment of latent infection) recommend that transaminase measurements – especially glutamic pyruvic transaminase and glutamic oxaloacetic transaminase – be obtained at baseline.** Furthermore, those with abnormal liver function before treatment initiation should undergo more cautious management of their regimen, including careful clinical **monitoring – the Summary of Product Characteristics for isoniazid and rifampicin recommend that this be undertaken monthly**. They did not feel that it was strong enough to recommend that people with abnormal liver function not be eligible for treatment."
Royal College of Paediatrics and Child Health	Full	7.1.5 7.2.7	306 322	Although it is specified in the Evidence to Recommendations that 'liver function should be assessed before treatment is initiated, as specified in the British National Formulary'. No specific guidance for baseline LFTs is provided for patients with latent or active TB.	Thank you for your comment. Although investigation of liver function is important before undertaking treatment, it is not within the scope of this guideline to define what constitutes 'normal' or 'appropriate' liver function – this is an issue that goes beyond TB.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					However, following review of the SPCs for isoniazid and rifampicin, the following text has been added to the Evidence to Recommendations table: "The group concluded that the evidence overall, in conjunction with their own clinical experience, supported their recommendation that liver function should be assessed before treatment is initiated, as specified in the British National Formulary. **Isoniazid, especially if given with rifampicin, may induce abnormalities in liver function, particularly in patients with pre-existing liver disorders, the elderly, the very young and the malnourished. The Summary of Product Characteristics for isoniazid and rifampicin (the drugs recommended by this guideline for the treatment of latent infection) recommend that transaminase measurements – especially glutamic pyruvic transaminase and glutamic oxaloacetic transaminase – be obtained at baseline.** Furthermore, those with abnormal liver function before treatment initiation should undergo more cautious management of their regimen, including careful clinical **monitoring – the Summary of Product Characteristics for isoniazid and rifampicin recommend that this be undertaken monthly**. They did not feel that it was strong enough to recommend that people with abnormal

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					liver function not be eligible for treatment."
CHIVA	Full	7.2.7.119	322	High risk for progression should also include infants (<12 months)	Thank you for your comment. The recommendation has now been amended to include children as follows: "Be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who: • are HIV-positive • **are younger than 5 years** • have excessive alcohol intake…"
CHIVA	Full	7.2.7.119	322	The advice to routinely perform CXRs in at risk groups who have LTBI and are not given chemoprophylaxis is unlikely to be based on good evidence. The detection yield of CXRs in this setting is likely very low, which questions the cost effectiveness of this approach (vs. performing CXRs in symptomatic individuals only).	Thank you for your comment. This recommendation was produced in order to safeguard patients who chose not to undergo treatment against the risk of developing active TB. Having defined monitoring timepoints at 3 and 12 months helps to remove the barriers to monitoring that may arise if the recommendation were to wait until the patient becomes symptomatic and must re-engage with TB services on their own.
Royal College of Paediatrics	Full	7.2.7.119	322	High risk for progression should also include infants (<12 months)	Thank you for your comment. The recommendation has now been amended to include children as follows:

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and Child Health					"Be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who: • are HIV-positive • **are younger than 5 years** • have excessive alcohol intake…"
Royal College of Paediatrics and Child Health	Full	7.2.7.119	322	The advice to routinely perform CXRs in at risk groups who have LTBI and are not given chemoprophylaxis is unlikely to be based on good evidence. The detection yield of CXRs in this setting is likely very low, which questions the cost effectiveness of this approach (vs. performing CXRs in symptomatic individuals only).	Thank you for your comment. This recommendation was produced in order to safeguard patients who chose not to undergo treatment against the risk of developing active TB. Having defined monitoring timepoints at 3 and 12 months helps to remove the barriers to monitoring that may arise if the recommendation were to wait until the patient becomes symptomatic and must re-engage with TB services on their own.
Birmingham & Solihull TB Service	Full	7.2.7.119	322	High risk for progression should also include infants (<12 months)	Thank you for your comment. The recommendation has now been amended to include children as follows: "Be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including people who: • are HIV-positive

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					• **are younger than 5 years** • have excessive alcohol intake…"
CHIVA	Full	7.2.7.124	323	Fully supportive of testing all for HIV	Thank you for your comment.
Royal College of Paediatrics and Child Health	Full	7.2.7.124	323	Fully supportive of testing all for HIV.	Thank you for your comment.
Birmingham & Solihull TB Service	Full	7.2.7.124	323	Fully supportive of testing all for HIV	Thank you for your comment.
Royal College of Paediatrics and Child Health	Full	7.2.7.124	323	What is the number needed to test for children to identify hepatitis B or C and is this screening cost-effective?	Thank you for your comment. *Offer testing for HIV before starting treatment for latent TB. See NICE guidelines on increasing the uptake of HIV testing among black Africans in England and increasing the uptake of HIV testing among men who have sex with men.* *Offer testing for hepatitis B and C before starting treatment for latent TB in adults. Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people. See NICE*

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults. New text in the Evidence to Recommendations table The group noted the increased risk of hepatotoxicity during treatment during latent tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore concluded that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment and that treatment could be carefully managed and monitored if undertaken. **They concluded that the reduced risk of hepatitis B or C coinfection in children, and the impact this would have on the cost-effectiveness of testing, meant that only a weak recommendation for testing could be made.** They also stated that health

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					economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing those at increased risk of coinfection would have been useful to their decision-making.
CHIVA	Full	7.2.7.124	323	What is the number needed to test for children to identify hepatitis B or C and is this screening cost-effective?	Thank you for your comment. This recommendation has been amended as follows; *Offer testing for HIV before starting treatment for latent TB. See NICE guidelines on increasing the uptake of HIV testing among black Africans in England and increasing the uptake of HIV testing among men who have sex with men.* *Offer testing for hepatitis B and C before starting treatment for latent TB in adults. Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults.* New text in the Evidence to Recommendations table The group noted the increased risk of hepatotoxicity during treatment during latent

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					tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore concluded that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment and that treatment could be carefully managed and monitored if undertaken. **They concluded that the reduced risk of hepatitis B or C coinfection in children, and the impact this would have on the cost-effectiveness of testing, meant that only a weak recommendation for testing could be made.** They also stated that health economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing those at increased risk of coinfection would have been useful to their decision-making.
Birmingham & Solihull TB Service	Full	7.2.7.124	323	What is the number needed to test for children to identify hepatitis B or C and is this screening cost-effective?	Thank you for your comment, this recommendation has been amended as follows; *Offer testing for HIV before starting treatment for latent TB. See NICE guidelines on increasing the uptake of HIV testing among black Africans in England and increasing the uptake of HIV testing*

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					among men who have sex with men. *Offer testing for hepatitis B and C before starting treatment for latent TB in adults. Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults.* New text in the Evidence to Recommendations table The group noted the increased risk of hepatotoxicity during treatment during latent tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore concluded that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment and that treatment could be carefully managed and monitored if undertaken. **They concluded that the reduced risk**

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of hepatitis B or C coinfection in children, and the impact this would have on the cost-effectiveness of testing, meant that only a weak recommendation for testing could be made. They also stated that health economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing those at increased risk of coinfection would have been useful to their decision-making.
Royal College of Paediatrics and Child Health	Full	7.2.7.124	323	There is no recommendation on whether or not to monitor or test liver function in children, and review suggests this may not be necessary in LATENT TB http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3133498/.	Thank you for your comment. Pre-treatment liver function tests in children are recommended as follows: Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin if hepatotoxicity is a concern; **this would include both liver function (including transaminase) tests and assessment of risk factors** • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV

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					or who have had a transplant *The recommendation above is not specific to children, though the stated tests apply to all ages.* Offer testing for hepatitis B and C before starting treatment for latent TB in adults. . **Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people.** See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults – *this recommendation references NICE guidance for testing for hepatitis B and C, diagnostic pathways that include a range of liver function tests.*
CHIVA	Full	7.2.7.124	323	There is no recommendation on whether or not to monitor or test liver function in children, and review suggests this may not be necessary in LATENT TB http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3133498/	Thank you for your comment. Pre-treatment liver function tests in children are recommended as follows: Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin if hepatotoxicity is a concern; **this would include both liver function (including transaminase)**

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					tests and assessment of risk factors • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant *The recommendation above is not specific to children, though the stated tests apply to all ages.* Offer testing for hepatitis B and C before starting treatment for latent TB in adults. . **Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people.** See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults – *this recommendation references NICE guidance for testing for hepatitis B and C, diagnostic pathways that include a range of liver function tests.*
Birmingham & Solihull TB Service	Full	7.2.7.124	323	There is no recommendation on whether or not to monitor or test liver function in children, and review suggests this may not be necessary in LATENT TB http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3133498	Thank you for your comment. Pre-treatment liver function tests in children are recommended as follows: Base the choice of regimen on the person's clinical circumstances. Offer:

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					• 3 months of isoniazid (with pyridoxine) and rifampicin if hepatotoxicity is a concern; **this would include both liver function (including transaminase) tests and assessment of risk factors** • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant *The recommendation above is not specific to children, though the stated tests apply to all ages.* Offer testing for hepatitis B and C before starting treatment for latent TB in adults. . **Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people.** See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults – *this recommendation references NICE guidance for testing for hepatitis B and C, diagnostic pathways that include a range of liver function tests.*
CHIVA	Full	8.6	355	No guidance provided on BCG for children born	Thank you for your comment. It has not been possible to update all sections and

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
		143 6	6	to mothers with low risk of HIV transmission. Children born to HIV-positive mothers who are at low risk of HIV transmission and at high risk of TB should be considered for BCG soon after birth / before discharge from the hospital – refer to BHIVA/CHIVA guidelines.	recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'.
Royal College of Paediatrics and Child Health	Full	8.6 143 6	355 6	No guidance provided on BCG for children born to mothers with low risk of HIV transmission. Children born to HIV-positive mothers who are at low risk of HIV transmission and at high risk of TB should be considered for BCG soon after birth / before discharge from the hospital – refer to BHIVA/CHIVA guidelines.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'.
Birmingham & Solihull TB	Full	8.6	355	No guidance provided on BCG for children born	Thank you for your comment. It has not been possible to update all sections and

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Service		143 6	6	to mothers with low risk of HIV transmission. Children born to HIV-positive mothers who are at low risk of HIV transmission and at high risk of TB should be considered for BCG soon after birth / before discharge from the hospital – refer to BHIVA/CHIVA guidelines.	recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	9	General	Previous recommendations should be open for comment if there is new evidence	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	10	1	There are many repetitions in advice which could be readily collated. The document has become unwieldy and its length will mean that the recommendations may not be implemented. In view of the classification of "must", "offer" and "consider", a document with the "must" recommendations would be a useful summary, ensuring as in the first comment that the evidence is good!. The list of recommendations begins	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.

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				with some very soft measures that really come under the GMC guidance on good clinical practice, rather than being specific for TB.	
Homerton Hospital NHS Foundation Trust (HHFT)	Full	10	1	A distinction should be made between evidence-based medicine and political policy (e.g. recommendations 184 onwards).	Thank you for your comment. The GDG considered the evidence in the light of current policy decisions and whilst some recommendations do pertain to a strategic approach the GDG considered an over-arching strategic multi-sector approach was the most appropriate means with which to deliver TB services to meet the needs of the whole population in particular those who are disproportionately affected by TB. This strategic approach also enables action by those who commission services, despite some of the inherent uncertainties in the evidence reviewed.
CHIVA	Full	9.2.7.152	385	Agree with need to offer DOT to children based on assessment of parents	Thank you for your comment.
Royal College of Paediatrics and Child Health	Full	9.2.7.152	385	Agree with need to offer DOT to children based on assessment of parents	Thank you for your comment.
Birmingham & Solihull TB	Full	9.2.7.152	385	Agree with need to offer DOT to children based	Thank you for your comment.

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Service				on assessment of parents	
CHIVA	Full	10.2.4.184	410 411	TB control boards must include paediatric representation (eg include consultant paediatricians with expertise in managing childhood TB). Health and social issues in children differ from those in adults, and it is therefore inappropriate to exclusively have representation from adult services. This has been recommended in the 2015 PHE TB strategy	Thank you for your comment. This recommendation does not specify who should be involved in TB control boards other than broad groups for example clinical leaders, commissioners – this can therefore include paediatricians and any other clinical groups considered appropriate.
Royal College of Paediatrics and Child Health	Full	10.2.4.184	410 411	TB control boards must include paediatric representation (e.g. include consultant paediatricians with expertise in managing childhood TB). Health and social issues in children differ from those in adults, and it is therefore inappropriate to exclusively have representation from adult services. This has been recommended in the 2015 PHE TB strategy.	Thank you for your comment. This recommendation does not specify who should be involved in TB control boards other than broad groups for example clinical leaders, commissioners – this can therefore include paediatricians and any other clinical groups considered appropriate.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	14	16	The BCG policy is fraught with inconsistencies. The understanding how BCG works and of neonatal immunity is both dated and flawed. The WHO guidance on using it for the whole population where the incidence of TB is >40 per 100,000 (e.g. boroughs in London and areas in other major cities) is obscured. This section must be significantly trimmed and reference to the Green Book should be sufficient (where a couple	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of

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				of pages covers the subject).	TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Stakeholders were invited to comment on this prior to the scope's finalisation and the commencement of guideline development.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	16	26	Remove "sneezed out" (no evidence for this form of transmission for TB; leprosy maybe!)	Thank you for your comment. This text has now been removed.
British Thoracic Society	Full	16	26	Remove "sneezed out" (no evidence for this form of transmission for TB; leprosy maybe!)	Thank you for your comment. This text has now been removed.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	16	28	Remove "rarely" and replace with "not" (placental transfer of TB is so rare as to be negligible)	Thank you for your comment. This text has now been amended as suggested.
British Thoracic	Full	16	28	Remove "rarely" and replace with "not" (placental	Thank you for your comment. This text has now

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Society				transfer of TB is so rare as to be negligible)	been amended as suggested.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	16	31 2	Replace "the risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is" with "Open coughing is the main route of infection". The evidence for these statements should be as good as elsewhere in the guidelines and therefore the experiments of Riley et al and their subsequent re-examination take precedence over observational studies on aeroplanes	Thank you for your comment. This text has now been removed and replaced as suggested.
British Thoracic Society	Full	16	31 2	Replace "the risk of becoming infected depends principally on how long and how intense the exposure to the bacterium is" with ''Open coughing is the main route of infection". The evidence for these statements should be as good as elsewhere in the guidelines and therefore the experiments of Riley et al and their subsequent re-examination take precedence over observational studies on aeroplanes	Thank you for your comment. This text has now been removed and replaced as suggested.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	16	35 17	This section is poorly written and includes many outdated myths. The reason for its inclusion in a clinical guidelines is unclear. The items in the pathogenesis of potential relevance are: a) the role of esat6 and cfp 10, used in IGRAs, regarding entry into macrophages and then subsequent lysis of these cells; b) the delay from	Thank you for your comment. The Committee were asked to review the information in this section and have stated that it still represents the most accurate description of the current knowledge of this area. Although there has been some evidence or theory suggesting otherwise, the evidence is not sufficient to change these

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
			9	inhalation to generating a T cell response detectable by tuberculin skin testing is about 3 weeks and therefore 6 weeks is used to be sure that all contacts will have developed an immune response; c) if there is no pre-existing immunity to TB, then haematogenous spread occurs early (miliary disease and other forms of extrapulmonary TB) and is associated with a higher mortality; d) HIV is associated with more extrapulmonary disease and is less infectious as a result of reduced immunity to TB. The concept that granulomas are protective has been disproved by videos of granulomas showing "metastatic" behaviour. The evidence that human cells are bactericidal rather than bacteriostatic is poor. The proportion developing early and late disease has never been subjected to rigorous analysis.	prevailing views on TB pathogenesis and epidemiology. The only text that the group decided to amend was the following: "Once inhaled the bacteria reach the lung and grow slowly over several weeks. The body's immune system is stimulated, which can be shown by a Mantoux test or an interferon gamma-release assay (IGRA). **In most people the immune system either kills the bacteria or builds a defensive barrier around the infection but the TB bacteria are not killed and lie dormant.**~~In over 80% of people the immune system kills the bacteria and they are removed from the body. In a small number of cases a defensive barrier is built round the infection but the TB bacteria are not killed and lie dormant.~~ This is called latent tuberculosis; the person is not ill and is not infectious. Sometimes at the time of the initial infection, bacteria get into the blood stream and can be carried to other parts of the body, such as bones, lymph glands or the brain, before the defensive barrier is built. It is estimated that one third of the world's population, two billion people, have latent tuberculosis."
British Thoracic	Full	16	35	This section includes some unproven statements and the reason for its inclusion in a clinical	Thank you for your comment. The Committee were asked to review the information in this

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Society			17 9	guideline is unclear and removal of this section should be considered. The items in the pathogenesis of potential relevance are: a) the role of ESAT6 and CFP 10, used in IGRAs, regarding entry into macrophages and then subsequent lysis of these cells; b) the delay from inhalation to generating a T cell response detectable by tuberculin skin testing is about 3 weeks and therefore 6 weeks is used to be sure that all contacts will have developed an immune response; c) if there is no pre-existing immunity to TB, then haematogenous spread occurs early (miliary disease and other forms of extrapulmonary TB) and is associated with a higher mortality; d) HIV is associated with more extrapulmonary disease and is less infectious as a result of reduced immunity to TB. The concept that granulomas are protective has been disproved by videos of granulomas showing "metastatic" behaviour. The evidence that human cells are bactericidal rather than bacteriostatic is poor. The proportion developing early and late disease has never been subjected to rigorous analysis.	section and have stated that it still represents the most accurate description of the current knowledge of this area. Although there has been some evidence or theory suggesting otherwise, the evidence is not sufficient to change these prevailing views on TB pathogenesis and epidemiology. The only text that the group decided to amend was the following: "Once inhaled the bacteria reach the lung and grow slowly over several weeks. The body's immune system is stimulated, which can be shown by a Mantoux test or an interferon gamma-release assay (IGRA). **In most people the immune system either kills the bacteria or builds a defensive barrier around the infection but the TB bacteria are not killed and lie dormant.**~~In over 80% of people the immune system kills the bacteria and they are removed from the body. In a small number of cases a defensive barrier is built round the infection but the TB bacteria are not killed and lie dormant.~~ This is called latent tuberculosis; the person is not ill and is not infectious. Sometimes at the time of the initial infection, bacteria get into the blood stream and can be carried to other parts of the body, such as bones, lymph glands or the brain, before the defensive barrier is built. It is estimated that one third of the world's population, two billion

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					people, have latent tuberculosis."
Oxford Immunotec	Full	16	35	Interferon gamma release assays also identify when a body's immune system has been stimulated so should be included in addition to the Mantoux test.	Thank you for your comment. This text has now been amended as suggested.
NA	Full	16	45	Question 2: Our trust has had experience of implementing this approach and would be willing to submit its experiences to the NICE shared learning database. Contact……..	Thank you for your comment
George Eliot NHS Trust	Full	17	2	Can we give BCG if IGRa negative and mantoux not done ?	Thank you for your comment. Although this recommendation was not within the scope of update, this recommendation has been updated to reflect the inclusion of IGRAs in the guidance (the original recommendation was part of the 2006 guideline and was made before IGRAs were recommended by NICE). New recommendation: "Offer BCG vaccination to new entrants who are Mantoux- **or IGRA-**negative who: • are from high-incidence countries, and • are previously unvaccinated (that is, without adequate documentation or a BCG scar), and • are aged: o younger than 16 years, or

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					○ 16–35 years from sub-Saharan Africa or a country with a TB incidence of 500 per 100,000 or more."
Homerton Hospital NHS Foundation Trust (HHFT)	Full	17	36	The diagnosis of TB must emphasize microbiology (smear and culture) first. CXR is next in view of isolating those likely to be infectious. All other tests may be helpful, but are considered merely supportive; IGRAs should not be mentioned in this context as they are primarily for contact tracing. NAAT is valuable as a first sign that their will be a positive culture and for drug sensitivity testing.	Thank you for your comment. The text has been rearranged to reflect this as follows: "TB is diagnosed in a number of ways. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. Tissue samples from biopsies may show changes that suggest TB, as do certain X-ray changes, particularly on chest X- rays. Newer rapid molecular diagnostics – nucleic acid amplification tests (NAATs) – that are able to detect small amounts of genetic material from the mycobacterium by repeatedly amplifying target sequences are also available. Mantoux tests and IGRAs can show if someone has been exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGRAs involve taking a blood sample, which is processed at a laboratory to identify interferon gamma

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					released from T cells in response to specific TB antigens."
British Thoracic Society	Full	17	36	The diagnosis of TB must emphasize microbiology (smear and culture) first. CXR is next in view of isolating those likely to be infectious. All other tests may be helpful, but are considered merely supportive. IGRAs or TST should not be mentioned in this section as they are primarily for contact tracing. NAAT is valuable as a first sign that there will be a positive culture and for drug sensitivity testing.	Thank you for your comment. The text has been rearranged to reflect this as follows: "TB is diagnosed in a number of ways. Definite diagnosis is achieved by culturing the TB bacterium from sputum or other samples. This not only confirms the diagnosis, but also shows which of the TB drugs the bacterium is sensitive to. Tissue samples from biopsies may show changes that suggest TB, as do certain X-ray changes, particularly on chest X- rays. Newer rapid molecular diagnostics – nucleic acid amplification tests (NAATs) – that are able to detect small amounts of genetic material from the mycobacterium by repeatedly amplifying target sequences are also available. Mantoux tests and IGRAs can show if someone has been exposed to TB and may have latent infection. Skin tests use a tiny dose of TB protein injected under the skin. In people who have been exposed to TB this gives a positive reaction, which is seen as a raised, red area. IGRAs involve taking a blood sample, which is processed at a laboratory to identify interferon gamma released from T cells in response to specific TB antigens."

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Oxford Immunotec	Full	17	44	Skin test positivity is described so to be consistent IGRA positivity should also be described. Hence the sentence should read: "IGRAs involve taking a blood sample, which is processed at a laboratory to identify interferon gamma released from T cells in response to specific TB antigens."	Thank you for your comment. The amendment has now been made as suggested.
Oxford Immunotec	Full	17	44	The sentence from "Newer rapid…" refers to tests used for active TB and so should come before the sentence beginning "Mantoux test…" on line 40 as this is now referring to tests for latent infection.	Thank you for your comment. This amendment has now been made as suggested.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	19	3	The incidence figures for London excluded the homeless and this should be noted.	Thank you for your comment. The text has been updated to reflect this: "For example, there were less than 4 new cases per year per 100,000 population in the south west of England in 2013, as compared to 35.5 new cases per year per 100,000 population in London – a figure that did not include the incidence of tuberculosis among people who are homeless (a key high-risk population)."
British Thoracic Society	Full	19	3	The incidence figures for London excluded the homeless and this should be noted.	Thank you for your comment. The text has been updated to reflect this: "For example, there were less than 4 new cases per year per 100,000 population in the south west

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					of England in 2013, as compared to 35.5 new cases per year per 100,000 population in London – a figure that did not include the incidence of tuberculosis among people who are homeless (a key high-risk population)."
Homerton Hospital NHS Foundation Trust (HHFT)	Full	23	1	The subject of latent TB should be made more succinct so that each group does not require repetition of the same material where the evidence is concurrent. There are some serious flaws in the presentation of evidence due to the failure to include several recent long term follow-up studies of positive IGRAs. The key to value in detecting LTBI lies in the epidemiology, i.e. contacts make up to 10% of all notified TB and those with residence OR travel to relatives in a high incidence area have the greatest likelihood of developing TB. Moreover concurrent conditions such as diabetes, HIV, chronic renal impairment and alcohol problems increase the risk significantly (see several publications by Horsburgh). Homelessness per se requires housing as a first intervention and this remains obscured. The use of a 5 mm cut-off for tuberculin skin tests regardless of BCG vaccination status is not well justified. If we are to go to an American view,	Thank you for this comment. The full guideline comprehensively presents all of the material and evidence considered, whereas a shortened, succinct version of the guidance detailing the recommendations is also made available concurrent with the full version. Thank you for your comment. The systematic review was limited to studies that provided comparative effectiveness data of IGRA and TST. Unless these studies met this, and the other, inclusion criteria in the protocol which was agreed by the guideline committee, they would be excluded from the review. Please see section 3.1 of Appendix H for a full description of the protocol. Thank you for your comment. The scope of this work is limited to opportunistic case-finding of patients presenting at a point of care, and does not cover large scale contact tracing or screening

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				where cut-offs relate to the likelihood of infection, this should be specifically stated. The review of evidence fails to note that different doses of tuberculin, some without proven parity with RT23, were used in the studies.	initiatives (these were explicitly out of scope for this update as they are the remit of the National Screening Committee). Owing to a lack of reporting, the relationship between BCG status in these populations and the diagnostic accuracy of the tests could not be quantitatively established from the evidence considered. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses.

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				The aim to increase uptake of LTBI treatment from age 35 to age 65 is a significant change and the justification and level of evidence presented is poor. The ATS statement on hepatotoxicity of antituberculosis therapy is a useful summary of the evidence (AJRCCM 2006; 174: 935). Most notably, there is an increased rate of death over the age of 50 years. By all means update this information, but the current data suggests that raising the age will do more harm than good. The effect of aging on the incidence of TB in the UK requires epidemiological study.	Thank you for this comment. Our systematic review, network meta-analysis, and original economic analysis suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a greater relative risk of death from TB in older people. The model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it (and their chance of doing so increase with age), than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages. Please see Section 7.2.2 of the full guideline for more detail.
Birmingham & Solihull TB Service	Full	25	3	Concerned about this recommendation as will have impact on resources, should the focus be on all those identified are screened.	Thank you for your response. The scope of this work is limited to opportunistic case-finding of patients presenting at a point of care, and does not cover large scale contact tracing or screening initiatives (these were explicitly out of scope for this update as they are the remit of the National Screening Committee). The work undertaken by Warwick Evidence (see Appendix H of the Full Guideline) describes a health economic model which suggested that for

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					children TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). We have passed your comment on to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Nursing	Full	25	3	Our members are concerned about this recommendation as they consider that it will have impact on resources. They wondered if the focus should be on all those identified are screened?	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline. The work undertaken by Warwick Evidence (see Appendix H of the Full Guideline) describes a health economic model which suggested that for children TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone).

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	25	8	The evidence that 5mm induration has sufficient sensitivity and specificity for contact tracing is not given and is poor. Presumably this is to promote the use of an IGRA at a lower threshold than in 2011. Most European countries use 10 mm as a cut-off.	Thank you for this comment. This aim of this work was to provide a systematic review and economic evaluation of the diagnostic tests for LTBI in three high -risk groups as part of opportunistic case-finding. Large-scale contact tracing and structured screening initiatives were outside of the scope of this work, and outside the scope of NICE's work more generally (it is the remit of the National Screening Committee). Given the lack of existing substantive evidence on which to recommend a 6 mm induration cutoff , the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the group noted that reliably measuring the difference between 5 mm and 6 mm in practice was extremely difficult. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing

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					should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA

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					alone).
British Thoracic Society	Full	25	10	The subject of latent TB should be made more succinct so that each group does not require repetition of the same material where the evidence is concurrent. There are some significant omissions in the presentation of evidence due to the failure to include several recent long term follow-up studies of positive IGRAs. The key to value in detecting LTBI lies in the epidemiology, i.e. contacts make up to 10% of all notified TB and those with residence OR travel to relatives in a high incidence area have the greatest likelihood of developing TB. Moreover concurrent conditions such as diabetes, HIV, chronic renal impairment and alcohol problems increase the risk significantly (see several publications by Horsburgh). Homelessness per se requires housing as a first intervention and this remains obscured. The use of a 5 mm cut-off for tuberculin skin tests regardless of BCG vaccination status is not well justified. The evidence that 5mm induration has sufficient sensitivity and specificity for contact tracing is not given and is poor. Presumably this is to promote the use of an IGRA at a lower threshold than in 2011. Most European countries	Thank you for these comments. A more concise presentation of the recommendations is provided in the NICE version of the guideline. The systematic review was limited to studies that provided comparative effectiveness data of IGRA and TST. Unless these studies met this, and the other, inclusion criteria they would be excluded from the review. Large scale contact tracing and structured screening initiatives were outside of the scope of this work. The scope of this work is limited to the opportunistic screening of patients presenting at a point of care and does not cover large scale contact tracing or screening initiatives. Owing to a lack of reporting, the relationship between BCG status in these populations and the diagnostic accuracy of the tests could not be quantitatively established from the evidence considered. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was

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				use 10 mm as a cut-off. If we are to go to an American view, where cut-offs relate to the likelihood of infection, this should be specifically stated. The review of evidence fails to note that different doses of tuberculin and different preparations, some without proven parity with RT23, were used in the studies. In addition these are at variance with countries that use differing TST cut-offs and which stratify the response according to risk (CDC/Canadian/ Australia). In addition there is no apparent consideration of the effect of the BCG vaccine. This point is reiterated below.	reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses.
				The aim to increase uptake of LTBI treatment from age 35 to age 65 is a significant change and the justification and level of evidence presented is poor. The ATS statement on hepatotoxicity of antituberculosis therapy is a useful summary of	Our systematic review, network meta-analysis, and original economic analysis suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a much greater relative risk of death from TB in those people who progress to active disease at older age. The health economic analysis

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				the evidence (AJRCCM 2006; 174: 935). Most notably, there is an increased rate of death over the age of 50 years. It is important to update this information, but the current data suggests that raising the age to > 50 may do more harm than good. The effect of aging on the incidence of TB in the UK requires epidemiological confirmation. While we agree that the current age stratification at 35 years of age is artificial and arbitrary, we do not know of large studies that provide robust estimates of age-stratified risk to provide assurance that the increased risk of hepatotoxicity is acceptable.	suggested that the potential benefits of treatment were very much greater than the potential risks: at all ages, the expected number of TB deaths averted by treatment was at least 50 times greater than the expected number of deaths associated with treatment. In younger people receiving more effective regimens, the difference was several thousand-fold. The GDG considered these numbers and noted that, when compared with no treatment, all treatments in all age-groups were associated with a substantial net reduction in likelihood of death. Group members noted that they would not necessarily put identical weight on deaths caused and averted by LTBI treatment, as clinicians have a strong impetus to minimise iatrogenic harm, and also TB deaths will occur further into the future (although the latter factor was properly reflected in the cost–utility model [see below], which estimated quality-adjusted life expectation and discounted future costs and consequences according to established practice). Nevertheless, the GDG agreed that the difference between risks and benefits was stark, and emphasised that undertreatment is likely to be associated with much greater harm than overtreatment. According to the health economic model, 6H or 3HR would lead to net health gain at a cost of

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					less than £20,000 per QALY gained, compared with no treatment. However, 6H did not perform as well as 3HR with regard to risk of hepatotoxicity. For this reason, where hepatotoxicity is a concern – for example, pre-treatment liver function tests raised concerns, or if the person has liver disease, alcoholism or is a drug user – 3HR is the preferred treatment.
British Thoracic Society	Full	25	10	TST cut off too low, European countries use 10mm as cut –off. Use of mantoux in contact screening or migrant screening is unrealistic since most TB centres have replaced TST with IGRA testing. High DNA rates in contacts and migrants needs to be taken into consideration	Thank you for your comment. The GDG used various cut-off points (5mm, 10mm and 15mm) for the three populations of interest, and obtained the return rate to have TST read from the study by Pareek et al.(2013). Given concerns that this may be high, we have varied this number in a scenario analysis included as an addendum to Appendix H.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	25	22	This is unclear. Is it the neonate who has not had 2 weeks treatment or the index case who should be considered non-infectious after 2 weeks treatment?	Thank you for your comment. For clarity, this has been amended to: "If a neonate has been in close contact with people with smear-positive pulmonary or laryngeal TB ~~and has~~**who have** not had at least 2 weeks of anti-TB treatment…"
British Thoracic Society	Full	25	22	This is unclear. Is it the neonate who has not had 2 weeks treatment or the index case who should be considered non-infectious after 2 weeks	Thank you for your comment. For clarity, this has been amended to: "If a neonate has been in close contact with

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				treatment? Better wording to ensure clarity.	people with smear-positive pulmonary or laryngeal TB ~~and has~~**who have** not had at least 2 weeks of anti-TB treatment…"
Homerton Hospital NHS Foundation Trust (HHFT)	Full	25	25	Inconsistent advice regarding the second test (see comment 10). The BCG test has greater sensitivity and specificity than the Mantoux.	Thank you for comment. However, no evidence was found in support of the BCG test.
British Thoracic Society	Full	25	25	There is some logic in continuing to screening young household contacts (especially 2-17) of even non-respiratory disease as may well have same respiratory adult source.	Thank you for your comment, The GDG discussed this concern but concluded that, due to the resource implications of contact-tracing and the relatively few cases identified by tracing contacts of people with non-infectious extrapulmonary TB, contact-tracing should be limited to those index cases who are infectious (those with pulmonary TB).
British Infection Association	Full	26	General	We welcome the reference to SMIs but these are multi-agency, not PHE. We suggest use the term "UK SMIs" (Dr P Cowling is Chair of the UK SMI Steering Committee)	Thank you for your comment. The recommendation has been amended as suggested.
Oxford	Full	26	General	Why was QuantiFERON TB Gold (QFT-G) included in this analysis? It has not been	Thank you for your comment. We included studies in our clinical effectiveness review which

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Immunotec				available for many years. It is very different from the current QuantiFERON Gold In Tube assay (Samples collected into a standard heparin tube rather than 3 dedicated tubes, incubation of T cells with antigens only occurs when the sample arrives in the laboratory rather than immediately blood is collected, uses 2 antigens rather than 3). These differences produce different results so adding the results of the defunct Gold assay to the In Tube assay is not appropriate. The inclusion of the QFT Gold test is again mentioned on page 57 and 58.	compared any IGRA vs TST. Please note, however, that, in the accompanying cost-effectiveness analysis, to derive sensitivity and specificity of QFT-GIT in identifying LTBI that progresses to active TB, we used information on QFT-GIT only.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	26	2	The reasons for 3 months before the next test and 6 weeks in a slightly older age group appears to be inconsistent (perhaps kowtowing to the myth that neonates do not have T cell immunity, when this can in fact develop within the womb!).	Thank you for your comment. The GDG agreed that repeat testing should occur after 6 weeks in both age groups. The recommendations now reflect this.
British Thoracic Society	Full	26	2	The reasons for 3 months before the next test and 6 weeks in a slightly older age group appears to be inconsistent (this may be in the mistaken understanding that neonates do not have T cell immunity, when this can in fact develop within the womb).	Thank you for your comment. The GDG agreed that repeat testing should occur after 6 weeks in both age groups. The recommendations now reflect this.
Birmingham & Solihull TB	Full	26	11	This doesn't correlate with the TB strategy, as by using tuberculin skin tests (TST) in new entrants	Thank you for your comment. The GDG was aware of this apparent conflict between our

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Service				may lead to DNA's compared to one step IGRA? I would be concerned that asking for patients to come back may lead to loss of patients.	guidance and the Collaborative TB Strategy for England. However, the group emphasised the different context in which the recommendations apply: where the Collaborative TB Strategy for England envisages a 'co-ordinated, local screening programme', the recommendations in this guideline are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document. The choice of test (TST -v- IGRA) may be influenced by setting: the analyses on which the recommendations in this guideline are based assumed relatively high TST read-rates, which is appropriate for the case-finding context. This may not hold in a screening situation, where there may be reason to prefer a test that can be accomplished in a single interaction.
Birmingham & Solihull TB Service	Full	26	11	Are confirmatory IGRA tests / two-step tests TST followed by IGRA no longer supported? i.e. every TST > 5mm is to be classed as positive (although reducing steps may increase numbers completing screening)	Thank you for your comment. In our model, we have not considered confirmatory IGRA. We have used a testing strategy TST +ve followed by IGRA in the recent arrivals population, but IGRA is not used here as a confirmatory test.
Oxford Immunotec	Full	26	19	Another bullet point should be added to Recommendation 8 to make it consistent with Recommendation 4 saying that interferon-gamma	Thank you for your comment. The suggested duplication of information in recommendation 4 (now 2) has not been undertaken.

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				release assays can be used if Mantoux testing is not available or is impractical (for example, situations in which large numbers need to be tested).	Recommendation 4 (now 2) applies to the diagnosis of latent TB in all children and young people, including children or young people aged between 2 and 17 years who have been in close contact with people with pulmonary or laryngeal TB (the population described in recommendation 8 (now 6)). If it is restated for this population, consistency would mean it would also be added to the other recommendations relating to the diagnosis of latent TB in children and young people. The guideline is already of considerable length, so the Developer is concerned that multiple repetitions of this would not only fail to add further clarity (or further guidance), but is more likely bring about greater confusion.
British Thoracic Society	Full	26	20	Why only *consider* LTBI treatment in positive mantoux, especially as younger children have a higher rate of progression to active disease with complications? We would consider it negligent not to offer treatment.	Thank you for your comment, we have amended this for the child and immunocompromised recommendations, to: "…~~consider~~ **offer** ~~treating~~ them **treatment** for latent TB infection."
Homerton Hospital NHS Foundation Trust (HHFT)	Full	26	29	The advice is inconsistent with the previous section, without stating that these recommendations apply to those 18 years and above. The 65 year cut-off is new and goes against information from TB treatment regarding hepatotoxicity over the age of 55 years. The advice is again inconsistent for BCG, as previous	Thank you for your comment. The recommendation has been edited for consistency: "Assess and manage TB in new entrants from high incidence countries who present to healthcare services as follows: • assess risk of HIV, including HIV prevalence

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				vaccination is no longer being used to determine a positive result (see previous sections). The IGRA becomes more important with age as non-specific Mantoux reactions become more frequent with age and exposure to other mycobacteria.	rates in the country of origin, and take this into account when deciding whether to give a BCG vaccination • offer testing for latent TB • assess for active TB if the test for latent TB is positive • offer treatment to people aged 65 years or younger in whom active TB has been excluded but who have a positive Mantoux test ~~inconsistent with their BCG history and~~ **or** a positive interferon-gamma release assay for latent TB infection • consider offering BCG for unvaccinated people who are Mantoux- **or interferon-gamma release assay-**negative • give 'inform and advise' information to people who do not have active TB and are not being offered BCG or treatment for latent TB infection." The systematic review, network meta-analysis, and original economic analysis (conducted by Imperial College) suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a greater relative risk of death from TB in older people. The model reflects that people aged 51–65 are approximately 5½ times more likely to

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					develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it (and their chance of doing so increase with age), than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages. Please see Section 7.2.2 of the full guideline for more detail.
Oxford Immunotec	Full	26	29	Recommendation 11 and Recommendation 14 (page 27 line 14) both describe screening new entrants from high incidence countries. They should be combined to remove ambiguity.	Thank you for your comment. These have been retained as separate recommendations. Additionally, it should also be noted that these recommendations are limited to opportunistic case-finding of patients presenting at the point of care and do not cover large scale contact tracing or screening initiatives (these were explicitly out of scope for this update as they are the remit of the National Screening Committee)
British Thoracic Society	Full	27	14	The use of the mantoux in new entrant screening appears to ignore the UK study by in Thorax - Pareek et al within primary care (where a single IGRA was most cost effective) and the costings appear discordant with the current pricing of IGRA's. In the context of a national programme this is even more of an issue and a reconsideration is needed and the ability to use	Thank you for your comment. The study you cite was considered as part of the evidence for cost effectiveness of diagnosis of LTBI in newly arrived migrants (see Appendix H, section 5.3.3). The study is of limited direct value, for decision-making purposes, as it does not account for positive and negative quality-of-life impacts associated with diagnosis (and subsequent

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				an IGRA should be offered as an option.	treatment). The preferred unit of effectiveness in the NICE reference-case for economic evaluations is Quality Adjusted Life Years (QALYs), with cost-effectiveness expressed as a cost-per-QALY figure. Measurements of cost-effectiveness such as cases prevented are not comparable across health domains and fail to take into account important factors such as patient quality of life. It is also important to consider that the original model undertaken to support this guideline represents the first time a transmission dynamic model has been used in the context of a cost-effectiveness analysis of LTBI diagnostic tests. In sensitivity analysis, when the number of secondary cases was set to zero (i.e. the transmission dynamic component of the model was 'turned off'), the results of the model fell broadly in line with other published studies that do not model secondary transmission. This lends weight to the importance of using transmission dynamic modelling in the subgroups considered. Thank you for your comment on the pricing of IGRA. This cost parameter has been subjected to additional sensitivity analysis in an addendum to Appendix H of the Full Guideline, with the cost of IGRA being reduced to £29and the cost of TST increased to £29. This had no impact on the base-case results. The GDGD stressed that these

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					recommendations apply to opportunistic case-finding only, and not national screening programmes.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	27	20	If "this" is unavailable – do you mean tuberculin or someone to do a Mantoux test is unavailable? Again the previous sections make the advice a bit unclear as to who is being considered.	Thank you for your comment. It may mean either of these. The utility of a Mantoux test is largely a function of the skill of the person administering the test, and appropriately skilled personnel are therefore necessary. If skilled personnel are not available, it may be more appropriate to use an IGRA. Alternatively, purified protein derivative is not always available in the UK. At times when it is unavailable, an IGRA should be used.
British Thoracic Society	Full	27	20	If "this" is unavailable – do you mean tuberculin or someone to do a Mantoux test is unavailable? Again the previous sections make the advice a bit unclear as to who is being considered.	Thank you for your comment. It may mean either of these. The utility of a Mantoux test is largely a function of the skill of the person administering the test, and appropriately skilled personnel are therefore necessary. If skilled personnel are not available, it may be more appropriate to use an IGRA. Alternatively, PPD is not always available in the UK. At times when it is unavailable, an IGRA should be used.

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Oxford Immunotec	Full	27 138	20 8	Recommendation 14 states that when screening new arrivals from high incidence countries a Mantoux with a 5mm cut-off is recommended. Many of these subjects will have received BCG vaccination on one or more occasion (see Hardy et al Thorax 2010 in which 79% of new entrants in Leeds who were screened for LTBI reported having received BCG). There are many studies showing that the Mantoux test will give false positive results in BCG vaccinated subjects especially if the high sensitivity (but low specificity) cut-off of 5mm is used. Page 128 line 24 of the Full Guideline suggests this by saying "it is acknowledged that the BCG vaccination history may have an impact on the diagnostic accuracy (and subsequent cost effectiveness) of the tests considered.5 mm". There appears to be an error in the text, but presumably this comment refers to the significant cross reaction to BCG when using the Mantoux with a 5mm cut-off. Why then is Mantoux preferred over interferon gamma release assays which are known to be more specific and so would not cross react with BCG vaccination in this population?	Thank you for your comment, The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses. Without further description of the studies mentioned in your comment, we cannot cross-check these with our included/excluded studies or review protocol.

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	27	21	Hospital employees from the tropics (also high incidence TB areas) tend to have more exposure to different organisms and more false-positive Mantoux reactions, especially using 5 mm. An IGRA is therefore a much more logical choice.	Healthcare workers in general were out-of-scope, but healthcare workers from high incidence countries are a part of the newly arrived migrants from high incidence countries population, and therefore the results of the heath economic analysis recommendations could be extrapolated to them. The cost-effectiveness analysis results show that for newly arrived migrants from high-prevalence countries, TST (≥5 mm) dominated the TST (≥5 mm) positive followed by QFT-GIT and T-SPOT.TB-alone strategies, represented good value for money in comparison with QFT-GIT alone (generating extra QALYs at a cost of around £1500 each), and had a 47% probability of being the optimal option if QALYs are valued at £20,000. The TST (≥5 mm) negative followed by QFT-GIT strategy generated most QALYs, but the small marginal benefit over TST (≥5 mm) alone was associated with an ICER of £58,720 per QALY.
British Thoracic Society	Full	27	21	Hospital employees from the tropics (also high incidence TB areas) tend to have more exposure to different organisms and more false-positive Mantoux reactions, especially using 5 mm. An IGRA is therefore a much more logical choice.	Healthcare workers in general were out-of-scope, but healthcare workers from high incidence countries are a part of the newly arrived migrants from high incidence countries population, and therefore the results of the heath economic analysis recommendations could be extrapolated to them. The cost-effectiveness analysis results show that for newly arrived migrants from high-

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					prevalence countries, TST (≥5 mm) dominated the TST (≥5 mm) positive followed by QFT-GIT and T-SPOT.TB-alone strategies, represented good value for money in comparison with QFT-GIT alone (generating extra QALYs at a cost of around £1500 each), and had a 47% probability of being the optimal option if QALYs are valued at £20,000. The TST (≥5 mm) negative followed by QFT-GIT strategy generated most QALYs, but the small marginal benefit over TST (≥5 mm) alone was associated with an ICER of £58,720 per QALY
British Thoracic Society	Full	28	19	R22 Agree use IGRA but why then not in R21 – internally inconsistent.	Thank you for your comment. R22 is out of scope for update as it relates to occupational health measures to prevent the transmission of TB in the workplace. Although R21 also relates to occupational health measures to prevent the transmission of TB in the workplace, it additionally relates to the diagnosis of latent TB in new entrants from high incidence countries, which is an area that was updated with a new review and economic modelling. For this reason, the CG117 recommendation could be updated. Although the 2 populations are similar, they are not the same.
Homerton Hospital NHS	Full	28	25	"Underserved groups" is jargon and unclear to whom it refers.	Thank you for your comment. PH37 originally referred to hard-to-reach groups but the committee felt this put the emphasis on people,

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Foundation Trust (HHFT)					rather than the service, and thought underserved groups was a better term. There is a definition of underserved groups included in the glossary to help clarify was it meant: "This term is used in this guideline to mean groups of adults, young people and children from any ethnic background, regardless of migration status. They are 'under-served' if their social circumstances, language, culture or lifestyle (or those of their parents or carers) make it difficult to: • recognise the clinical onset of TB • access diagnostic and treatment services • self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer) • attend regular appointments for clinical follow-up. The groups classified as under-served in this guideline are: • people who are homeless • people who misuse substances • prisoners

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					• vulnerable migrants."
British Thoracic Society	Full	28	25	"Underserved groups" is jargon and unclear to whom it refers.	Thank you for your comment. There is a definition of underserved groups included in the glossary as follows: "This term is used in this guideline to mean groups of adults, young people and children from any ethnic background, regardless of migration status. They are 'under-served' if their social circumstances, language, culture or lifestyle (or those of their parents or carers) make it difficult to: • recognise the clinical onset of TB • access diagnostic and treatment services • self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer) • attend regular appointments for clinical follow-up. The groups classified as under-served in this guideline are: • people who are homeless • people who misuse substances

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					• prisoners • vulnerable migrants."
Oxford Immunotec	Full	28	27	Clarify that Recommendation 25 refers to testing the people who are substance misusers and not the people providing these services (especially as Recommendation 23 refers to testing healthcare workers).	Thank you for your comment. We have amended the text to: "Substance misuse services with access to an interferon-gamma release assay should provide testing for people younger than 65 years who misuse substances …"
Homerton Hospital NHS Foundation Trust (HHFT)	Full	28	30	Define "high incidence area" ?WHO >40 per 100,000 or another cut-off. (Also relevant to all subsequent paragraphs)	Thank you for your comment. A high incidence area is defined in the glossary as an area in which TB notifications are greater than 40 per 100,000 people per annum.
British Thoracic Society	Full	28	30	Define "high incidence area" ?WHO >40 per 100,000 or another cut-off. (Also relevant to all subsequent paragraphs)	Thank you for your comment, A high incidence area is defined in the glossary as an area in which TB notifications are greater than 40 per 100,000 people per annum.
Homerton Hospital NHS Foundation Trust	Full	28	36 41	This is an unusual paragraph, as it implies that if a service is failing it doesn't matter if you don't screen prisoners and is therefore an example of stigmatization rather than a recommendation from evidence.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for

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(HHFT)					example, because of a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic Society	Full	28	36 - 41	This is an unusual paragraph, as it implies that if a service is failing it doesn't matter if you don't screen prisoners and is therefore an example of stigmatization rather than a recommendation from evidence.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Birmingham & Solihull TB Service	Full	30	5 - 19	Does this recommendation imply that patients with these conditions should be screened for latent TB if from, or living in high incidence areas?	We apologise, but the Analyst has not been able to identify the text referred to.
Birmingham & Solihull TB Service	Full	30	27	Rifapentine is not mentioned as an option for latent TB treatment. Was the evidence considered especially the impact of weekly versus daily latent TB treatment may have on the completion rates amongst vulnerable groups e.g. prisoners, homeless etc.	Thank you for your comment. As rifapentine is not currently licensed in the UK, the Committee was unable to make recommendations on its use. It was, however, included in the evidence base as a comparator.

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Birmingham & Solihull TB Service	Full	31	3	"Concerns about hepatotoxicity" is very vague you could argue that the concern is being aged over 35 – should the risks be spelt out?	Thank you for your comment. Concerns might include abnormal pre-treatment liver function tests, liver disease, alcoholism or drug use. These have been explicitly stated in the Evidence to Recommendations table.
Oxford Immunotec	Full	32	General	The top of the page indicates that studies suggest that IGRA perform better in children in low burden countries compared to high burden countries. Since England is a low burden country all studies performed in high burden countries should be excluded.	Thank you for your comment. We used Bayesian MCMC to estimate study prevalence and test performance accounting for the underlying prevalence in each of the studies in the evidence base. To estimate prevalence, we excluded studies from high incidence (>40/100,000) countries.
British Infection Association	Full	32	14 15	Do you mean 4 samples in total, or 3 sputa preferably including an early morning sample?	Thank you for your comment. 3 samples preferably including an early morning sample. This has been clarified in the recommendation as follows: "Send multiple respiratory samples (3 deep cough sputum samples, preferably ~~with~~ **including** 1 early morning sample) for TB microscopy and culture."
Homerton Hospital NHS Foundation	Full	33	21	This recommendation does not accord with the only randomized controlled trial of steroids to prevent the need for surgery by recommending	Thank you for your comment. The group concluded that a gradual withdrawal of the corticosteroids – which was previously recommended – was still appropriate. The GDG

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Trust (HHFT)				withdrawal of steroids after 2-3 weeks.	considered this to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions.
British Thoracic Society	Full	33	21	This recommendation does not accord with the only randomized controlled trial of steroids to prevent the need for surgery by recommending withdrawal of steroids after 2-3 weeks.	Thank you for your comment. The group concluded that a gradual withdrawal of the corticosteroids – which was previously recommended – was still appropriate. The GDG considered this to be a key element of the regimen design, as sudden withdrawal of corticosteroids is known to be associated with adverse withdrawal reactions.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	33	40	By "instability include >15 degrees from vertical alignment as per Cochrane reviews.	Thank you for your comment. This has now been included in the Evidence to Recommendations table as follows; " In line with the definitions used in the evidence base, spinal instability would include kyphosis of more than 15 degrees from vertical alignment."
British Thoracic Society	Full	33	40	By "instability include >15 degrees from vertical alignment as per Cochrane reviews.	Thank you for your comment. This has now been included in the Evidence to Recommendations table as follows; "In line with the definitions used in the evidence base, spinal instability would include kyphosis of more than 15 degrees from vertical alignment."

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Oxford Immunotec	Full	34	General	When describing the IGRAs why only mention QFT – "one type of which is QFT-GIT"? To ensure there is no implied favouritism both IGRAs should be mentioned so the T-SPOT.TB test should also be included here.	Thank you for your comment. We have included studies in our clinical effectiveness review which compares IGRA vs TST. In the cost-effectiveness analysis, to derive sensitivity and specificity of QFT-GIT in identifying LTBI that progresses to active TB, we used information on QFT-GIT only.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	34	33	The randomized controlled trial data and Mitchison reviews on developing drug resistance would not recommend sequential introduction of drugs, but rather re-introduction of all drugs simultaneously. The advice should state "at full dose" (as long as no anaphylaxis has been encountered).	Thank you for your comment. The GDG reviewed the evidence from both available RCTs and found sequential reintroduction of drugs to be associated with a better outcome, though the small number of events and patients involved meant that the effect estimate did not reach statistical significance. However, the committee combined this evidence with their own experience of managing treatment interruptions, and concluded that sequential reintroduction should be used over simultaneous reintroduction in people who have experienced drug-induced hepatotoxicity. Hepatotoxicity may be caused by many drugs, therefore sequential reintroduction can help to pinpoint which drugs are causing the problem. This rationale is stated within the Evidence to Recommendations table for this recommendation. The GDG also discussed the Mitchison paper highlighted by the stakeholder. However, as a

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					theoretical exploration of the mechanisms by which drug resistance might arise, the group did not feel it provided a strong enough evidence base upon which to change the current recommendation. Additional text has been added to the recommendation to encourage drugs to be reintroduced at the full dose: "… sequentially reintroduce each of the anti-TB drugs **at full dose** over a period of no more than 10 days, starting with ethambutol and either isoniazid (with pyridoxine) or rifampicin…"
British Thoracic Society	Full	34	33	The randomized controlled trial data by Sharma and Mitchison reviews on developing drug resistance would not recommend sequential introduction of drugs, but rather re-introduction of all drugs simultaneously. The prior advice predicated on joint full dose Ethambutol introduction of single drugs and there need to be more studies of full reintroduction in larger numbers.	Thank you for your comment. The GDG reviewed the evidence from Sharma et al, which is included in the description of the evidence base. For example, the evidence statement reads, "Very low quality evidence from 2 randomised controlled trials in 220 people with active tuberculosis who had experienced drug-induced hepatotoxicity showed sequential reintroduction of antituberculosis drugs to be associated with a lower recurrence of drug-induced hepatotoxicity than simultaneous reintroduction, though the effect was not statistically significant (OR (95% CI) = 0.44 (0.18 to 1.03))." This pooled evidence from both available RCTs and found sequential reintroduction of drugs to be

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					associated with a better outcome (that is, a lower incidence of hepatotoxicity), though the small number of events and patients involved meant that the effect estimate did not reach statistical significance. However, the committee combined this evidence with their own experience of managing treatment interruptions, and concluded that sequential reintroduction should be used over simultaneous reintroduction in people who have experienced drug-induced hepatotoxicity. Hepatotoxicity may be caused by many drugs, therefore sequential reintroduction can help to pinpoint which drugs are causing the problem. This rationale is stated within the Evidence to Recommendations table for this recommendation. The GDG also discussed the Mitchison paper highlighted by the stakeholder. However, as a *theoretical* exploration of the mechanisms by which drug resistance might arise, the group did not feel it provided a strong enough evidence base upon which to change the current recommendation.
British Thoracic Society	Full	35	137	There is inconclusive evidence that treatment of migrants over 50 is beneficial, the Newham project has shown that DILI much higher in age greater than 45 often leading to discontinuation of treatment.	Thank you for this comment. Our systematic review, network meta-analysis, and original economic analysis suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a greater relative risk of death from TB in older

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					people. The model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it (and their chance of doing so increase with age), than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages. Please see Section 7.2.2 of the full guideline for more detail.
Birmingham & Solihull TB Service	Full	36	17	Pleural tissue would improve the yield of positive cultures.	Thank you for your comment. Pleural biopsy is now recommended in the diagnosis of pleural TB.
Oxford Immunotec	Full	39	General	The T-SPOT.TB test does not include the antigen TB7.7. This antigen is only found in the QFT Gold In Tube test.	Thank you for your comment. This has now been amended throughout the document
British Thoracic Society	Full	40 41	General	The BCG policy is seemingly inconsistent. The WHO guidance on using it for the whole population where the incidence of TB is >40 per 100,000 (e.g. boroughs in London and areas in other major cities) is obscured. This section could be significantly trimmed and reference to the Green Book should be sufficient (where a couple of pages covers the subject).	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of

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					TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Birmingham & Solihull TB Service	Full	40	5	Include urine culture- non-invasive and reasonable yield	Thank you for your comment. Urine culture is included within this recommendation already.
Oxford Immunotec	Full	40	44	Recommendation 128 is repeated on page 42, line 31 (Recommendation 140). One should be deleted.	Thank you for your comment. This has now been amended.
Birmingham & Solihull TB Service	Full	45	8	Is the evidence for the use of steroids in pericardial TB still considered robust in view of recent trial evidence?	Thank you for your comment. Although not extensive, the GDG noted that there was some evidence to show that corticosteroids decreased mortality, although this effect was not statistically significant. Overall, the GDG concluded that the evidence supported the use of corticosteroids in patients with pericardial tuberculosis. Although the meta-analysis did not provide strong evidence in terms of corticosteroid use reducing mortality, this meta-analysis was unable to include the long-term

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					survival data from the Strang paper due to the format in which it was reported. When viewed in isolation, the survival analysis in this paper showed a clear protective effect.
Birmingham & Solihull TB Service	Full	45	8	Should the risks versus benefits of high dose steroids be mentioned especially in HIV infected patients?	Thank you for your comment. The GDG were unable to make such recommendations as they had not seen any relevant evidence on this subject.
Birmingham & Solihull TB Service	Full	48	2	It may be useful to state that PCR tests for detection of mutations conferring resistance to rifampicin will only be positive in 95% of rifampicin resistant isolates, as there are other mutations not detected by current tests, and that it is not a rule out test (and not a rule –in test either)	Thank you for your comment. This section is about raising awareness of TB and ensuring professionals can recognise symptoms of TB, understand referral pathways, and understand stigma associated with TB, etc. Drug resistance and clinical methods of detecting drug resistance are discussed in section 1.4 of the NICE guideline.
Birmingham & Solihull TB Service	Full	48	18	Maybe preferable to say that when full sensitivity test results are available, and after discussion with microbiologists in the testing laboratory. Alternative tests currently in use are both phenotypic and genotypic.	Thank you for your comment. Although genotypic tests may provide useful information, it is only the results of phenotypic testing – the gold standard – that should led to treatment modification.
Oxford	Full	51	General	The text states that "Skilled personnel are needed to administer both tests". The T-SPOT.TB test	Thank you for your comment. This statement refers to the fact that the test needs to be

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Immunotec				only requires collection of a standard blood sample. This is not usually considered to require skilled personnel so this comment should be amended so that it does not apply to the T-SPOT.TB test.	administered by somebody trained and able to collect a blood sample.
Oxford Immunotec	Full	51	General	The text states that "sample can be analysed within 12 hours". Samples used in the T-SPOT.TB test do not require any processing for 32 hours so change this limitation to indicate that T-SPOT.TB samples only need to be analysed within 32 hours.	Thank you for your comment, we will amend the text to reflect this.
Birmingham & Solihull TB Service	Full	51	13	Useful to suggest this is decided jointly with the TB clinician, microbiologist and Infection Control and ward nursing teams.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment. Areas that have not been reviewed in this update will be taken into consideration when NICE next reviews this guideline. NICE may undertake a more rapid update of discrete areas of the guideline if new and relevant evidence is published.

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Birmingham & Solihull TB Service	Full	52	12	Although the US guidelines state a surgical mask, based on a single paper, it would be helpful to state an FFP mask without a valve, particularly if the patient is unable to cooperate well. Manufacturers will provide the performance characteristics for this type of mask, and the patient can be fit tested.	Thank you for your comment. However, this level of detail was not judged to be necessary (particularly since the GDG did not see any evidence on this), though the current recommendation provides sufficient flexibility that this is an option for those who wish to do it.
NHS England	Full	54 38	12 5	We recommend that the patient's general practitioner (GP) should be included in decisions to discharge even if just on an information basis. For patients who have good relationships with their GP who maybe the first person the TB patient contacts if they have any issues regarding treatment or adverse effects i.e. reactions to anti TB drugs.	Thank you for your comment. The GDG discussed this, but did not feel that they could support a recommendation to undertake this in all cases. However, GPs should be informed of the decision to discharge, and follow local discharge policy arrangements.
NHS England	Full	56 64	7 15 7 16	We recommend that 'social contacts' be explicitly included here as some TB patients may spend more time with social contacts i.e. drinking in a bar and that 'casual contacts' does not fully encapsulate the range of contacts that this can mean.	Thank you for your comment. We have amended as suggested and the recommendation now reads as follows; **"**Do not routinely assess social contacts of people with TB, who will include most workplace contacts."
Oxford Immunotec	Full	58	General	The exclusion criteria should include subjects who have received anti-TB chemoprophylaxis in studies investigating the sensitivity of the tests through incidence. If these subjects are treated	Many thanks for highlighting this, the sensitivity of the tests was derived based on people who have not been treated with anti-LTBI chemoprophylaxis and further developed active TB.

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				they are much less likely to convert to active TB thereby dramatically reducing the perceived sensitivity of the tests. Therefore this exclusion criterion should be added and all studies used should be checked to ensure no chemoprophylaxis was given.	
George Eliot NHS Trust	Full	60	2	Can we give BCG if IGRa negative and mantoux not done ?	Thank you for your comment. Although this recommendation was not within the scope of update, this recommendation has been updated to reflect the inclusion of IGRAs in the guidance (the original recommendation was part of the 2006 guideline and was made before IGRAs were recommended by NICE). New recommendation: "Offer BCG vaccination to new entrants who are Mantoux- **or interferon gamma release assay-** negative who: • are from high-incidence countries, and • are previously unvaccinated (that is, without adequate documentation or a BCG scar), and • are aged: o younger than 16 years, or o 16–35 years from sub-Saharan Africa or a country with a TB incidence of 500 per 100,000 or more."

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NHS England	Full	60 50	20 183	We note that there are inconsistencies in the recommendation for people with substance misuse, homeless and prisons. Some parts of the document recommend commissioning of an X-ray i.e. the mobile X-ray service and other sections recommend the use of IGRA. These sections should be brought together to clearly show why one system should be used in preference to the other.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment. Areas that have not been reviewed in this update will be taken into consideration when NICE next reviews this guideline. NICE may undertake a more rapid update of discrete areas of the guideline if new and relevant evidence is published.
Oxford Immunotec	Full	61	General	Using exposure to MTB as a proxy for sensitivity and specificity will introduce considerable variability since different studies have used different methods for categorising high and low exposure groups. Hence the overall sensitivity or specificity of a test will be affected by the method of categorisation of high and low risk subjects. Therefore using this proxy introduces additional variability so it should not be used.	Thank you for your comment. . We are aware that exposure to MTB as a proxy for deriving sensitivity and specificity would introduce variability. Hence, we have not included this information in order to derive sensitivity and specificity.
NHS England	Full	62 50	20 34	We would like the GDG to consider adding 'commissioning of IGRA' to be added to this section (and others as required) to ensure that	Thank you for your comment. The use of IGRA is discussed within an earlier section of the guideline. To avoid repetition within an already

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				commissioners have the opportunity to consider the best process for different population needs.	lengthy guideline we have tried not to duplicate information elsewhere in the guideline.
NHS England	Full	63 59	11 45	1.6.4 Incident and outbreak response/recommendation 231. We note that this recommendation includes a level of detail that is not the remit of TB Control Boards as outlined in step 1 of the 2015 National TB Strategy and recommend that the GDG remove this from the guidance. The direct responsibility for 'Incident and outbreak response' is that of PHE Health Protection Teams.	Thank you for your comment. , this recommendation has been amended as follows; "Multidisciplinary TB teams should refer any incident in a congregate setting to the local health protection team for risk assessment within 5 working days of suspicion of a potential incident. They should tell the local TB control board a referral has been made.".
Oxford Immunotec	Full	63	44	As interferon gamma release assays may also be used in contact tracing (where Mantoux may be less reliable, for example BCG vaccinated people) this bullet point should refer to both Mantoux testing and interferon gamma release assays so add interferon gamma release assays to the bullet point	Thank you for your comment. This has now been amended to "In asymptomatic close contacts younger than 65 years, consider standard testing for latent TB, followed by consideration of BCG vaccination or treatment for latent TB infection once active TB has been ruled out for people who: • are previously unvaccinated, and • are contacts of a person with sputum-smear-positive TB, and • are Mantoux- or interferon gamma release

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					assay-negative."
Oxford Immunotec	Full	67	7	The previous bullet point already refers to "documentary evidence of TB Tskin (or interferon-gamma release assay) testing and/or BCG scar check by an occupational health professional" there is therefore repetition by then stating "Mantoux result within the past 5 years, if available". These two bullet points can therefore be combined.	Thank you for your comment. This has now been amended.
Oxford Immunotec	Full	67	14	Recommendation 297 has not been updated to reflect the 2015 Recommendations so it now contradicts Recommendation 21 on page 28, line 11. Therefore Recommendation 297 should now be changed to reflect Recommendation 21.	Thank you for your comment. Amended to: "Offer BCG vaccination to employees of any age who are new to the NHS and are from countries of high TB incidence, or who have had contact with patients in settings with a high TB prevalence, and who are Mantoux- or interferon-gamma release assay-negative."
Homerton Hospital NHS Foundation Trust (HHFT)	Full	69	6 15	Individual behaviour; difficulty treating patients when they are well; more likely to participate if the NNT is much lower. Impossibility of randomization as too many different sub groups	Thank you for your comment. The modelling detailed in appendix I of the full guideline considered that patients may not adhere to treatment and would have a risk of developing active disease as a result. The risks of harm to the patient, which may dissuade them in addition to the fact that they are otherwise well, were explored in the economic analysis. The testing strategies that appeared to be optimal in the economic modelling presented to the GDG by

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					Warwick Evidence were considered to be high-sensitivity, low-specificity strategies which may lead to an increased number of people being treated for LTBI when no infection is present. Given the risks of treatment, the GDG requested additional work from Warwick Evidence to examine the trade-offs in mortality risks between active TB and LTBI-treatment-induced hepatotoxicity in high-sensitivity, low-specificity versus low-sensitivity, high-specificity testing strategies. The GDG considered that rates of hepatotoxicity in children were sufficiently low as to limit this additional work to the immunocompromised and newly-arrived migrant subpopulations. The results suggested that, on average, for each 1 death from hepatitis prevented from by moving from a high-sensitivity, low-specificity strategy to a high-specificity, low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (secondary cases are not considered in this calculation). The GDG concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. It was stressed that these numbers are sensitive to

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					the underlying prevalence of LTBI and that, at lower prevalence, a higher-specificity strategy is likely to be more important. The analysis was based on the assumption of treatment with 6 months of isoniazid; more toxic regimens may give different results.
British Thoracic Society	Full	69	6 15	Individual behaviour; difficulty treating patients when they are well; more likely to participate if the NNTis much lower. Impossibility of randomization as too many different sub groups	Thank you for your comment. Thank you for your comment. The modelling detailed in appendix I of the full guideline considered that patients may not adhere to treatment and would have a risk of developing active disease as a result. The risks of harm to the patient, which may dissuade them in addition to the fact that they are otherwise well, were explored in the economic analysis. The testing strategies that appeared to be optimal in the economic modelling presented to the GDG by Warwick Evidence were considered to be high-sensitivity, low-specificity strategies which may lead to an increased number of people being treated for LTBI when no infection is present. Given the risks of treatment, the GDG requested additional work from Warwick Evidence to examine the trade-offs in mortality risks between active TB and LTBI-treatment-induced hepatotoxicity in high-sensitivity, low-specificity versus low-sensitivity, high-specificity testing strategies. The GDG considered that rates of hepatotoxicity in children were sufficiently low as

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					to limit this additional work to the immunocompromised and newly-arrived migrant subpopulations. The results suggested that, on average, for each 1 death from hepatitis prevented from by moving from a high-sensitivity, low-specificity strategy to a high-specificity, low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (secondary cases are not considered in this calculation). The GDG concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. It was stressed that these numbers are sensitive to the underlying prevalence of LTBI and that, at lower prevalence, a higher-specificity strategy is likely to be more important. The analysis was based on the assumption of treatment with 6 months of isoniazid; more toxic regimens may give different results.
NHS England	Full	71 415	General	Commissioning and clinical guidance for TB control boards and clinical commissioning groups has now been published. The GDG may wish to consider the approaches set out in this	Thank you for your comment and for providing this information. This has been discussed with the GDG. They confirmed that the specific commissioning guidance provided here is with

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				commissioning and clinical guidance which can be found at: http://www.england.nhs.uk/resources/resources-for-ccgs/out-frwrk/dom-1/tb-strategy/	reference to the elements of the TB strategy that relate to the screening of migrant communities for LTBI. This is out of scope for this guideline.
NHS England	Full	75 416	4 3	Recommendation 195. We note that some TB control responsibilities are expected to be provided by service providers (e.g. around cohort review) but the role of control boards to support the expansion of this work is limited by the resources of the TB Control Boards.	Thank you for this comment. It is not clear what you mean by the expansion of this work as there is not a recommendation to expand the work of service providers around cohort review. The recommendations do not suggest the expansion of cohort review. The GDG did not consider their recommendations to have this meaning.
TB Alert	Full	76	1.8.2.8	There are three topics missing from the list: monitoring / coordinating the TB awareness training (under workforce development), monitoring / coordinating addressing TB stigma and associated myths in communities at significant risk through the local authority PH teams and/or third sector organisations. Lastly: 'Incorporating the news and experiences of local people who have been affected by TB, their carers and the services working to support them'	Thank you for your comment. The topic lists is not intended to be exhaustive, only examples – some of the points you make are covered in the awareness raising recommendation in the guideline.
Public Health England	Full	76	24	We would like to suggest the text: "The National Knowledge Service is a relatively new national NHS body which is investigating ways of making patient and public information available to patients and the NHS, amongst other functions. One of the initial pilot projects is in tuberculosis,	Thank you for your comment. The text has been amended as requested and now reads as follows; "The National Knowledge Service–TB is a Department of Health-initiated service which is now run by Public Health England. The service

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				and is linked to this guideline. See www.hpa.org.uk/tbknowledge for more detail" is changed to: "The National Knowledge Service – TB is a Department of Health initiated service which is now run by Public Health England. The service provides information to professionals both in healthcare and non-healthcare settings, involved in the management of TB patients. In some instances it also provide information for patients and members of the public. An example of a recently released resource is: TB in the workplace."	provides information to professionals both in healthcare and non-healthcare settings, involved in the management of TB patients. In some instances it also provides information for patients and members of the public. An example of a recently released resource is: TB in the Workplace. See www.hpa.org.uk/tbknowledge for more detail"
Birmingham & Solihull TB Service	Full	83	8	It is recommended that One whole-time equivalent case manager for per 20 incident cases that needed enhanced case management. By not having these patients shared nurses would not be able to utilise their skills. It will also not be practical in some geographical areas, as if providing community service and having to visit patients with complex needs over a large geographical stretch will be challenging. Suggestion is that where increased number of complex cases, total number of cases be 35.	Thank you for this comment**.** The responsibility for providing advice on setting staffing levels has now transferred to NHS Improvement. The recommendations have been revised to take account of this. An additional recommendation has also been included stating that "Commissioners should ensure NHS Improvement's principles of safe staffing are applied when commissioning TB services".
NHS England	Full	83	14	We note that there is no evidence stated to support the recommendation that there should be one whole-time equivalent case manager per 80	Thank you for your comment. The responsibility for providing advice on setting staffing levels has now transferred to NHS Improvement. The

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		430		latent TB cases for standard case management. Whilst we recognise this is a pragmatic recommendation it does not allow enough flexibility for local innovation that may better meet local and patients' needs. We recommend that the wording is amended to allow for local solutions/innovation.	recommendations have been revised to take account of this. It is local commissioners' choice to implement NICE recommendations to meet local need and to allow for local solutions and innovations as they consider appropriate. However an additional recommendation has also been included stating that "Commissioners should ensure NHS Improvement's principles of safe staffing are applied when commissioning TB services".
NHS England	Full	84	2	We are disappointed that the GDG was unable to consider evidence beyond 2009 for sections that include 'diagnosis of latent TB'. As an example: Pareek et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost effectiveness analysis. The Lancet: Infectious Diseases, vol 11, June 2011. The development and recommendations of the 2015 TB strategy included evidence from publications since 2009. The evidence had a significant impact on the development of the Strategy and puts the recommendations of the NICE guidance into conflict with some sections and recommendations TB strategy.	Thank you for your comment. The preferred unit of effectiveness in the NICE reference-case for economic evaluations is Quality Adjusted Life Years (QALYs), with cost-effectiveness expressed as a cost-per-QALY figure. The Pareek, 2011 paper used other metricsf cost-effectiveness i.e.cases prevented, which are not comparable across health domains and fail to take into account important factors such as patient quality of life. It is also important to consider that the Warwick Evidence model represents the first time a transmission dynamic model has been used in the context of a cost-effectiveness analysis of LTBI diagnostic tests, and that when the number of secondary cases are set to zero the results of the model fall broadly in line with other published studies. This lends weight to the importance of utilising

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					transmission dynamic modelling in the subgroups considered. The Pareek paper is also concerned with large scale screening of all people from high incidence countries (at varying thresholds of incidence) whereas the work undertaken by Warwick evidence is concerned with opportunistic case-finding, it is therefore difficult and probably inappropriate to compare the cost implications of these two different studies.
Birmingham & Solihull TB Service	Full	89	16	Barriers to implementation – complex screening protocols and reliance on two stage tests for latent TB may impact on implementation.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
Birmingham & Solihull TB Service	Full	89	26	Would another useful research topic include looking at increasing treatment completion rates for latent TB?	Thank you for your comment. This is included under the following research recommendation: "Strategies to improve treatment completion in those infected with latent TB infection and at risk of non-adherence. Is Directly Observed Preventative Therapy (DOPT) and other support strategies effective and cost effective compared self-administered therapy in promoting the uptake of and adherence to treatment in those populations who should be offered DOT as part of enhanced case management for latent TB?"

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	105	9	Where did the figure of 10-15 % come from? The Cochrane review said 1.6% after 2-5 years and current models indicate a similar percentage thereafter. The recent surveys of IGRA positivity and development of TB are similarly less convincing for this high percentage.	Thank you for your comment. The text has now been amended to: "However, ~~in 10–15%~~**in a small proportion** of infected individuals **(approximately 1.6%)** clinical disease may develop at some point in their lives." This represents the most up-to-date network meta-analysis of randomised control trials and evidence synthesis available. Progression to active TB is varied probabilistically in the model to account for parameter uncertainty. We consider progression rates in untreated individuals ranging from 1/15x to 15x the base case progression rate of 0.001955. The upper end of this range exceeds the progression rates estimated for HIV-positive individuals by Horsburgh et al. (2010). As progression rates increase, so does the cost-effectiveness of treating individuals with LTBI. Please see section 6.2 of Appendix I for more information.
British Thoracic Society	Full	105	9	Please substantiate progression figure of 10-15 %. The Cochrane review said 1.6% after 2-5 years and current models indicate a similar percentage thereafter. The recent surveys of IGRA positivity and development of TB are similarly less convincing for this high percentage. The evidence base for this needs stating.	Thank you for your comment. The text has now been amended to: "However, ~~in 10–15%~~**in a small proportion** of infected individuals **(approximately 1.6%)** clinical disease may develop at some point in their lives." This represents the most up-to-date network meta-analysis of randomised control trials and

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					evidence synthesis available. Progression to active TB is varied probabilistically in the model to account for parameter uncertainty. We consider progression rates in untreated individuals ranging from 1/15x to 15x the base case progression rate of 0.001955. The upper end of this range exceeds the progression rates estimated for HIV-positive individuals by Horsburgh et al. (2010). As progression rates increase, so does the cost-effectiveness of treating individuals with LTBI. Please see section 6.2 of Appendix I for more information.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	105	16 26	No mention of the cut-off differences within US and European guidelines and no indication why the diameter should be reduced to 5 mm for all tested. Slide re reduced PPD with anti-TNF etc.	Thank you for your comment. This systematic review and economic analysis, including transmission dynamic model, provides a synthesis of evidence which stands apart from these other guideline documents. Given the lack of existing substantive evidence on which to recommend a 6 mm induration cut off, the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the group noted that reliably measuring the difference between 5 mm and 6 mm in practice was

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					extremely difficult. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that

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					TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).
British Thoracic Society	Full	105	16 26	No mention of the cut-off differences within US and European guidelines and no indication why the diameter should be reduced to 5 mm for all tested. Slide re reduced PPD with anti-TNF etc.	Thank you for your comment. This systematic review and economic analysis, including transmission dynamic model, provides a synthesis of evidence which stands apart from these other guideline documents. Thank you for your comment. This systematic review and economic analysis, including transmission dynamic model, provides a synthesis of evidence which stands apart from these other guideline documents. Given the lack of existing substantive evidence on which to recommend a 6 mm induration cut off, the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					group noted that reliably measuring the difference between 5 mm and 6 mm in practice was extremely difficult. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the

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					most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).
Homerton Hospital NHS Foundation Trust (HHFT)	Full	105	29	TB7.7 not in RD1 and therefore potentially in some BCG vaccines; this antigen is to be removed from the QFN-platinum	Thank you for highlighting this. This has now been amended and the text now reads as follows; "More recently, selective immunological tests – IGRAs – have been developed using the tuberculosis antigens 'early secretion antigen target 6′ (ESAT-6) and 'culture filtrate protein 10′ (CFP-10), as well as tb7.7 in the QuantiFERON Gold and Gold in Tube assays, which are not present in BCG, and are found in only a few species of environmental mycobacteria."
British Thoracic Society	Full	105	29	TB7.7 not in RD1 and therefore potentially in some BCG vaccines; this antigen is to be removed from the QFN-platinum	Thank you for highlighting this. This has now been amended and the text now reads as follows; "More recently, selective immunological tests – IGRAs – have been developed using the tuberculosis antigens 'early secretion antigen target 6′ (ESAT-6) and 'culture filtrate protein 10′ (CFP-10), as well as tb7.7 in the QuantiFERON

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Gold and Gold in Tube assays, which are not present in BCG, and are found in only a few species of environmental mycobacteria."
Homerton Hospital NHS Foundation Trust (HHFT)	Full	108	40	Recent evidence from 3 papers not included. Needs immediate update before publication, especially for positive predictive values.	Thank you for this comment. Without the specific references it is difficult to comment further as to why this evidence was not included.
British Thoracic Society	Full	108	40	Recent evidence from 3 papers not included. Needs immediate update before publication, especially for positive predictive values.	Thank you for this comment. Without the specific references it is difficult to comment further as to why this evidence was not included.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	114	1	No clear understanding of role of pre-employment screening regarding subsequent claims against NHS of poor infection control. Variability of PPD means that IGRA given more credence as more objective.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated, as was the case with the recommendations on occupational health measures to prevent the transmission of TB in the workplace. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not,

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					therefore, open for comment.
British Thoracic Society	Full	114	1	There needs to be more clarity of the role of pre-employment screening regarding subsequent claims against NHS of poor infection control. Variability of PPD means that IGRA given more credence as more objective. However there is also emerging data on the reversion phenomena in US healthcare settings which need factoring in and that a repeat may be of value probability setting.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated, as was the case with the recommendations on occupational health measures to prevent the transmission of TB in the workplace. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	118	16 17	Need to update IGRA test accuracy with more recent large surveys: Zellweger et al. AJRCCM 2015; 191: 1176; Dabielsen et al. Dan Med J 2014; 61: A4856; Saunders et al. IJTLD 2014; 18: 640; King et al 2015 AJRCCM; epub; Sloot et al AJRCCM 2014; 190: 1044.	Thank you for your comment and for forwarding these references, the publication of which post-dates the cut-off date for the searches undertaken by Warwick Evidence. The authors had a look at them to determine if they would add to the existing evidence. It appears that none would meet the eligibility criteria for the review; see

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					reasons below. Risk of Tuberculosis after Recent Exposure. A 10-Year Follow-up Study of Contacts in Amsterdam Rosa Sloot et al., 2014 (Unclear if authors compared IGRA vs TST) Risk assessment of tuberculosis in contacts by interferon-γ release assays (IGRAs) Zellweger et al., 2015 (Contacts and does not compare IGRA with TST) An interferon-gamma release assay test performs well in routine screening for tuberculosis Danielsen et al., 2014 (No comparison made between TST and IGRAs) Predictors of contact tracing completion and outcomes in tuberculosis: A 21-year retrospective cohort study Saunders et al., 2014 (Contact tracing) T-SPOT®.TB Interferon-Gamma Release Assay (IGRA) Performance in Healthcare Worker Screening at 19 US Hospitals King et al., 2015 (Study conducted in healthcare workers)
British Thoracic Society	Full	118	16 17	Need to update IGRA test accuracy with more recent large surveys: Zellweger et al. AJRCCM 2015; 191: 1176; Dabielsen et al. Dan Med J 2014; 61: A4856; Saunders et al. IJTLD 2014;	Thank you for your comment and for forwarding these references, the publication of which post-dates the cut-off date for the searches undertaken by Warwick Evidence. The authors had a look at

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				18: 640; King et al 2015 AJRCCM; epub; Sloot et al AJRCCM 2014; 190: 1044.	them to determine if they would add to the existing evidence. It appears that none would meet the eligibility criteria for the review; see reasons below. Risk of Tuberculosis after Recent Exposure. A 10-Year Follow-up Study of Contacts in Amsterdam Rosa Sloot et al., 2014 (Unclear if authors compared IGRA vs TST) Risk assessment of tuberculosis in contacts by interferon-γ release assays (IGRAs) Zellweger et al., 2015 (Contacts and does not compare IGRA with TST) An interferon-gamma release assay test performs well in routine screening for tuberculosis Danielsen et al., 2014 (No comparison made between TST and IGRAs) Predictors of contact tracing completion and outcomes in tuberculosis: A 21-year retrospective cohort study Saunders et al., 2014 (Contact tracing) T-SPOT®.TB Interferon-Gamma Release Assay (IGRA) Performance in Healthcare Worker Screening at 19 US Hospitals King et al., 2015 (population was not healthcare workers from high incidence countries)

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	123	15	Much of the discrepancy relates to different values for a positive Mantoux (5, 10 or 15 mm), for different quantities of tuberculin (2 IU, 10 IU, 5 TU); evidence is presented that is inconsistent with the removal of BCG vaccination in determining a positive TST in the UK	Thank you for your comment, The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses.
British Thoracic Society	Full	123	15	Much of the discrepancy relates to different values for a positive Mantoux (5, 10 or 15 mm), for different quantities of tuberculin (2 IU, 10 IU, 5 TU); evidence is presented that is inconsistent with the removal of BCG vaccination in	Thank you for your comment. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be

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				determining a positive TST in the UK	affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses.
Oxford Immunotec	Full	124	17	Why was QuantiFERON TB Gold (QFT-G) included in this analysis? It has not been available for many years. It is very different from the current QuantiFERON Gold In Tube assay:	Thank you for your comment. We included studies in the clinical effectiveness review which compares IGRA vs TST. In the cost-effectiveness analysis, to derive sensitivity and specificity of QFT-GIT in identifying LTBI that progresses to active TB, we used information on QFT-GIT only.
Oxford Immunotec	Full	126	33	The derivation of sensitivity and specificity in Table 12 are not clearly shown either in the Full	Thank you for your comment. In section 6 of Appendix H we show how this information has

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				guideline or in Appendix H. A sample calculation of both sensitivity and specificity should be given to indicate exactly how these values were obtained. Oxford Immunotec tried to meet with Paul Sutcliffe, the author of the cost model review to obtain some guidance on how these parameters were calculation but we were told that NICE did not permit him to speak with any Stakeholders.	been derived from the literature and include WinBUGS code for the children population and how it was used to derive prevalence, sensitivity and specificity.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	126	34	The idea of sensitivity implies that this will predict TB, but this itself is uncertain; these tables can only be interpreted in the light of predictive values for the different tests	Thank you for this comment. The sensitivity of the tests was derived based on people who have not been treated with anti-LTBI chemoprophylaxis and further developed active TB.
British Thoracic Society	Full	126	34	The idea of sensitivity implies that this will predict TB, but this itself is uncertain; these tables can only be interpreted in the light of predictive values for the different tests	Thank you for this comment. The sensitivity of the tests was derived based on people who have not been treated with anti-LTBI chemoprophylaxis and further developed active TB.
Oxford Immunotec	Full	126	34	Sensitivity of T-SPOT.TB assay in children is shown as 50%. How is this obtained? It might be assumed to come from Appendix H, Table 62 (Information used to derive sensitivity in the children population). However, there is no data for	Thank you for your comment. In the WinBUGS (WinBUGS is statistical software for Bayesian analysis using Markov chain Monte Carlo (MCMC) methods.) models, we also included studies that provided information on test

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				the T-SPOT.TB test in this table. Additionally in the discussions on sensitivity and specificity in children on pages 116 to 120 of Appendix H there is no mention of the T-SPOT.TB assay – only QFT and TST are discussed.	agreement between IGRAs and TST in order to estimate sensitivity and specificity of TST +ve followed by an IGRA and for simultaneous testing strategies. From this, the model was able to derive an estimate of sensitivity and specificity for T-SPOT.TB alone. Due to the lack of direct evidence on people having T-SPOT.TB positive who progress to active TB, there is larger than normal uncertainty present in the estimate of sensitivity (reflected in the large confidence interval). This is a consequence of using indirect evidence to source this parameter. for T-SPOT.TB. It should also be noted that, when looking at policy conclusions, IGRAs were treated as a class of tests, and no recommendations were made to prefer a QFT test over a T-SPOT, or vice versa. Again, as above, the lack of data on the T-SPOT.TB means that conclusions around IGRAs in this population were based mainly on data for the QFT-GIT for which evidence was available. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (with

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					a mean ICER in the PSA around £19,000 per QALY gained, compared with TST [≥5 mm] alone).
Oxford Immunotec	Full	126	34	The 95% credible interval for the sensitivity of the T-SPOT.TB test in children is 2.45 – 97.64. This is very large, showing that there can be little confidence in the value stated (50%). Also note that the credible intervals of all the tests that were used overlap each other indicating that the studies used in this analysis have not been able to discriminate between different assays. This is a weakness of the model as the data used for sensitivity was then fed into the cost effectiveness evaluations. This method of measuring sensitivity was then used to derive the recommendation for testing in children. If there is little confidence in the value for sensitivity then there can be little confidence in the result of the cost effectiveness evaluation so any results obtained from it should not be used as the basis for determining this recommendation.	The credible interval derived for T-SPOT.TB is large, and it shows considerable uncertainty in the estimate, reflecting the uncertainty present in the clinical data drawn from the systematic review. There is larger than normal uncertainty present in the estimate of sensitivity (reflected in the large confidence interval). This is a consequence of using indirect evidence to source this parameter. In the WinBUGS (WinBUGS is statistical software for Bayesian analysis using Markov chain Monte Carlo (MCMC) methods.) models, we also included studies that provided information on test agreement between IGRAs and TST in order to estimate sensitivity and specificity of TST +ve followed by an IGRA and for simultaneous testing strategies. From this, the model was able to derive an estimate of sensitivity and specificity for T-SPOT.TB alone. Due to the lack of direct evidence on people having T-SPOT.TB positive who progress to active TB, there is uncertainty present in the estimate of sensitivity for T-SPOT.TB. It should also be noted that, when looking at policy conclusions, IGRAs were treated as a class of tests, and no recommendations

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					were made to prefer a QFT test over a T-SPOT, or vice versa. Hence, conclusions on the accuracy and cost-effectiveness of IGRAs in these populations will be drawn mainly on the data from the QFT-GIT as it was the most widely used IGRA in the evidence. It is important to note that the primary results reported in our paper are all based on probabilistic simulations (10,000 Monte-Carlo replicates) which include the uncertainty in all the model parameters in the output. Again, as above, the lack of data on the T-SPOT.TB means that conclusions around IGRAs in this population were based mainly on data for the QFT-GIT for which evidence was available. The model for children suggested that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (with a mean ICER in the PSA around £19,000 per QALY gained, compared with TST [≥5 mm] alone).
Oxford Immunotec	Full	126	34	Specificity of T-SPOT.TB assay in children is shown as 77.58%. How is this obtained? It might	Thank you for your comment. In the WinBUGS (WinBUGS is statistical software for Bayesian

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				be assumed to come from Appendix H, Table 63 (Information used to derive specificity in the children population). However, there is no data for the T-SPOT.TB test in this table.	analysis using Markov chain Monte Carlo (MCMC) methods.) models, we also included studies that provided information on test agreement between IGRAs and TST in order to estimate sensitivity and specificity of TST +ve followed by an IGRA and for simultaneous testing strategies. From this, the model was able to derive an estimate of sensitivity and specificity for T-SPOT.TB alone. Hence, due to the lack of information on people having T-SPOT.TB positive and further developing active TB may account for the wide range around the sensitivity and specificity for T-SPOT.TB. The health economic analysis suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for case-finding of LTBI in children, with a 2-step testing approach using TST (≥5 mm) negative followed by QFT-GIT having a 32% probability of being cost-effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status
Oxford Immunotec	Full	126	34	The 95% credible interval for the sensitivity of the T-SPOT.TB test in immunosuppressed is shown as 35.17 – 0.9144. Presumably this should be 35.17 – 91.44. Again this is a very large range	Thank you for your comment.. The 95% credible interval for the T-SPOT.TB is 35.17 - 91.44. We will make this change in the report.

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				giving little confidence in the results of the analysis.	
Oxford Immunotec	Full	126	34	The sensitivity of the T-SPOT.TB assay in the recently arrived is shown as 70.01. How is this derived? Perhaps it comes from Appendix H. Here table 66, page 750 shows "Information required to derive sensitivity in the recently arrived population". The data for the T-SPOT.TB test is obtained from just one study (Kik et al., 2010). The data extraction and parameter calculations relating to Kik et al 2010 are shown on page 702 - 704 of Appendix H. The T-SPOT.TB sensitivity is calculated as follows: "6/8 = 75.00% (95% CI: 40.93, 92.85)". However, the value in Table 12 of the Full Guideline is 70.01%. This is not 75.00% so how is this value obtained?	Thank you for your comment. In Section 6 of Appendix H, we detailed how information from clinical studies in our three populations of interest have been used to derive prevalence, sensitivity and specificity. The WinBUGS (WinBUGS is statistical software for Bayesian analysis using Markov chain Monte Carlo (MCMC) methods.)code for recent arrivals is similar to the children population, but using sample data from the recent arrivals clinical studies.
Oxford Immunotec	Full	126	34	The 95% credible interval for the sensitivity of the T-SPOT.TB test in the recently arrived is 39.78 – 92.42. This is very large, showing that there can be little confidence in the value stated (70.01%). Also note that the credible intervals of all the tests that were used overlap each other indicating that the studies used in this analysis have not been able to discriminate between different assays. This is a weakness of the model as the data used for sensitivity was then fed into the cost effectiveness evaluations. This method of	Thank you for your comment. The economic analysis incorporates the full range of uncertainty in the distributions of parameters derived from the clinical systematic review and gives probabilistic estimates of cost-effectiveness which reflect the parameter uncertainty present in a transparent way. The cost-effectiveness analysis results show that for newly arrived migrants from high-prevalence countries, TST (≥5 mm) dominated the TST (≥5 mm) positive followed by QFT-GIT and T-SPOT.TB-alone strategies, represented

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				measuring sensitivity was then used to derive the recommendation for testing in the recently arrived. If there is little confidence in the value for sensitivity then there can be little confidence in the result of the cost effectiveness evaluation so any results obtained from it should not be used as the basis for determining this recommendation.	good value for money in comparison with QFT-GIT alone (generating extra QALYs at a cost of around £1500 each), and had a 47% probability of being the optimal option if QALYs are valued at £20,000.
Oxford Immunotec	Full	129	47	The concluding comments for children "suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for case-finding of LTBI in children" and "The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status." How is it therefore possible to produce the recommendation for children based on this methodology?	Thank you for your comment. The economic analysis incorporates the full range of uncertainty in the distributions of parameters derived from the clinical systematic review and gives probabilistic estimates of cost-effectiveness which reflect the parameter uncertainty present in a transparent way. The health economic analysis suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for case-finding of LTBI in children, with a 2-step testing approach using TST (≥5 mm) negative followed by QFT-GIT having a 32% probability of being cost-effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status. The precise relationship between BCG status and diagnostic accuracy could not be determined, and the GDG considered these uncertainties in their deliberations.

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Oxford Immunotec	Full	130	50	The concluding comments for immunosuppressed "suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for case-finding of LTBI in immunocompromised people" and "The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status." How is it therefore possible to produce the recommendation for immunocompromised people based on this methodology?	Thank you for your comment. The economic analysis incorporates the full range of uncertainty in the distributions of parameters derived from the clinical systematic review and gives probabilistic estimates of cost-effectiveness which reflect the parameter uncertainty present in a transparent way. The economic analysis suggests there is some uncertainty around the cost-effectiveness of different diagnostic tests for identifying LTBI in immunocompromised people, with a two-step testing approach using QFT-GIT followed by TST (≥5 mm) for people with negative IGRAs having a 40% probability of being cost-effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status. The precise relationship between BCG status and diagnostic accuracy could not be determined, and the GDG considered these uncertainties in their deliberations.
Oxford Immunotec	Full	131	36	The concluding comments for recent arrivals from high incidence countries "suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for the opportunistic screening of LTBI in newly arrived people from high-incidence countries" and "The analysis was based on clinical evidence with high	Thank you for this comment. The scope of this work is limited to the opportunistic screening of patients presenting at a point of care and does not cover large scale contact tracing or screening initiatives. Owing to a lack of reporting, the relationship between BCG status in these populations and the diagnostic accuracy of the

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				levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status." How is it therefore possible to produce the recommendation for recent arrivals from high incidence countries based on this methodology?	tests could not be quantitatively established from the evidence considered. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses. The economic suggests there is some uncertainty around the cost-effectiveness of different diagnostic tests for the opportunistic screening of LTBI in newly arrived people from high-incidence countries, with a single TST (≥5 mm) having a

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					47% probability of being cost effective at a QALY value of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status. The GDG considered these uncertainties when making their recommendations
Oxford Immunotec	Full	131	43	The section "Evidence to recommendations" assumes that the comparative accuracy of the various tests has been correctly determined by the cost effectiveness review (Appendix H). As has been indicated above the confidence of the determination of sensitivity and specificity is questionable so the conclusions drawn in the "Evidence to recommendations" section may also be suspect.	Thank you for your comment. The economic analysis incorporates the full range of uncertainty in the distributions of parameters derived from the clinical systematic review and gives probabilistic estimates of cost-effectiveness which reflect the parameter uncertainty present in a transparent way. The health economic analysis suggests there is considerable uncertainty around the cost-effectiveness of different diagnostic tests for case-finding of LTBI. In children, a 2-step testing approach using TST (≥5 mm) negative followed by QFT-GIT has a 32% probability of being cost-effective at a QALY value of £20,000. For immunocompromised people, a two-step testing approach using QFT-GIT followed by TST (≥5 mm) for people with negative IGRAs has a 40% probability of being cost-effective at a QALY value of £20,000. For people from high-incidence countries, a single TST (≥5 mm) has a 47% probability of being cost effective at a QALY value

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					of £20,000. The analysis was based on clinical evidence with high levels of heterogeneity and underreporting of potentially influential variables such as BCG vaccination status, and the GDG considered these uncertainties and others in making their recommendations.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	132	General	The evidence that the neonate T cell immunity "is underdeveloped" is not supported by evidence; the problem with other vaccines is the passive immunity reducing the antigen introduced by vaccination. The epidemiological "high" levels of TB are due to exposure being a key factor in the diagnosis of TB in children, i.e. a circular loop in logic.	Thank you for your comment. It has been shared with the GDG. However, they did not feel that it provided strong enough evidence from which to change the rationale for their recommendations, nor change the recommendations themselves.
British Thoracic Society	Full	132	General	The evidence that the neonate T cell immunity "is underdeveloped" is not supported by evidence; the problem with other vaccines is the passive immunity reducing the antigen introduced by vaccination. The epidemiological "high" levels of TB are due to exposure being a key factor in the diagnosis of TB in children.	Thank you for your comment. It has been shared with the Committee. However, they did not feel that it provided a strong enough basis from which to change the rationale for their recommendations, nor change the recommendations themselves, as the evidence referred to has not been cited (and therefore could not be appraised and taken into account).

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	133 138	10	Sensitivity is not the only aim, but should be compared to the potential harms of preventive treatment.	Thank you for this comment. Additional analysis has been conducted examining the relative benefits and harms of switching to a high sensitivity testing strategy in terms of additional mortality from hepatotoxicity and active TB deaths avoided. This is detailed in appendix H of the full guideline. The testing strategies that appeared to be optimal in the economic modelling presented to the GDG by Warwick Evidence were considered to be high-sensitivity, low-specificity strategies which may lead to an increased number of people being treated for LTBI when no infection is present. Given the risks of treatment, the GDG requested additional work from Warwick Evidence to examine the trade-offs in mortality risks between active TB and LTBI-treatment-induced hepatotoxicity in high-sensitivity, low-specificity versus low-sensitivity, high-specificity testing strategies. The GDG considered that rates of hepatotoxicity in children were sufficiently low as to limit this additional work to the immunocompromised and newly-arrived migrant subpopulations. The results suggested that, on average, for each 1 death from hepatitis prevented from by moving from a high-sensitivity, low-specificity strategy to a high-specificity, low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population

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					(secondary cases are not considered in this calculation). The GDG concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. It was stressed that these numbers are sensitive to the underlying prevalence of LTBI and that, at lower prevalence, a higher-specificity strategy is likely to be more important. The analysis was based on the assumption of treatment with 6 months of isoniazid; more toxic regimens may give different results.
Oxford Immunotec	Full	134	General	The "Quality of evidence" section confirms that much of the data used in the cost effectiveness review which was used to compare the tests is poor. Yet despite this lack of good data these draft recommendations show substantial changes from the 2011 guidelines.	Thank you for your comment. The Evidence to Recommendations table in section 3.1.3.5 details the deliberations made by the GDG in light of the evidence presented. The economic analysis incorporates the full range of uncertainty in the distributions of parameters derived from the clinical systematic review and gives probabilistic estimates of cost-effectiveness which reflect the parameter uncertainty present in a transparent way. This work also represents the first time a probabilistic economic model and a transmission dynamic model have been used concurrently to evaluate the optimal diagnostic strategy for high-

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					risk LTBI patients. The testing strategies that appeared to be optimal in the economic modelling presented to the GDG by Warwick Evidence were considered to be high-sensitivity, low-specificity strategies which may lead to an increased number of people being treated for LTBI when no infection is present. Given the risks of treatment, the GDG requested additional work from Warwick Evidence to examine the trade-offs in mortality risks between active TB and LTBI-treatment-induced hepatotoxicity in high-sensitivity, low-specificity versus low-sensitivity, high-specificity testing strategies. The GDG considered that rates of hepatotoxicity in children were sufficiently low as to limit this additional work to the immunocompromised and newly-arrived migrant subpopulations. The results suggested that, on average, for each 1 death from hepatitis prevented from by moving from a high-sensitivity, low-specificity strategy to a high-specificity, low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (secondary cases are not considered in this calculation). The GDG concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a

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					greater probability of false-positive diagnoses. It was stressed that these numbers are sensitive to the underlying prevalence of LTBI and that, at lower prevalence, a higher-specificity strategy is likely to be more important. The analysis was based on the assumption of treatment with 6 months of isoniazid; more toxic regimens may give different results.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	135	4	The increase of age to 65 evidence needs to be referenced	Thank you for this comment. Our systematic review, network meta-analysis, and original economic analysis suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a much greater relative risk of death from TB in those people who progress to active disease at older age. The health economic analysis suggested that the potential benefits of treatment were very much greater than the potential risks: at all ages, the expected number of TB deaths averted by treatment was at least 50 times greater than the expected number of deaths associated with treatment. In younger people receiving more effective regimens, the difference was several thousand-fold. The GDG considered these numbers and noted that, when compared with no treatment, all treatments in all age-groups were associated with a substantial net reduction in likelihood of death. Group members noted that they would not necessarily put identical weight on

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					deaths caused and averted by LTBI treatment, as clinicians have a strong impetus to minimise iatrogenic harm, and also TB deaths will occur further into the future (although the latter factor was properly reflected in the cost–utility model [see below], which estimated quality-adjusted life expectation and discounted future costs and consequences according to established practice). Nevertheless, the GDG agreed that the difference between risks and benefits was stark, and emphasised that undertreatment is likely to be associated with much greater harm than overtreatment. According to the health economic model, 6H or 3HR would lead to net health gain at a cost of less than £20,000 per QALY gained, compared with no treatment. However, 6H did not perform as well as 3HR with regard to risk of hepatotoxicity. For this reason, where hepatotoxicity is a concern – for example, pre-treatment liver function tests raised concerns, or if the person has liver disease, alcoholism or is a drug user – 3HR is the preferred treatment.
British Thoracic	Full	135	4	The increase of age to 65 evidence needs to be	Thank you for this comment. Our systematic review, network meta-analysis, and original

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Society				referenced	economic analysis suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a much greater relative risk of death from TB in those people who progress to active disease at older age. The health economic analysis suggested that the potential benefits of treatment were very much greater than the potential risks: at all ages, the expected number of TB deaths averted by treatment was at least 50 times greater than the expected number of deaths associated with treatment. In younger people receiving more effective regimens, the difference was several thousand-fold. The GDG considered these numbers and noted that, when compared with no treatment, all treatments in all age-groups were associated with a substantial net reduction in likelihood of death. Group members noted that they would not necessarily put identical weight on deaths caused and averted by LTBI treatment, as clinicians have a strong impetus to minimise iatrogenic harm, and also TB deaths will occur further into the future (although the latter factor was properly reflected in the cost–utility model [see below], which estimated quality-adjusted life expectation and discounted future costs and consequences according to established practice). Nevertheless, the GDG agreed that the difference between risks and benefits was stark, and emphasised that undertreatment is likely to be

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					associated with much greater harm than overtreatment. According to the health economic model, 6H or 3HR would lead to net health gain at a cost of less than £20,000 per QALY gained, compared with no treatment. However, 6H did not perform as well as 3HR with regard to risk of hepatotoxicity. For this reason, where hepatotoxicity is a concern – for example, pre-treatment liver function tests raised concerns, or if the person has liver disease, alcoholism or is a drug user – 3HR is the preferred treatment.
Oxford Immunotec	Full	136	7	Recommendation 2 says consider using an interferon gamma test where a Mantoux is positive or may be less reliable, for example BCG vaccinated. This is not consistent with Recommendation 14, page 138, line 8 which only suggests using an interferon gamma test if a Mantoux is unavailable. The same applies to healthcare workers in Recommendation 21 on page 139, line 8.	Thank you for your comment. Recommendation 2 refers only to children and young people, not to all populations. No change has been made.
British Society for Antimicrobial	Full	136	15	If a neonate has been in close contact with people with pulmonary TB and has not had at	Thank you for your comment. The recommendation has now been amended and

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Chemotherapy (BSAC				least 2 weeks of anti-TB treatment: Should this read; If a neonate has been in close contact with people with pulmonary TB WHO HAVE not had at least 2 weeks of anti-TB treatment:	now reads as follows; "If a neonate has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment…"
Alder Hey Children's NHS TRUST	Full	136	15	If a neonate has been in close contact with people with pulmonary TB and has not had at least 2 weeks of anti-TB treatment: Should this read; If a neonate has been in close contact with people with pulmonary TB WHO HAVE not had at least 2 weeks of anti-TB treatment:	Thank you for your comment. The recommendation has now been amended and now reads as follows; "If a neonate has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment…"
Oxford Immunotec	Full	136	20	The cut-off for Mantoux has been reduced from 6mm to 5mm. There does not appear to be any comparative data to indicate that a 5mm cut-off is 5more accurate than a 6mm cut-off - although the section cited to provide more information (section 4.1.3.4) does not appear to be correct as this section (page 185) discusses drug regimens not TST thresholds.	Thank you for your comment. We will correct the reference. Given the lack of existing substantive evidence on which to recommend a 6 mm induration cut off, the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold. There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the group noted that reliably measuring the difference

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					between 5 mm and 6 mm in practice was extremely difficult.
British Society for Antimicrobial Chemotherapy (BSAC	Full	136	26 27	"if the test for active TB is negative, continue isoniazid treatment for a total of 6 months" There is no "test" for active TB – This could say; if the ASSESSMENT for active TB is negative, continue isoniazid treatment for a total of 6 months	Thank you for your comment. This part of the recommendations have now been amended to "if this assessment for active TB is negative…"
Alder Hey Children's NHS TRUST	Full	136	27	"if the test for active TB is negative, continue isoniazid treatment for a total of 6 months" There is no "test" for active TB – This could say; if the ASSESSMENT for active TB is negative, continue isoniazid treatment for a total of 6 months	Thank you for your comment. This part of the recommendations have now been amended to "if this assessment for active TB is negative…"
British Society for Antimicrobial Chemotherapy (BSAC	Full	137	21	If the Mantoux test is positive (5 mm or larger, regardless of BCG history) This will substantially increase the number of children assessed for TB – is this included in the cost effectiveness analysis?	Thank you for your comment. Using a cut-off of 5mm in the child population as oppose to a 10mm cut-off would increase the number of children testing positive for LTBI. Both the additional costs and the potential negative health consequences associated with this increase in treatment are included in the model. The testing strategies that appeared to be optimal in the economic modelling presented to the GDG by Warwick Evidence were considered to be high-

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					sensitivity, low-specificity strategies which may lead to an increased number of people being treated for LTBI when no infection is present. Given the risks of treatment, the GDG requested additional work from Warwick Evidence to examine the trade-offs in mortality risks between active TB and LTBI-treatment-induced hepatotoxicity in high-sensitivity, low-specificity versus low-sensitivity, high-specificity testing strategies. The GDG considered that rates of hepatotoxicity in children were sufficiently low as to limit this additional work to the immunocompromised and newly-arrived migrant subpopulations. The results suggested that, on average, for each 1 death from hepatitis prevented from by moving from a high-sensitivity, low-specificity strategy to a high-specificity, low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (secondary cases are not considered in this calculation). The GDG concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. It was stressed that these numbers are sensitive to the underlying prevalence of LTBI and that, at

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					lower prevalence, a higher-specificity strategy is likely to be more important. The analysis was based on the assumption of treatment with 6 months of isoniazid; more toxic regimens may give different results.
Royal College of Nursing	Full	138	3.1.4.14	The use of Mantoux as first line to screen for latent TB in new immigrant population is at odds with recent PHE guidance around developing services for screening new migrants.	Thank you for your comment. Although the scope and methodology for the Public Health England guidance overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the PHE guidance centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
Public Health	Full	138	8	3.1.3 diagnosis of latent TB in migrants. 1) We disagree with the recommendation that	Thank you for these comments. Each is responded to below:

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England			13	suggests use of TST (Mantoux) as a primary and only diagnostic strategy for migrants based on (a) internal and external consistency, including consistency of recommendation with other large groups, such as in outbreak situations (short guideline 1.2.1.16, p27) or other under-served groups (short guideline 1.2.1.23-24, p29), (b) concerns about the limited underpinning evidence, particularly with respect to effectiveness and cost effectiveness, (c) feasibility and practicality particularly if using this strategy on a large scale (e.g. migrant screening), (d) patient acceptability and (e) ethics of unnecessary treatment of false positives. We will describe the rationale for each of these points below	
Public Health England	Full	138	8 13	a) Consistency: The recommendation is a significant deviation to previous (4)(HPA) and international (WHO) recommendations(1). In the current guideline, the recommendation of the primary testing procedure for LTBI varies significantly. 1. For contact tracing, a two stepped approach (TST□IGRA, if positive) 2. For outbreaks, prisons, substance	Thank you for these comments. The recommendations you cite reflect differences in the evidence reviewed for and the priorities inherent in the populations to which they apply. It is only in the third category of person (migrants who have recently arrived from a country with high TB prevalence) that evidence has been reviewed and new recommendations drafted for this guideline (though minor changes have been made to contact-tracing, as well, to reflect

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				abusers etc. an IGRA only approach is preferred 3. For migrants only TST is recommended. The reasons for these differences are unclear. If the reason for the outbreak recommendation (which mentions large numbers) is feasibility, the same should apply to large numbers of migrants, such as expected in the national new migrant LTBI screening programme.	evidence reviewed elsewhere). The recommendations of this guideline are not intended to apply to formal screening programme(s). Rather, they are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document. We acknowledge that the choice of test may be influenced by setting: it may be reasonable to prefer a test that can be accomplished in a single interaction in a screening programme. However, this question is beyond the scope of this guideline.
Public Health England	Full	138	8 13	b) Underlying evidence for this recommendation. In summary we feel there are major limitations of the clinical effectiveness review due to the number and limitations of underlying papers and assumptions about constructs for measuring LTBI, as well as major limitations in the cost effectiveness review due to the clinical parameters (including those from the clinical effectiveness review, the assumption of return rates for reading TST (90% is unreasonably high), and particularly around the high prices for IGRA (we currently purchase Quantiferon for about £20 less) and low prices for TST (prices are 10 years old). We will describe these limitations in detail	Thank you for this summary. Please see responses to individual points below.

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				below.	
Public Health England	Full	138	8 13	(c) Feasibility and practicality particularly if using this strategy on a large scale (e.g. migrant screening) The Collaborative TB strategy for England recommends the implementation of a primary care based systematic national LTBI testing and treatment programme for migrants. NHS England is funding this programme with £10m and it is vital to ensure success.	Thank you for this comment. It is very important to emphasise that large-scale screening initiatives are beyond the scope of this guideline. Where the Collaborative TB Strategy for England envisages a 'co-ordinated, local screening programme', the recommendations in this guideline are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document,
Public Health England	Full	138	8 13	i) As with other screening programmes, it is important to ensure that the most valid and acceptable test is administered; and this in turn will increase testing uptake. TST relies on migrants to return for reading, and an assumption of 90% return (Warwick CEA) is very optimistic (verbal information from the PREDICT study team). Any decrease in return rate will affect effectiveness and cost-effectiveness of the programme.	Thank you for this comment. The recommendations of this guideline are not intended to apply to formal screening programme(s). Rather, they are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document, The model's base-case assumption of a 94% return rate was drawn from a UK study in a setting that was directly applicable to this decision problem (Pareek et al.'s 2013 analysis of case-finding among people registered with primary care practices). In addition, these return rates are consistent with

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					what was used in CG117. In that guideline, proportion of TST results read (at first or second attempt) was 90%. The sources used for this input were Diel et al., 2006; Bothamley et al.,2002 and GDG consensus). For these reasons, the GDG was satisfied that the parameter used was an accurate reflection of reality. However, in view of stakeholders' suggestion that the figure might be optimistic, additional sensitivity analysis was undertaken to explore the model's sensitivity to this parameter. This showed that TST (≥5 mm) remains the most cost-effective strategy as long as the probability of the TST result being read is 76% or higher. The GDG agreed that return rates could be assumed to exceed this figure with a very high degree of confidence. The sensitivity analyses are detailed in an addendum to Appendix H of the full guideline, and the GDG's consideration of the issue has been expanded in the relevant LETR table (section 3.1.4.5).
Public Health England	Full	138	8 13	ii) In addition TST relies on specialist skills to ensure the correct administration and reading of the results. TB nurses have these skills, but relying on TB nurses to administer all these tests would be an expensive and inefficient way of spending resources. GP practice nurses do not	Thank you for this comment. Again, it should be emphasised that large-scale screening initiatives – in which the resource implications of providing large numbers of tests would become more pertinent – are beyond the scope of this guideline.

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				have these skills and would require a complex and expensive training programme before they can do this.	
Public Health England	Full	138	8 13	iii) It is worth noting that we have major and ongoing procurement problems with Staten Serum Institute (the TST manufacturer). Whilst TST deliveries have now been re-established, these stockouts need to be well considered and TST recommendations ideally limited to those groups where it is most useful (e.g. pre-BCG vaccination).	Thank you for this comment. The GDG was aware of this issue, which was the primary reason for the additional recommendation: 'If Mantoux testing is unavailable, offer an interferon-gamma release assay.'
Public Health England	Full	138	8 13	(d) Patient acceptability and (e) ethics of unnecessary treatment of false positives. i) A single blood test is preferable and more acceptable to most patients.	Thank you for this comment. We are unaware of evidence to support this assertion. The GDG's experience is that, while some people prefer a test that can be accomplished in a single visit, others are keen to avoid the requirement to provide a blood sample.
Public Health England	Full	138	8 13	ii) The test specificity of both IGRAs have been demonstrated significantly higher than TST, consistently across studies. A TST only recommendation for migrants with a high proportion of BCG vaccinated individuals (who may or may not remember) will risk a higher false positive rate (generated by the poorer specificity of TST) and unnecessary drug treatment. Basing treatment decisions on a test with poor specificity	Thank you for this comment. Warwick Evidence's review, which was subsequently used to parameterise their original health economic decision model, broadly confirms the finding that IGRAs are more specific than TST (especially when a 5 mm induration threshold is used for the latter). However, it also suggests that TST ≤5 mm is likely to be a more sensitive diagnostic test than any IGRA (though what is meant by

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				may result in avoidable morbidity, perhaps mortality (e.g. through hepatotoxicity). This risk is increased by the recommendation to decrease the TST positivity value to 5mm.	'sensitivity' and 'specificity' in this context is an important question, which you rightly raise below; see our response to your point 2.iii). The balance between maximising sensitivity and specificity is the core of any diagnostic review – in other words, the risks associated with false negatives and false positives need to be balanced in an evidence-based analysis. You are correct to state that the adoption of a high-sensitivity–low-specificity strategy will result in avoidable patient harm, owing to treatment-related adverse events in the raised number of false-positive cases. Critically, however, it is also true that the adoption of a low-sensitivity–high-specificity strategy will result in avoidable patient harm, because false-negative cases will go on to develop active TB that could have been prevented. It may be implicit in your comments that, due to their iatrogenic nature, we should be more assiduous in preventing the harms that are associated with the former scenario. The GDG discussed this issue, and concluded that they would not necessarily put the same weight on harms caused and harms not avoided. Nevertheless, the group concluded that evidence suggesting a high-sensitivity–low-specificity strategy (TST ≤5 mm) is associated with a net increase in quality-adjusted life expectation, when compared with strategies that might benefit from

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					higher specificity but also suffer from inferior sensitivity, was compelling. We note – and share – your particular concern about the possibility of mortality due to treatment-related hepatotoxicity. To explore stakeholder comments such as this, the risk of the most extreme consequence of this balancing of harms – that of patient mortality – was explored in additional analysis undertaken by Warwick Evidence (see addendum to appendix H). The results suggested that, for each 1 death from hepatitis prevented from by moving from a high-sensitivity–low-specificity strategy to a high-specificity–low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (secondary cases are not considered in this calculation). Following detailed consideration of all these issues, the concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. See the relevant LETR table (3.1.4.5)

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Public Health England	Full	138	8 13	More detailed appraisal of underlying evidence (Warwick review) in support of (b) 1) The review of cost-effectiveness studies for migrants includes only two studies, the CCG117 review(4) and the Pareek paper(5). The CCG117 analysis favours a two-stepped approach (TST□IGRA). However, the Pareek paper demonstrates that using a higher incidence threshold of 150 per 100,000 results in IGRA based screening being cost effective at £20,819 per case prevented.	Thank you for this comment. Pareek et al.'s (2011) study is of limited direct value, for decision-making purposes, as it does not account for positive and negative quality-of-life impacts associated with diagnosis (and subsequent treatment). The preferred unit of effectiveness in the NICE reference-case for economic evaluations is Quality Adjusted Life Years (QALYs), with cost-effectiveness expressed as a cost-per-QALY figure. Measurements of cost-effectiveness such as cases prevented are not comparable across health domains and fail to take into account important factors such as patient quality of life. It is also important to consider that the original model undertaken to support this guideline represents the first time a transmission dynamic model has been used in the context of a cost-effectiveness analysis of LTBI diagnostic tests. In sensitivity analysis, when the number of secondary cases was set to zero (i.e. the transmission dynamic component of the model was 'turned off'), the results of the model fell broadly in line with other published studies that do not model secondary transmission. This lends weight to the importance of using transmission dynamic modelling in the subgroups considered.

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Public Health England	Full	138	8 13	2) The clinical effectiveness review analyses comparative performance of TST and IGRAs based on two conceptual models – the incidence of TB (calculated with ratios of cumulative incidence ratios, R-CIRs) and ratios of diagnostic odds ratios (R-DORs). i) The R-CIRs are based on only two rather small low burden country studies, Kik (n=433-91 exclusions=342, setting: community based contact investigation with index case from high incidence country) (6) and Harstad (n=823, setting: LTBI testing of asylum seekers from high incidence countries)(7). BCG vaccination was only reported in Kik (80%, 274/342), the TST cut off used was 10 and 15mm. The pooled R-CIR is 1.57 (0.52-4.76) in favour of IGRA. The wide confidence intervals caused by small sample sizes of these limited number of studies demonstrates that these findings represents the absence of evidence that IGRA is performing significantly better than TST. The studies are very different – one is more of a screening one (Harstad) the other a contact tracing study. Taken on its own, Harstad finds a R-CIR of 2.55 with wide CIs because of sample size issues (0.57-11.39). Any evidence of TB progression or BCG impact on the latter should be viewed as very limited, and the validity of	Thank you for this comment. The report discusses in detail the poor quality of some of the evidence, and highlights the heterogeneity of studies precluding meta-analysis. The uncertainty in the parameters sourced from the clinical review is incorporated into the health economic model in a robust and transparent way - resulting in probabilistic estimates of cost-effectiveness. The impact of the parameter uncertainty on the cost-effectiveness of the interventions is further explored through a thorough sensitivity analysis as detailed in the Full Guideline and Appendix H. The comparative study referred to in your comment (11) does not match the population of interest in the inclusion/exclusion criteria for the clinical review. It should be noted that the evidence synthesis that was used to parameterise the original health economic decision model included only studies reporting direct outcome measures (i.e. longitudinal determination of TB status in people with various test results).

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				combining two such different studies has to be debated. ii) It is important to note that the other measure - R-DORs are an indirect measure based on an exposure gradient identified across different groups, considering factors such as place of birth, ethnicity and country prevalence. Here, three small size low burden country studies were identified: Lucas(8), Orlando(9) and Saracino(10). All three studies are cross sectional studies providing a snapshot of test positivity for TST and IGRA tests, the main outcome is the agreement between the tests (kappa). None of the studies provides a direct outcome measure (e.g. TB event), so any interpretation about test positivity in different groups (or difference thereof) has to be viewed with extreme caution. The pooled diagnostic odds ratio of these studies was 0.96 (0.63, 1.33). It is worth noting that there is evidence elsewhere demonstrating a better correlation of IGRA positivity with exposure risk compared with TST(11).Whilst it is certainly worth trying to use these types of studies to provide evidence for test comparisons, the interpretation of absence of any findings demonstrate the difficulty using this methodology, rather than evidence for or against test property superiority of IGRAs. iii) A common way to look at test properties of	

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				TST and the two IGRAs is to evaluate their ability to detect active TB cases. Whilst this is obviously not the same as detecting latent TB, one would expect the results to be roughly consistent with findings from the Warwick group. Here there have been a number of large and robust meta-analyses, which unambiguously demonstrated the higher specificity of the IGRAs compared to TST with comparable sensitivity(12,13). The other, and perhaps most valid way to look at this is to follow up contacts of active cases and compare TB progression rates amongst LTBI positives detected by different tests. Whilst actual progression rates in the literature to be extremely variable there is little debate about the superior specificity of IGRAs and there is some review level evidence of the superiority of IGRAs to predict progression (14).	
Public Health England	Full	138	8 13	It appears that these results have been used to inform parametrisation of the cost effectiveness model and a distribution calculated which underlies the actual analysis. The values used to define sensitivity and specificity appear to have a rather wide distribution, possibly due to the limited evidence generated from the clinical effectiveness review (see above). As the cost-effectiveness is calculated based on these inputs, the model results will be limited by its underlying evidence	Thank you for this comment. The uncertainty in the parameters sourced from the clinical review is incorporated into the health economic model in a robust and transparent way - resulting in probabilistic estimates of cost-effectiveness. The impact of the parameter uncertainty on the cost-effectiveness of the interventions is further explored through a thorough sensitivity analysis as detailed in the Full Guideline and Appendix H.

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				and would deem far from robust.	
Public Health England	Full	138	8 13	3) The cost effectiveness analysis uses a number of values to parametrise the model. i) The costs for testing appear derived from Pooran (15) who in turn took these figures from 2005/6 NHS costs for the Royal Free and Blackburn Hospitals for QuantiFERON and T-Spot.TB. The TST costs were derived from NICE (2006 and 2007). The costs were specified as QFT-GIT £48.73, T.SPOT.TB £59.57, TST £17.48. It is worth noting that these figures are 10 years old and that we were already able to secure prices of £29 for QuantiFERON in London and are aiming to achieve even lower prices (around £20) per test within the remit of a national procurement approach for the LTBI screening programme. Conversely, in keeping with an increase of labour costs (which largely determines TST pricing) we think that TST costs from 10 years ago are too low as an estimate.	Thank you for this comment. The costs obtained from Pooran et al. (2010) and CG117 were inflated to present values. These costs included kit, consumables and processing and phlebotomy. We are unaware of any more recent or accurate sources for these costs. It is unclear whether the numbers you cite represent the cost of the test alone; if so, it is unsurprising that it should be lower than the cost included in the model, which also included other elements such as staff time to administer the test and deliver results. Although we could not identify any 'better' estimates for test cost parameters, Warwick Evidence undertook a series of sensitivity analyses to explore the possible impact of any inaccuracy on model results; these are detailed in an addendum to Appendix H of the Full Guideline. Separate analyses used a cost of £29 for QFT-GIT and a cost for TST of £29. In both instances, TST ≤5 mm remained the option with the highest probability of cost effectiveness in the analysis for recently arrived migrants from countries with a high prevalence of TB. This demonstrates that the

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					costs of the tests themselves have a minor impact on the model, as they are very substantially smaller than the costs of LTBI treatment and those associated with activation of TB. Therefore, it can safely be concluded that any mis-estimation of test costs (within any plausible bounds) would not affect conclusions.
Public Health England	Full	138	8 13	ii)) TST requires two appointments and as the review correctly states requires skilled personnel. This makes the feasibility and effectiveness of LTBI testing using TST setting dependent (e.g. primary care may require more referrals and secondary care input making this more expensive and less efficacious). The model parametrisation assumes a 90% return rate for TST reading – experience with previous pilots and unpublished data demonstrates that this is unrealistically high. Conversely, IGRA blood tests have been successfully performed by routine phlebotomy services in a number of pilot areas.	Thank you for this comment. The model's base-case assumption of a 94% return rate was drawn from a UK study in a setting that was directly applicable to this decision problem (Pareek et al.'s 2013 analysis of case-finding among people registered with primary care practices). In addition, these return rates are consistent with what was used in CG117. In that guideline, proportion of TST results read (at first or second attempt) was 90%. The sources used for this input were Diel et al., 2006; Bothamley et al.,2002 and GDG consensus). For these reasons, the GDG was satisfied that the parameter used was an accurate reflection of reality. However, in view of stakeholders' suggestion that the figure might be optimistic, additional sensitivity analysis was undertaken to explore the model's sensitivity to this parameter. This showed that TST (≥5 mm) remains the most cost-effective

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					strategy as long as the probability of the TST result being read is 76% or higher. The GDG agreed that return rates could be assumed to exceed this figure with a very high degree of confidence. The sensitivity analyses are detailed in an addendum to Appendix H of the full guideline, and the GDG's consideration of the issue has been expanded in the relevant LETR table (section 3.1.4.5).
Public Health England	Full	138	8 13	iii)) Likewise the cost of adherence to LTBI treatment were taken as £677.07 from 2014 tariff We think these are slightly exaggerated costs. Required is one initial (£185) and minimum two follow up appointments (£102). E.g. £389. We were unsure whether drugs were included but if not Rifinah is £84.34 for three month course so even then only £473.34. This is below the lower bound of the sensitivity analysis.	Thank you for this comment. A breakdown of the resource use including the cost of six months of Isoniazid is presented in Appendix 17 of Appendix H in the Full Guideline.
Public Health England	Full	138	8 13	iv) The number of secondary cases from the model is referenced as taken from Pareek(5) – but he only took this to estimate his model from a reasonably old estimate here: National Collaborating Centre for Chronic Conditions. Tuberculosis: appendices. London: Royal College of Physicians, 2006.	Thank you for this comment. The GDG concluded that this was the most appropriate source of evidence for this parameter, and no better quality evidence was found in the review. The parameter was subject to sensitivity analysis; see Table 43 of Appendix H.

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				v) The recommendations and the Warwick model appears to be summarising the evidence from different migrant populations, treating 'migrants' as one group. In reality, the term 'migrants' describes highly heterogeneous populations. Any progression or secondary transmission estimate should account for these differences. For example, refugees (and possibly asylum seekers) would be expected to have high progression rates, for settled migrants they would depend on their risk based on country of origin, time of stay in the UK, age and other risk factors. Pareek and colleagues therefore established a WHO incidence estimate threshold of 150 per 100,000 in their country of origin as the best compromise of cost effectiveness and number of LTRBI positives (and thereby prevented cases)(5). It is unclear, but appears that NICE reviews were based on lower threshold levels (e.g. 40 per 100,000)	Thank you for this comment. The migrants considered in the report were defined as newly arrived migrants. Settled migrants and any large scale screening initiatives were beyond the scope of this analysis, which is designed to evaluate the most cost effective diagnostic test for opportunistic case-finding of patients presenting to care. The decision to use a threshold of 40 per 100,000 to define high prevalence country of origin was chosen as it was in line with previous NICE guidance on screening recently arrived migrants (See NICE CG117), which the GDG confirmed as appropriate. This is discussed in section 1.5 and 1.7 of appendix H. We believe that the study you cite by Pareek et al. is of limited direct value, for decision-making purposes, as it does not account for positive and negative quality-of-life impacts associated with diagnosis (and subsequent treatment). The preferred unit of effectiveness in the NICE reference-case for economic evaluations is Quality Adjusted Life Years (QALYs), with cost-effectiveness expressed as a cost-per-QALY figure. Measurements of cost-effectiveness such as cases prevented are not comparable across health domains and fail to take into account important factors such as patient quality of life.

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				4) We would therefore fully agree with the authors' conclusions that "The evidence relied mostly on indirect measures of association derived between the test results (i.e., TST and/or IGRAs) and constructs of validity for LTBI (e.g., duration/proximity of exposure to a person with active TB, risk of development of active TB)." [Warwick review, p320] and "Although we appraised and summarised a large amount of evidence, much of it was inconclusive due to unexplained heterogeneity in the effect estimates, poor reporting, missing data, and great uncertainty around the effect estimates for the association between test results and the constructs of validity for LTBI." [ibid, p320] and that therefore "Findings should be viewed by clinicians and policy makers cautiously because of the limited evidence, the lack of a gold standard diagnostic test and the assumptions made. Clinicians should be mindful of the variation in performance of the different testing strategies amongst different populations." [ibid,p33]	Thank you for this comment. The report discusses in detail the poor quality of some of the evidence, and highlights the heterogeneity of studies precluding meta-analysis. The uncertainty in the parameters sourced from the clinical review is incorporated into the health economic model in a robust and transparent way - resulting in probabilistic estimates of cost-effectiveness. The impact of the parameter uncertainty on the cost-effectiveness of the interventions is further explored through a thorough sensitivity analysis as detailed in the Full Guideline and Appendix H.
Public Health England	Full	138	8 13	5) Given the considerable feasibility, resource and even ethical implications of a large scale shift to LTBI testing with TST, recommendations should reflect these uncertainties by providing the clinician or programme with the flexibility required.	Thank you for this comment. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is,

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				In particular the large scale settings, such as outbreaks or new large scale LTBI screening programme should be exempted from any TST recommendations. Even if a dual testing strategy would be slightly more cost effective, in reality and when testing large numbers of people (i.e. in an outbreak or screening scenario) this is impractical, leads to higher loss to follow up, increased treatment of false positive persons (including the risk of serous hepatotoxicity) and may lead to higher costs in treatment of these cases. This would be aggravated by two things: the high BCG vaccination rate in the target population and the potential increase of the upper age limit leading to an increase in cases who have been hospitalised or worse with severe hepatotoxicity.	their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). We agree with you that implementing a TST-based strategy may cause additional issues in 'large scale settings' and the guideline's recommendations reflect this. The development of a 'new large scale LTBI screening programme' is beyond the scope of this guideline – recommendations relating to newly arrived migrants are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document, As regards 'outbreaks', recommendation 1.2.3.6 states, 'In an incident situation when large numbers of people may need to be screened, consider a single interferon-gamma release assay for people aged 18–65 years'. Please see comments above with regard to the GDG's views on the balance of benefits and harms associated with false-positive and false-

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					negative diagnoses.
Public Health England	Full	138	8 13	References 1. World Health Organization. Guidelines on the management of latent tuberculosis infection [Internet]. 2014. Available from: http://www.who.int/tb/publications/ltbi_document_page/en/ 2. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of Latent Tuberculosis Infection: A Network Meta-analysis. Ann Intern Med. 2014 Sep 16;161(6):419–28. 3. Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013;7:CD007545. 4. NICE. Tuberculosis - full guideline [Internet]. NICE. 2011 [cited 2012 Apr 20]. Available from: http://www.nice.org.uk/nicemedia/live/13422/53638/53638.pdf 5. Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, et al. Screening of immigrants in the UK for imported latent	Thank you for providing these references with your comments.

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				tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis. 2011 Jun;11(6):435–44. 6. Kik SV, Franken WPJ, Mensen M, Cobelens FGJ, Kamphorst M, Arend SM, et al. Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts. Eur Respir J Off J Eur Soc Clin Respir Physiol. 2010 Jun;35(6):1346–53. 7. Harstad I, Winje BA, Heldal E, Oftung F, Jacobsen GW. Predictive values of QuantiFERON-TB Gold testing in screening for tuberculosis disease in asylum seekers. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2010 Sep;14(9):1209–11. 8. Lucas M, Nicol P, McKinnon E, Whidborne R, Lucas A, Thambiran A, et al. A prospective large-scale study of methods for the detection of latent Mycobacterium tuberculosis infection in refugee children. Thorax. 2010 May;65(5):442–8. 9. Orlando G, Merli S, Cordier L, Mazza F, Casazza G, Villa AM, et al. Interferon-gamma releasing assay versus tuberculin skin testing for latent tuberculosis infection in targeted screening programs for high risk immigrants. Infection. 2010 Jun;38(3):195–204.	

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				10. Saracino A, Scotto G, Fornabaio C, Martinelli D, Faleo G, Cibelli D, et al. QuantiFERON-TB Gold In-Tube test (QFT-GIT) for the screening of latent tuberculosis in recent immigrants to Italy. New Microbiol. 2009 Oct;32(4):369–76. 11. Arend SM, Thijsen SFT, Leyten EMS, Bouwman JJM, Franken WPJ, Koster BFPJ, et al. Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. Am J Respir Crit Care Med. 2007 Mar 15;175(6):618–27. 12. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-γ release assays for detecting active tb: A metaanalysis. Chest. 2010 Apr 1;137(4):952–68. 13. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med. 2008 Aug 5;149(3):177–84. 14. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-gamma release assays and tuberculin skin testing for predicting progression from latent TB infection to disease state: a meta-analysis. Chest [Internet]. 2012 Apr	

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				5 [cited 2012 Apr 26]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22490872 15. Pooran A, Booth H, Miller RF, Scott G, Badri M, Huggett JF, et al. Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. BMC Pulm Med. 2010 Feb 22;10(1):7.	
Homerton Hospital NHS Foundation Trust (HHFT)	Full	141	1	1.79 not 1/79	Thank you for highlighting this. The error has now been corrected.
British Thoracic Society	Full	141	1	1.79 not 1/79	Thank you for highlighting this. The error has now been corrected.
Abbott Molecular	Full	142	14 18	Abbott would like to mention that its assays, Abbott RealT*im*e MTB and Abbott RealT*im*e MTB RIF/INH are commercially available assays for qualitative detection and drug resistance of MTB, respectively **<u>Please find enclosed copy of the package</u>**	Thank you for your comment.

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				insert for the Abbott RealTi*me* MTB and Abbott RealTi*me* MTB RIF/INH. Not for distribution	
Homerton Hospital NHS Foundation Trust (HHFT)	Full	142	35 38	Adenosine deaminase tests have no role in the diagnosis of TB (they merely measure the number abd proportion of lymphocytes). WHO review has covered this extensively see also 179, 18 Table all on page 180, re pleural and CSF 181, 5 re pericardial 181,10 re GI specimens (I guess only ascitic fluid)	Thank you for your comment. As per the NICE guidelines manual, the evidence for ADA was reviewed objectively, and given consideration equal to that available for other tests and – where the committee concluded that the evidence was strong enough – recommendations were made on its use. Although the World Health Organisation has similar methods to those used by NICE, and it is likely that similar evidence was reviewed, decisions made both within the reviewing and by the NICE GDG may be different for decision made by the WHO. The decision-making by the WHO committee reflect the fact that the World Health Organisation considered the use of such tests internationally, across a broader range of settings with more diverse resource and staffing availability, as well as different training capacities, whereas NICE considers their use solely for use in England and Wales. Where recommended, NICE recommends the use of ADAs as one part of a battery of investigations, and never as a standalone test that would be interpreted in isolation from the

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					other tests recommended. The rationales for ADAs given in the guideline are as follows: *Pleural TB* Considerable evidence (65 evaluations) investigating the use of ADAs in the diagnosis of pleural tuberculosis was identified. Although the group noted the low quality of the evidence, as well as the between-study variation in reference standard used and the estimates of effect for both sensitivity and specificity, they also noted that when the estimates were pooled the test performed well. The GDG was generally unfamiliar with this test and had very little experience of its use in practice, but they could not ignore the volume of evidence and the accuracy achieved by the test. They noted that most of the study's conducted the test using Giusti's method, and that practice should reflect this. They also noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability is consistently met. The GDG did, however, note that adenosine deaminase is not a tuberculosis-specific marker, rather it is a general marker for immune reactions occurring within lymphocytes and its presence could also be suggestive of other infections. It is

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					particularly important that other conditions, such as sarcoidosis (which in addition to being associated with raised adenosine deaminase levels has a similar clinical and radiological profile), be ruled out. Therefore the group were not comfortable in recommending its use in the absence of other tests, nor did they feel that its use should necessarily be routine. *CNS TB* The group also noted that ADAs performed well in the diagnosis of tuberculous meningitis, with a threshold for test interpretation of 4 U/l achieving good sensitivity. The group concluded that this test may be particularly useful, therefore in confirming negative results provided by other tests. It is important to avoid false negative results in the diagnosis of CNS tuberculosis given the severe consequences of missing a diagnosis. *GI TB* Having considered the evidence for the use of ADAs, the GDG concluded that the high pooled sensitivity 94.9% (95% CI 89.7 to 97.5%) and specificity 96.2% (95% CI 93.9 to 97.7%) was good grounds on which to recommend the use of ADAs in the diagnosis of gastrointestinal tuberculosis, although the evidence base included a number of case-control studies. The group

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					noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability was consistently met and that practice should reflect this. *Pericardial TB* On reviewing the evidence for ADAs, the group noted that at 88% (95% CI 82 to 91%) the pooled sensitivity across the 5 studies was considerably above the threshold for acceptability. The group concluded that this was sufficient justification for adding this test to the diagnostic pathway for pericardial tuberculosis as well.
British Thoracic Society	Full	142	35 38	Adenosine deaminase tests have no role in the diagnosis of TB (they merely measure the number and proportion of lymphocytes). WHO review has covered this extensively see also 179, 18 Table all on page 180, re pleural and CSF 181, 5 re pericardial 181,10 re GI specimens (I guess only ascitic fluid)	Thank you for your comment. As per the NICE guidelines manual, the evidence for ADA was reviewed objectively, and given consideration equal to that available for other tests and – where the committee concluded that the evidence was strong enough – recommendations were made on its use. Although the World Health Organisation has similar methods to those used by NICE, and it is likely that similar evidence was reviewed, decisions made both within the reviewing and by the NICE committee may be different for decision made by the WHO. The decision-making by the WHO committee

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					reflect the fact that the World Health Organisation considered the use of such tests internationally, across a broader range of settings with more diverse resource and staffing availability, as well as different training capacities, whereas NICE considers their use solely for use in England and Wales. Where recommended, NICE recommends the use of ADAs as one part of a battery of investigations, and never as a standalone test that would be interpreted in isolation from the other tests recommended. The rationales for ADAs given in the guideline are as follows: *Pleural TB* Considerable evidence (65 evaluations) investigating the use of ADAs in the diagnosis of pleural tuberculosis was identified. Although the group noted the low quality of the evidence, as well as the between-study variation in reference standard used and the estimates of effect for both sensitivity and specificity, they also noted that when the estimates were pooled the test performed well. The GDG was generally unfamiliar with this test and had very little experience of its use in practice, but they could not ignore the volume of evidence and the accuracy achieved by the test. They noted that most of the study's conducted the test using

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					Giusti's method, and that practice should reflect this. They also noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability is consistently met. The GDG did, however, note that adenosine deaminase is not a tuberculosis-specific marker, rather it is a general marker for immune reactions occurring within lymphocytes and its presence could also be suggestive of other infections. It is particularly important that other conditions, such as sarcoidosis (which in addition to being associated with raised adenosine deaminase levels has a similar clinical and radiological profile), be ruled out. Therefore the group were not comfortable in recommending its use in the absence of other tests, nor did they feel that its use should necessarily be routine. *CNS TB* The group also noted that ADAs performed well in the diagnosis of tuberculous meningitis, with a threshold for test interpretation of 4 U/l achieving good sensitivity. The group concluded that this test may be particularly useful, therefore in confirming negative results provided by other tests. It is important to avoid false negative results in the diagnosis of CNS tuberculosis given the severe consequences of missing a diagnosis.

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					GI TB Having considered the evidence for the use of ADAs, the GDG concluded that the high pooled sensitivity 94.9% (95% CI 89.7 to 97.5%) and specificity 96.2% (95% CI 93.9 to 97.7%) was good grounds on which to recommend the use of ADAs in the diagnosis of gastrointestinal tuberculosis, although the evidence base included a number of case-control studies. The group noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability was consistently met and that practice should reflect this. *Pericardial TB* On reviewing the evidence for ADAs, the group noted that at 88% (95% CI 82 to 91%) the pooled sensitivity across the 5 studies was considerably above the threshold for acceptability. The group concluded that this was sufficient justification for adding this test to the diagnostic pathway for pericardial tuberculosis as well.
British Thoracic Society	Full	149	General	GDG also noted that a chest x-ray may also show signs of past infection and therefore TB cannot be diagnosed with certainty from a chest x-ray alone. A CT thorax should be mentioned to differentiate between active and old TB	Thank you for your comment. The GDG agreed that a CT thorax can be a useful diagnostic tool and it has now been included in the recommendation.

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	155	2	replace "without" with "whilst" so ensuring that every effort is made to obtain material for culture	Thank you for your comment. This changes the meaning of the recommendation. The GDG feel their original recommendation should remain. Obtaining material for culture "should be before starting treatment if possible, or, failing that, within 7 days of starting treatment in people with life-threatening disease." However, if a person is symptomatic, treatment should be started without waiting for the *results* of the culture.
British Thoracic Society	Full	155	2	replace "without" with "whilst" so ensuring that every effort is made to obtain material for culture	Thank you for your comment. This changes the meaning of the recommendation. The GDG feel their original recommendation should remain. Obtaining material for culture "should be before starting treatment if possible, or, failing that, within 7 days of starting treatment in people with life-threatening disease." However, if a person is symptomatic, treatment should be started without waiting for the *results* of the culture.
British Society for Antimicrobial Chemotherapy (BSAC	Full	155	6 7	Take a posterior-anterior chest X-ray; do further diagnostic investigations (as detailed below and summarised in table 1) if chest X-ray appearances suggest TB. This only applies to Adults as Children will mostly have AP CXR.	Thank you for your comment The GDG discussed the available options and concluded that it was better not to specify the type of chest X-ray as in practice, clinicians would order a "chest X-ray", leaving the radiologist to determine the type.

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Alder Hey Children's NHS TRUST	Full	155	6 7	Take a posterior-anterior chest X-ray; do further diagnostic investigations (as detailed below and summarised in table 1) if chest X-ray appearances suggest TB.	Thank you for your comment. The GDG discussed the available options and concluded that it was better not to specify the type of chest X-ray. In practice, clinicians would order a "chest X-ray", leaving the radiologist to determine the type.
British Thoracic Society	Full	179	General	Diagnosis of pleural TB add blind pleural biopsy and bronchoscopy / BAL useful as there is some evidence in approximately 30% of pleural disease that there is parenchymal disease as well. ADA studies small and mostly observational, would not recommend for routine use	Thank you for your comment. Pleural biopsy has been added to the recommendations. As per the NICE guidelines manual, the evidence for ADA was reviewed objectively, and given consideration equal to that available for other tests and – where the committee concluded that the evidence was strong enough – recommendations were made on its use. Although the World Health Organisation has similar methods to those used by NICE, and it is likely that similar evidence was reviewed, decisions made both within the reviewing and by the NICE committee may be different for decision made by the WHO. The decision-making by the WHO committee reflect the fact that the World Health Organisation considered the use of such tests internationally, across a broader range of settings with more diverse resource and staffing availability, as well as different training capacities, whereas NICE

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					considers their use solely for use in England and Wales. Where recommended, NICE recommends the use of ADAs as one part of a battery of investigations, and never as a standalone test that would be interpreted in isolation from the other tests recommended. The rationales for ADAs given in the guideline are as follows: *Pleural TB* Considerable evidence (65 evaluations) investigating the use of ADAs in the diagnosis of pleural tuberculosis was identified. Although the group noted the low quality of the evidence, as well as the between-study variation in reference standard used and the estimates of effect for both sensitivity and specificity, they also noted that when the estimates were pooled the test performed well. The GDG was generally unfamiliar with this test and had very little experience of its use in practice, but they could not ignore the volume of evidence and the accuracy achieved by the test. They noted that most of the study's conducted the test using Giusti's method, and that practice should reflect this. They also noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability is consistently met.

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					The GDG did, however, note that adenosine deaminase is not a tuberculosis-specific marker, rather it is a general marker for immune reactions occurring within lymphocytes and its presence could also be suggestive of other infections. It is particularly important that other conditions, such as sarcoidosis (which in addition to being associated with raised adenosine deaminase levels has a similar clinical and radiological profile), be ruled out. Therefore the group were not comfortable in recommending its use in the absence of other tests, nor did they feel that its use should necessarily be routine. *CNS TB* The group also noted that ADAs performed well in the diagnosis of tuberculous meningitis, with a threshold for test interpretation of 4 U/l achieving good sensitivity. The group concluded that this test may be particularly useful, therefore in confirming negative results provided by other tests. It is important to avoid false negative results in the diagnosis of CNS tuberculosis given the severe consequences of missing a diagnosis. *GI TB* Having considered the evidence for the use of ADAs, the GDG concluded that the high pooled sensitivity 94.9% (95% CI 89.7 to 97.5%) and

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					specificity 96.2% (95% CI 93.9 to 97.7%) was good grounds on which to recommend the use of ADAs in the diagnosis of gastrointestinal tuberculosis, although the evidence base included a number of case-control studies. The group noted that at thresholds for test interpretation above 30 U/l, the threshold for test accuracy acceptability was consistently met and that practice should reflect this. *Pericardial TB* On reviewing the evidence for ADAs, the group noted that at 88% (95% CI 82 to 91%) the pooled sensitivity across the 5 studies was considerably above the threshold for acceptability. The group concluded that this was sufficient justification for adding this test to the diagnostic pathway for pericardial tuberculosis as well.
British Society for Antimicrobial Chemotherapy (BSAC	Full	179	9 10	Offer all patients presenting with extrapulmonary TB a chest posterior-anterior X-ray This only applies to Adults as Children will mostly have AP CXR.	Thank you for highlighting this. The Committee discussed the available options and concluded that it was better not to specify the type of chest X-ray. In practice, clinicians would order a "chest X-ray", leaving the radiologist to determine the type.
Alder Hey Children's	Full	179	9 10	Offer all patients presenting with extrapulmonary TB a chest posterior-anterior X-ray. This only applies to Adults as Children will mostly have AP	Thank you for highlighting this. The Committee discussed the available options and concluded that it was better not to specify the type of chest

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NHS TRUST				CXR.	X-ray. In practice, clinicians would order a "chest X-ray", leaving the radiologist to determine the type.
British Thoracic Society	Full	182	13	Disseminated TB consider adding NAAT for bone marrow examination	Thank you for your comment. However, no evidence meeting the inclusion criteria specified within the review protocols was identified for the use of NAATs on bone marrow. The Committee therefore did not feel able to recommend these tests on these specimens, particularly given the concerns raised by stakeholders elsewhere with regards to the resource implications of increasing the recommended applications for NAATs. They also concluded that these would – theoretically – only be useful in certain patients.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	186	1	Doses in children not changed despite evidence from pharmacokinetic studies that doses should be increased	Thank you for your comment. Prescribers should refer to the British National Formulary for Children for dosing guidance.
British Thoracic Society	Full	186	1	Doses in children not changed despite evidence from pharmacokinetic studies that doses should be increased	Thank you for your comment. Prescribers should refer to the British National Formulary for Children for dosing guidance.
British Thoracic	Full	186	1	Doses in children not changed despite evidence from pharmacokinetic studies that doses should	Thank you for your comment. Prescribers should refer to the British National Formulary for Children

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Society				be increased	for dosing guidance.
Alder Hey Children's NHS TRUST	Full	186	19	Recommendation 4.1.5 Use fixed-dose combination tablets as part of any TB treatment regimen. If this guidance recommends that drug components of the combination products may need to be supplemented in children, this needs be made clear. Getting small children to swallow lots of tablets is difficult, and our clinicians prefer to use the combination products alone. The problem that this presents is described in the manufacturer's SPC for Rifater "the ratio of the three drugs in Rifater may not be appropriate in children (eg higher mg/kg doses of INH are usually given in children than in adults). Rifater can be used only in special cases, after careful consideration of the mg/kg dose of each component." Our clinicians balance the risk of underdosing some components against likely poor compliance with a more complex regimen, and use the combination product alone which would result in lower mg/kg doses in some cases. It would be good if the NICE could provide some guidance on best practice on this matter.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. The use of combination formulations for any drug-susceptible or drug-resistant disease was explicitly listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.

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British Infection Association	Full	204	General	suggested additional recommendation: NHSE should work with PHE to develop an expert consultative service for clinicians (similar to Imported Fever Service). this would go beyond the recommendation in para 204 which is targeted at MDR TB. It should be available to advise on wider diagnostic and management conundrums with TB. Furthermore, it would make sense if the service were national rather than regional as recommended in line 32/3	Thank you for your comment. No evidence was reviewed for this.
British Thoracic Society	Full	208	2	IN CNS TB - 2006/11 allowed ethambutol/streptomycin/prothionamide as the 4th drug. Evidence for all 3 , but prothionamide crosses blood-brain barrier well.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. The combination of antituberculosis drugs used, except where related to drug interactions, was explicitly listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review' because it was concluded that the standard 4-drug combination was accepted practice for the majority of patients. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not,

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					therefore, open for comment.
British Thoracic Society	Full	208	9	In reality most experienced TB clinicians treat for 9-12 months in view of the risk catastrophic consequences of undertreatment – this needs rephrasing so it is clear it only relates to deformity and not other factors.	Thank you for your comment. This specifically refers to patients who do not have CNS involvement. For this population, the GDG noted the following: "The deterioration of the spine in spinal TB can often leave a patient with long term bending of the spine, fusion of vertebrae, back pain or other residual effects. Although this can be concerning for both patient and clinician, the GDG emphasised that this is not an automatic reason for extending treatment beyond 6 months, as after 6 months of treatment these residual effects are not generally the result of persistent disease. Rather, they are the continued effects of previous deterioration when the disease was still present, and should be examined and dealt with by surgery or other interventions. It was concluded that this point also highlights the importance of a multidisciplinary team in the management of patients with spinal TB. It was noted that one other possible reason for the extension of treatment beyond 6 months in the past is perhaps the idea that the penetration of drugs into the disc space is conceivably more limited than for other sites of the body due to the

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					vascularisation of this area. However, the GDG did not feel that this was a strong enough reason to recommend an extension of treatment in people with spinal TB beyond 6 months."
British Thoracic Society	Full	223	General	Use of steroids useful in patients ventilated on ITU (RCT thorax showed significant improvement compared to placebo.	Thank you for your comment. This does not fall within the scope of the guideline as it is not about the management of the TB itself.
Oxford Immunotec	Full	240	General	Fig 42 caption says "Pooled ratio of diagnostic odds ratio (R-DOR)"; however, this is a diagram of ratio of cumulative incidence ratio. The caption should be corrected.	Thank you for highlighting this. It has now been corrected.
British Thoracic Society	Full	247	29	Although rifampicin and isoniazid do not need dose adjustment, there is good pharmacokinetic indicating that pyrazinamide needs adjusting and is described in both the CDC and BTS renal guidance.	Thank you for your comment. However, this table is a summary of information in the BNF and SPCs, which NICE refers clinicians to use in their prescribing.
British Society for Antimicrobial Chemotherapy (BSAC	Full	254	1	"ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately." This contradicts the recommendation to give ethambutol to everyone with active TB. The Royal College of Ophthalmologists suggest	Thank you for your comment. Donald (2006) and the Royal College of Ophthalmologists document were not directly relevant to any of the reviews conducted for this guidance – the data presented did not consider the use of ethambutol in children *with eye disease or visual impairment*, rather they was concerned with the use of ethambutol in any child with TB (furthermore, these documents were narrative rather than a systematic reviews).

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				that children don't need any special precautions when using ethambutol (RCOphth Document reference: 2010/PROF/121) Also note INT J TUBERC LUNG DIS 10(12) :1318-1330 2006 Ethambutol Dosage for the Treatment of Children: Literature review and Recommendations . Donald PR et al. This reported that in only 2 of 3871 children (0.05%) receiving Ethambutol doses of 15-30 m/kg was Ethambutol stopped due to possible ocular toxicity; They therefore concluded that children of all ages can be given Ethambutol in daily doses of 20mg/kg (range 15-25 mglkg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern.	However, the Committee discussed this statement and agreed that the word 'caution' was too strong. They concluded that it was important that clinicians are aware of the minimal risk of visual changes associated with ethambutol in order to watch for them. Their intention was not to encourage clinicians to avoid using ethambutol in children under 5. The text has been amended to: "Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug. In very young children who are not yet able to report symptomatic visual changes accurately, ethambutol can still be used though clinicians should be alert for signs of visual change."
Alder Hey Children's NHS TRUST	Full	254	1	"ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately." This contradicts the recommendation to give ethambutol to everyone with active TB. The Royal College of Ophthalmologists suggest that children don't need any special precautions when using ethambutol (RCOphth Document	Thank you for your comment. Donald (2006) and the Royal College of Ophthalmologists document were not directly relevant to any of the reviews conducted for this guidance – the data presented did not consider the use of ethambutol in children *with eye disease or visual impairment*, rather they was concerned with the use of ethambutol in any child with TB (furthermore, these documents were narrative rather than a systematic reviews). However, the Committee discussed this statement and agreed that the word 'caution' was

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				reference: 2010/PROF/121) Also note INT J TUBERC LUNG DIS 10(12) :1318-1330 2006 Ethambutol Dosage for the Treatment of Children: Literature review and Recommendations . Donald PR et al. This reported that in only 2 of 3871 children (0.05%) receiving Ethambutol doses of 15-30 m/kg was Ethambutol stopped due to possible ocular toxicity; They therefore concluded that children of all ages can be given Ethambutol in daily doses of 20mg/kg (range 15-25 mglkg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern.	too strong. They concluded that it was important that clinicians are aware of the minimal risk of visual changes associated with ethambutol in order to watch for them. Their intention was not to encourage clinicians to avoid using ethambutol in children under 5. The text has been amended to: "Patients who cannot understand warnings about visual side effects should, if possible, be given an alternative drug. **In very young children who are not yet able to report symptomatic visual changes accurately, ethambutol can still be used though clinicians should be alert for signs of visual change.**"
Homerton Hospital NHS Foundation Trust (HHFT)	Full	255	26	No references given for rifampicin and malformations (there is human evidence against this in larger samples of safety); evidence for bleeding is again not available, but a PubMed serach reveals merely a single case report from Barcelona with free text which cannot be accessed). These statements should not be included on the grounds they might affect adherence	Thank you for your comment. These were issues raised within the SPCs for the drugs available, not as a result of the evidence review (which yielded no eligible papers). The Evidence to Recommendations text (under 'Other Considerations') now says, "The BNF and SPCs note that pregnancy is a risk factor for isoniazid-associated peripheral neuropathy, and patients who are pregnant should therefore receive prophylactic pyridoxine when taking isoniazid. Additionally, since isoniazid is excreted in breast milk, **they note that** there is a risk of neuropathy in breastfed

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					infants whose mothers are taking isoniazid; therefore they should be monitored for early signs of these effects and consideration should be given to treating the infant prophylactically with pyridoxine. **According to the SPCs,** the use of rifampicin in pregnant women in the third trimester is associated with an elevated risk of neonatal bleeding, and very high doses of rifampicin in first trimester have been associated with malformations of the foetus in animal studies **(though notably not in human studies)**. The GDG concluded that the lack of evidence, as well as the severity of the potential consequences of mismanagement, make specialist input essential in the treatment of tuberculosis in patients who are pregnant or breastfeeding."
British Thoracic Society	Full	255	26	No references given for rifampicin and malformations (there is human evidence against this in larger samples of safety); evidence for bleeding is again not available, but a PubMed serach reveals merely a single case report from Barcelona with free text which cannot be accessed). These statements should not be included on the grounds they might affect adherence	Thank you for your comment. These were issues raised within the SPCs for the drugs available, not as a result of the evidence review (which yielded no eligible papers). The Evidence to Recommendations text (under 'Other Considerations') now says, "The BNF and SPCs note that pregnancy is a risk factor for isoniazid-associated peripheral neuropathy, and patients who are pregnant should therefore receive prophylactic pyridoxine

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					when taking isoniazid. Additionally, since isoniazid is excreted in breast milk, **they note that** there is a risk of neuropathy in breastfed infants whose mothers are taking isoniazid; therefore they should be monitored for early signs of these effects and consideration should be given to treating the infant prophylactically with pyridoxine. **According to the SPCs,** the use of rifampicin in pregnant women in the third trimester is associated with an elevated risk of neonatal bleeding, and very high doses of rifampicin in first trimester have been associated with malformations of the foetus in animal studies **(though notably not in human studies)**. The GDG concluded that the lack of evidence, as well as the severity of the potential consequences of mismanagement, make specialist input essential in the treatment of tuberculosis in patients who are pregnant or breastfeeding."
Homerton Hospital NHS Foundation Trust (HHFT)	Full	260	8	This ignores the RCT evidence that all drugs can be reintroduced together at normal dose (Sharma et al CID 2010; 50: 833)	Thank you for your comment. The GDG reviewed the evidence from Sharma et al, which is included in the description of the evidence base. For example, the evidence statement reads, "Very low quality evidence from 2 randomised controlled trials in 220 people with active tuberculosis who had experienced drug-induced

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					hepatotoxicity showed sequential reintroduction of antituberculosis drugs to be associated with a lower recurrence of drug-induced hepatotoxicity than simultaneous reintroduction, though the effect was not statistically significant (OR (95% CI) = 0.44 (0.18 to 1.03)).” This pooled evidence from both available RCTs and found sequential reintroduction of drugs to be associated with a better outcome (that is, a lower incidence of hepatotoxicity), though the small number of events and patients involved meant that the effect estimate did not reach statistical significance. However, the committee combined this evidence with their own experience of managing treatment interruptions, and concluded that sequential reintroduction should be used over simultaneous reintroduction in people who have experienced drug-induced hepatotoxicity. Hepatotoxicity may be caused by many drugs, therefore sequential reintroduction can help to pinpoint which drugs are causing the problem. This rationale is stated within the Evidence to Recommendations table for this recommendation.
British Thoracic Society	Full	260	8	Re-introduction of drugs after TB treatment includes the only RCT (Sharma et al) in Appendix D9, but this evidence has not been included in the recommendations. There is a concern that the gradual introduction of drugs with lower doses will	Thank you for your comment. The GDG reviewed the evidence from Sharma et al, which is included in the description of the evidence base. For example, the evidence statement reads, “Very low quality evidence from 2 randomised

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				lead to drug-resistance, as noted by Mitchison 1998.	controlled trials in 220 people with active tuberculosis who had experienced drug-induced hepatotoxicity showed sequential reintroduction of antituberculosis drugs to be associated with a lower recurrence of drug-induced hepatotoxicity than simultaneous reintroduction, though the effect was not statistically significant (OR (95% CI) = 0.44 (0.18 to 1.03)).” This pooled evidence from both available RCTs and found sequential reintroduction of drugs to be associated with a better outcome (that is, a lower incidence of hepatotoxicity), though the small number of events and patients involved meant that the effect estimate did not reach statistical significance. However, the committee combined this evidence with their own experience of managing treatment interruptions, and concluded that sequential reintroduction should be used over simultaneous reintroduction in people who have experienced drug-induced hepatotoxicity. Hepatotoxicity may be caused by many drugs, therefore sequential reintroduction can help to pinpoint which drugs are causing the problem. This rationale is stated within the Evidence to Recommendations table for this recommendation.
Homerton Hospital NHS	Full	260	15	The severity of a cutaneous reaction should be noted , e.g. Stevens-Johnson or one that has not responded to high-dose anti-histamine and/or	Thank you for your comment. The Evidence to Recommendations text now says,

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Foundation Trust (HHFT)				steroids	"The group discussed other adverse events that can occur during antituberculosis chemotherapy and which may lead to treatment interruptions, and concluded that cutaneous reactions were also an area of concern. However, they concluded that for a treatment interruption to be justifiable, a cutaneous reaction needed to be acute and/or significant **– for example, a Stevens-Johnson reaction or one that has not responded to treatment**. Many cutaneous reactions to antituberculosis chemotherapy will not warrant an interruption to treatment."
British Thoracic Society	Full	260	15	The severity of a cutaneous reaction should be noted , e.g. Stevens-Johnson or one that has not responded to high-dose anti-histamine and/or steroids	Thank you for your comment.. The Evidence to Recommendations text now says, "The group discussed other adverse events that can occur during antituberculosis chemotherapy and which may lead to treatment interruptions, and concluded that cutaneous reactions were also an area of concern. However, they concluded that for a treatment interruption to be justifiable, a cutaneous reaction needed to be acute and/or significant **– for example, a Stevens-Johnson reaction or one that has not responded to treatment**. Many cutaneous reactions to antituberculosis chemotherapy will not warrant an interruption to treatment."

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British Thoracic Society	Full	133, 138	10	Sensitivity is not the only aim, but should be compared to the potential harms of preventive treatment.	Thank you for your comment. The testing strategies that appeared to be optimal in the economic modelling presented to the GDG by Warwick Evidence were considered to be high-sensitivity, low-specificity strategies which may lead to an increased number of people being treated for LTBI when no infection is present. Given the risks of treatment, the GDG requested additional work from Warwick Evidence to examine the trade-offs in mortality risks between active TB and LTBI-treatment-induced hepatotoxicity in high-sensitivity, low-specificity versus low-sensitivity, high-specificity testing strategies. The GDG considered that rates of hepatotoxicity in children were sufficiently low as to limit this additional work to the immunocompromised and newly-arrived migrant sub-populations. The results suggested that, on average, for each 1 death from hepatitis prevented from by moving from a high-sensitivity, low-specificity strategy to a high-specificity, low-sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (of secondary cases are not considered in this calculation). The GDG concluded that the harms associated with under-diagnosis of LTBI substantially outweighed those of over-diagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-

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					sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. It was stressed that these numbers are sensitive to the underlying prevalence of LTBI and that, at lower prevalence, a higher-specificity strategy is likely to be more important.
Oxford Immunotec	Full	275 286)	General	The model assumes that the chest x-ray and sputum examination are 100% accurate at diagnosing people who have initial active TB. This is clearly not the case. Chest x-ray sensitivity and specificity have been estimated to be 67–77% and 66–76% (Al Zahrani K et al Am J Respir Crit Care Med. 2000 and De Villiers RV et al Australasian Radiology 2004) while sputum smear microscopy is known to have a sensitivity of around 50% with sputum culture being little better. This incorrect assumption will have a major impact on the results obtained using this model, and so is another weakness of the model.	Thank you for your comment. The assumption of 100% accuracy for TST and CXR was considered appropriate in this context. A proportion of patients opportunistically screened for LTBI will present with active disease, which is assumed to be detected in the model based on a sputum-smear examination and CXR. This probability of active disease at presentation is independent of the tests used to diagnose LTBI because it happens upstream in the model from the administration of the TST or IGRA and therefore any impact on the results in terms of the optimal testing strategy will be minimal. This assumption has been used in other studies (see Kowada et al. (2013) for example) and was approved by the committee as an appropriate simplifying assumption during the development of the model.
Oxford Immunotec	Full	277	General	The model suggests that people who begin with LTBI and are not treated will develop active TB at a later point. This is confirmed on page 278 which	Thank you for your comment. In the context of this analysis, LTBI refers to that proportion of patients with LTBI who will develop active disease

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				states that secondary cases of LTBI will progress to active TB.	in the future, and therefore excludes those patients with LTBI who remain asymptomatic during their lifetimes. In the model, the probability of progression to active disease is therefore intrinsically linked to the specificity of the testing strategy and cannot be readily simplified to a single number.
Oxford Immunotec	Full	280	General	Fig 50 caption states IGRA but the data in the figure states QFT-GIT. Which is correct?	Thank you for your comment. We will make this correction to the caption. It should state 'Pathway for the QFT-GIT alone diagnostic strategy in children
Oxford Immunotec	Full	280 284	General	The pathways seem to assume that all people being tested are infected. Presumably there are other pathways for subjects who are not infected (both those who receive a correctly negative result and those that receive a false positive result). These pathways should also be shown.	Thank you for your comment. Please see Appendix 16 of Appendix H of the Full Guideline, which details an example decision-tree structure showing the pathways taken by patients who are infected/not infected by LTBI.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	286	5	Table 20; the first RCTs showed that the standard regimen 2SHE(Z)/10HE was a good treatment and therefore can be used in rifampicin monoresistance without using the more toxic and less effective regimens for MDRTB	Thank you for your comment**.** The GDG discussed the use of streptomycin-based regimen, but concluded that it was no longer part of current practice.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Thoracic Society	Full	286	5 20	Treatment of monoresistance is poorly supported by the evidence. Before rifampicin was introduced, the gold standard for treatment was 2SHEZ/10HE. This has been included in a number of RCTs which are mentioned in Appendix D8. There is no evidence to support the use of 2HZE/16HE. This was a factual error that has persisted through several editions of the guidelines and must be corrected according to the available evidence.	Thank you for your comment. The GDG discussed the use of streptomycin-based regimen, but concluded that it was no longer part of current practice. The GDG agree that there is no evidence to support the use of 2HZE/16HE and so it has not been recommended by this guidance. For all monoresistances – except for rifampicin monoresistance, which in clinical practice is considered a proxy to multidrug resistant tuberculosis and which should be managed as such – the Committee recommend rifampicin-based regimens. Rifampicin is considered to be the most potent first-line antituberculosis drug and its inclusion in the treatment of all rifampicin-susceptible disease – throughout both the initial and continuation phases – was concluded by the committee to be essential to a successful therapeutic regimen and therefore to be best practice.
British Thoracic Society	Full	286	5	Table 20; the first RCTs showed that the standard regimen 2SHE(Z)/10HE was a good treatment and therefore can be used in rifampicin monoresistance without using the more toxic and less effective regimens for MDRTB	Thank you for your comment. The GDG discussed the use of streptomycin-based regimen, but concluded that it was no longer part of current practice.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Oxford Immunotec	Full	287	General	In the first 3 lines of section 6.3.2 there is some duplication of text.	Thank you for your comment. The duplicated text has now been removed.
Oxford Immunotec	Full	287	General	The calculated sensitivity and specificity in the model represent sensitivity and specificity of detecting people with LTBI that will progress to active TB, not the sensitivity and specificity of detecting LTBI in general. While this is theoretically correct, how practical is it to identify subjects with LTBI who then progress to active TB? Because only 5 - 10% of subjects with LTBI progress to active disease in a lifetime, many thousands of people will have to be tested, not treated for LTBI but followed up for many years in order to identify sufficient subjects to accurately determine these definitions of sensitivity and specificity. The studies published to date fall well short of this methodology which explains why the 95% credible intervals are so wide. Therefore, these definitions for sensitivity and specificity should not be used.	Thank you for your comment. The guideline considers both the health economics of testing for LTBI, and also the health economics of treating patients with LTBI in light of the uncertainty around progression rates to active TB, and the relative benefits and harms to people undergoing treatment. Identifying all patients who will progress to active TB is not possible currently, but it is possible to consider the risk of progression and the uncertainty in that risk in a transparent way, as has been done in the modelling presented in the guidance.
Oxford Immunotec	Full	290	General	In 6.3.3 the 4th line says "cost for QFT-GIT" – this should be the cost of IGRAs as it refers to both QFT and the T-SPOT.TB test.	Thank you for your comment. Pooran et al. (2010) presented probabilities and cost used in their economic analysis for screening of LTBI in Table 1. From this table, we obtained a cost for QFT-GIT, and inflated using appropriate methods.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS National Services Scotland	Full	292	14-16	The majority of public health organisations do not/no longer consider nebuliser treatment to be an aerosol generating procedure (CDC, HPS, DoH/PHE,WHO).	Thank you for your comment. However, the GDG discussed this point, but concluded that caution – and therefore the stated infection control measures – was still advisable when patients are undergoing nebuliser treatment. This is because nebuliser treatment can produce droplets of respiratory secretions, which is in turn a risk factor for the transmission of infection.
Health Protection Scotland	Full	292	14 16	The majority of public health organisations do not/no longer consider nebuliser treatment to be an aerosol generating procedure (CDC, HPS, DoH/PHE,WHO).	Thank you for your comment. However, the GDG discussed this point, but concluded that caution – and therefore the stated infection control measures – was still advisable when patients are undergoing nebuliser treatment. This is because nebuliser treatment can produce droplets of respiratory secretions, which is in turn a risk factor for the transmission of infection.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	292	25	replace "respiratory" with "cough" as before	Thank you for your comment. However, the GDG concluded that 'respiratory' was more appropriate as it encompasses a potentially broader (though still useful) range of measures.
British Thoracic Society	Full	292	25	replace "respiratory" with "cough" as before	Thank you for your comment. However, the GDG concluded that 'respiratory' was more appropriate as it encompasses a potentially broader (though

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					still useful) range of measures.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	293	4	More important for the patient to cover their mouth when coughing and to wear the mask, if isolated in a negative pressure room	Thank you for your comment. However, advising patients to cover their mouth when coughing is captured within the following recommendation: "Offer people advice on simple respiratory hygiene measures." The Committee did not feel that there was sufficient justification to recommend that people wear masks at all times in negative if isolated in a negative pressure room.
British Thoracic Society	Full	293	4	More important for the patient to cover their mouth when coughing and to wear the mask, if isolated in a negative pressure room	Thank you for your comment. However, advising patients to cover their mouth when coughing is captured within the following recommendation: "Offer people advice on simple respiratory hygiene measures." The Committee did not feel that there was sufficient justification to recommend that people wear masks at all times in negative if isolated in a negative pressure room.
Homerton Hospital NHS Foundation	Full	319	General	Reference to Smith et al 2011 not on PubMed; Crofts et al 2008 not balanced against expected moratlity from age and co-morbid conditions	Thank you for your comment. Full references for all included studies are provided in section 14 of the full guideline. Smith et al. (2011) can be found in 14.1.15. The PubMed Link is:

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Trust (HHFT)					http://www.ncbi.nlm.nih.gov/pubmed/21220436. The estimate of age-specific mortality taken from Crofts et al. (2008) relates solely to the risk of TB-related death; background mortality is estimated according to standard life tables.
British Thoracic Society	Full	319	General	Reference to Smith et al 2011 not on PubMed; Crofts et al 2008 not balanced against expected moratlity from age and co-morbid conditions	Thank you for your comment. Full references for all included studies are provided in section 14 of the full guideline. Smith et al. (2011) can be found in 14.1.15. The PubMed Link is: http://www.ncbi.nlm.nih.gov/pubmed/21220436. The estimate of age-specific mortality taken from Crofts et al. (2008) relates solely to the risk of TB-related death; background mortality is estimated according to standard life tables.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	321	General	Need to use more recent data on rate of development of TB disease in those with evidence of LTBI – much lower than previously thought and therefore affecting value of preventive treatment	Thank you for your comment. This represents the most up-to-date network meta-analysis of randomised control trials and evidence synthesis available. Progression to active TB is varied probabilistically in the model to account for parameter uncertainty. We consider progression rates in untreated individuals ranging from 1/15x to 15x the base case progression rate of 0.001955. The upper end of this range exceeds the progression rates estimated for HIV-positive individuals by Horsburgh et al. (2010). As progression rates increase, so does the cost-effectiveness of treating individuals with LTBI.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Please see section 6.2 of Appendix I for more information.
British Thoracic Society	Full	321	General	Need to use more recent data on rate of development of TB disease in those with evidence of LTBI – much lower than previously thought and therefore affecting value of preventive treatment	Thank you for your comment. This represents the most up-to-date network meta-analysis of randomised control trials and evidence synthesis available. Progression to active TB is varied probabilistically in the model to account for parameter uncertainty. We consider progression rates in untreated individuals ranging from 1/15x to 15x the base case progression rate of 0.001955. The upper end of this range exceeds the progression rates estimated for HIV-positive individuals by Horsburgh et al. (2010). As progression rates increase, so does the cost-effectiveness of treating individuals with LTBI. Please see section 6.2 of Appendix I for more information.
British Thoracic Society	Full	322	21	Include patients undergoing chemotherapy	Thank you for your comment. This has now been included in the recommendation.
British	Full	322	21	Add rifampicin monotherapy if index case INH	Thank you for your comment. Although searched

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Thoracic Society				resistant or intolerant of INH	for, no evidence was identified that examined the treatment of latent TB exclusively in people in whom the infection was suspected to be drug resistant (for example, because the index case had drug resistant tuberculosis). The GDG did not, therefore, make recommendations on which regimen should be used in this population.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	324	12	TB7.7 is not in the RD1 region	Thank you for your comment. The error has now been corrected throughout the document.
British Thoracic Society	Full	324	12	TB7.7 is not in the RD1 region	Thank you for your comment. The error has now been corrected throughout the document.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	324	18 25	Varies according to previous exposure to TB/leprosy not geographical region.. This myth has been revised for at least 10 years (see contradiction on p326, line 27)	Thank you for your comment. The text has now been amended to: "Significant variations in estimates of efficacy against pulmonary TB have been shown for different BCG vaccines according to previous exposure to TB or to leprosy ~~in various geographical settings~~. ~~While a number of explanations have been put forward for this, geographical latitude seems to have a particularly important effect, accounting for~~

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					~~over 40% of the variability in efficacy. Thus nearly zero efficacy against tuberculosis in India, is contrasted with a 64% protective efficacy in people of Indian origin with the same vaccine in a higher, more temperate, latitude. Though the effect of climate on environmental mycobacteria has been suggested as the cause of the latitude effect, this has not been proven.~~"
British Thoracic Society	Full	324	18 25	Varies according to previous exposure to TB/leprosy not geographical region. This myth has been revised for at least 10 years (see contradiction on p326, line 27)	Thank you for your comment. The text has now been amended to: "Significant variations in estimates of efficacy against pulmonary TB have been shown for different BCG vaccines according to previous exposure to TB or to leprosy ~~in various geographical settings~~. ~~While a number of explanations have been put forward for this, geographical latitude seems to have a particularly important effect, accounting for over 40% of the variability in efficacy. Thus nearly zero efficacy against tuberculosis in India, is contrasted with a 64% protective efficacy in people of Indian origin with the same vaccine in a higher, more temperate, latitude. Though the effect of climate on environmental mycobacteria has been suggested as the cause of the latitude effect, this has not been proven.~~"
Homerton Hospital	Full	324	36	Duration due to environmental mycobacteria giving same effect as BCG, rather than a waning	Thank you for your comment. It has been discussed with the Committee. However, they

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NHS Foundation Trust (HHFT)				efficacy (proven by in vitro T cell antigen-stimulation tests with PPD	concluded that it should remain as it is.
British Thoracic Society	Full	324	36	Duration due to environmental mycobacteria giving same effect as BCG, rather than a waning efficacy (proven by in vitro T cell antigen-stimulation tests with PPD).	Thank you for your comment. It has been discussed with the Committee. However, they concluded that it should remain as it is.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	325	9 11	Delete sentence; BCG in systematic reviews and meta-analyses prevents primary (i.e. no pre-existing immunity to) TB, but not post-primary disease.	Thank you for your comment. We apologise, but the Analyst has not been able to identify the text referred to.
British Thoracic Society	Full	325	9 11	Delete sentence; BCG in systematic reviews and meta-analyses prevents primary (i.e. no pre-existing immunity to) TB, but not post-primary disease.	We apologise, but the Analyst has not been able to identify the text referred to.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	328	13	Comment needed on other WHO recommendation on universal vaccination where incidence > 40 per 100,000	We apologise, but the Analyst has not been able to identify the text referred to.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Thoracic Society	Full	328	13	Comment needed on other WHO recommendation on universal vaccination where incidence > 40 per 100,000	We apologise, but the Analyst has not been able to identify the text referred to.
British Thoracic Society	Full	329	25	Cost should include costs for the main forms of TB prevented, namely longterm care of patients invalided by TB meningitis	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust	Full	329	27 37	Cost should include costs for the main forms of TB prevented, namely longterm care of patients invalided by TB meningitis	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
(HHFT)					scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	335	15	If no evidence no comment and no repetition of trials of efficacy of NCG in different circumstances	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					recommendations are not, therefore, open for comment.
British Thoracic Society	Full	335	15	If no evidence no comment and no repetition of trials of efficacy of BCG in different circumstances	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust	Full	337	5	Remove geographical qualifications so end sentence after "international".	Thank you for your comment. This text has now been removed.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
(HHFT)					
British Thoracic Society	Full	337	5	Remove geographical qualifications so end sentence after "international".	Thank you for your comment. This text has now been removed.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	338	17	Discrepancy between policy to trace all contacts as being part of an at risk group and qualification that BCG will only benefit contacts of pulmonary (respiratory sic) TB	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic Society	Full	338	17	Discrepancy between policy to trace all contacts as being part of an at risk group and qualification that BCG will only benefit contacts of pulmonary	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(respiratory sic) TB	update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	357	1	This whole section on adherence misses out on the key interventions; housing for the homeless; specialist addiction services for those with addiction; adequate prison health service, with screening at time of imprisonment; access to health services for migrants for not just TB, but other illnesses such as HIV, Hep B/C, vaccinations etc which will be cost-saving measures overall	Thank you for your comment. This section relates to the evidence considered in the development of PH37. These issues are covered in section 9.2 on Adherence and treatment completion
British Thoracic Society	Full	357	1	This whole section on adherence misses out on the key interventions; housing for the homeless; specialist addiction services for those with addiction; adequate prison health service, with	Thank you for your comment. This section relates to the evidence considered in the development of PH37. These issues are covered in section 9.2 on Adherence and treatment completion

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				screening at time of imprisonment; access to health services for migrants for not just TB, but other illnesses such as HIV, Hep B/C, vaccinations etc which will be cost-saving measures overall	
Homerton Hospital NHS Foundation Trust (HHFT)	Full	392	1	This section needs a bit of common sense. Grade A evidence should be stated early on, if there is any. Comparisons should be drawn with the Int Union against TB documents, which have evidence of reducing TB incidence in countries throughout the world (WHO reports and TB control programs)	Thank you for your comment. This section relates to the evidence considered in the development of PH37. The quality of evidence is described in each evidence statement and in the accompanying evidence reviews.
British Thoracic Society	Full	392	1	This section needs clarity in terms of actual evidence Grade A evidence should be stated early on, if there is any. Comparisons should be drawn with the Int Union against TB documents, which have evidence of reducing TB incidence in countries throughout the world (WHO reports and TB control programs)	Thank you for your comment. This section relates to the evidence from PH37. The quality of evidence is described in each evidence statement.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	403	22	The BMC Public Health (Bothamley et al, 2011) re UK cities quite clearly demonstrates how staffing ratios are linked with either improving or worsening TB incidence.	Thank you for your comment. This paper was included in the effectiveness review for service delivery appendix G7. Your comment does not conflict with the staffing ratios that are recommended.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Thoracic Society	Full	403	22	The BMC Public Health (Bothamley et al, 2011) re UK cities quite clearly demonstrates how staffing ratios are linked with either improving or worsening TB incidence.	Thank you for your comment. This paper was included in the effectiveness review for service delivery appendix G7. Your comment does not conflict with the staffing ratios that are recommended.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	410	2 6	An evidence based statement might indicate that the poor effectiveness of PHE in reducing TB requires a return to a physician-led service? The PHE have been good at collecting data but have had no powers to implement any recommendations. Many have had no understanding about the delivery of a service for TB patients.	Thank you for your comment. The guideline acknowledges the need for a strategic approach to TB prevention and control.
British Thoracic Society	Full	410	2 6	PHE have been good at collecting data but have had no powers to actually implement any recommendations. It is important that a NHS driven service is critical to deliver this.	Thank you for your comment. The guideline acknowledges the need for a strategic approach to TB prevention and control.
Public Health England	Full	410	19	It would be beneficial to add to this list of bullet points 'the need to enable access to suitable accommodation for the period of treatment'	Thank you for this comment. A specific sub-section of the guideline covers accommodation for the period of treatment and beyond. The GDG did not consider it is necessary to repeat this here.
Homerton Hospital	Full	413	General	The amount of new funding (£10m) will buy 500k IGRA tests, which is not enough to implement	Thank you for this comment. This section of the guideline chapter has been clarified to highlight

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Foundation Trust (HHFT)				even the recommendation on extended screening. A realistic assessment of the number of front-line staff (which incur the highest proportions of cost for a TB service) is required, i.e. 9,000 cases per year need 225 TB nurses + 90 support workers/outreach/nurses and 36 wte physicians and 90 admin workers under current guidelines. Unless the TB control boards can deliver this minimum of staffing, any progress will be minimal. Control boards may them merely take away front line staff from clinical activity.	the funding is for the TB control board personnel to support co-ordination, improving efficiency through improved resource sharing amongst other things and where appropriate to advocate for appropriate staffing following the workforce review which is within their remit. The funding is not to support the delivery of all TB services this remains the remit of commissioners via local government and or CCGs. The need for clear evaluation of the impact of the TB control boards was recognised by the GDG they make a research recommendation on this.
British Thoracic Society	Full	413	General	The amount of new funding (£10m) will buy 500k IGRA tests, which is not enough to implement even the recommendation on extended screening. A realistic assessment of the number of front-line staff (which incurr the highest proportions of cost for a TB service) is required, i.e. 9,000 cases per year need 225 TB nurses + 90 support workers/outreach/nurses and 36 wte physicians and 90 admin workers under current guidelines. Unless the TB control boards can ensure delivery of this minimum of staffing (in addition to latent TB detection), any progress will be minimal. Control boards may be in danger of then merely taking away front line staff from clinical activity.	Thank you for this comment. This section of the guideline chapter has been clarified to highlight the funding is for the TB control board personnel to support co-ordination, improving efficiency through improved resource sharing amongst other things and where appropriate to advocate for appropriate staffing following the workforce review which is within their remit. The funding is not to support the delivery of all TB services this remains the remit of commissioners via local government and or CCGs. The need for clear evaluation of the impact of the TB control boards was recognised by the GDG they make a research recommendation on this.

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Public Health England	Full	415	7	It would be beneficial to add 'and accommodation' after 'services' in this line	Thank you for your comment. There is a specific section of the guideline on accommodation.
Public Health England	Full	415	11	It would be beneficial to add 'and accommodation' after 'services' in this line	Thank you for your comment. There is a specific section of the guideline on accommodation.
Public Health England	Full	416	1	It would be beneficial to add 'and accommodation' after 'services' in this line	Thank you for your comment. There is a specific section of the guideline on accommodation.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	420	2	It will be dangerous to duplicate the BT Advisory service. Rather the BTS should be paid to continue and enhance its role. Already there is cohort review which should amalgamate opinions from TB experts and could usefully review MDRTB at 3 monthly intervals.	Thank you for your comment. The recommendation to consider regional MDR TB is not intended to duplicate or replace the BT advisory service it is one element to consider alongside that of BTS advisory service. The aim of the recommendation is to improve systematic access to, and use of, the advisory service or other expertise for MDR TB.
British Thoracic Society	Full	420	2	The use of regional MDT's was previously supported in BTS audits of network working. However this does not replace or duplicate the function of BTS National MDR Advisory service but should ensure a pathway to an MDR centre	Thank you for your comment. The recommendation to consider regional MDR TB is not intended to duplicate or replace the BT advisory service it is one element to consider alongside that of BTS advisory service. The aim

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				exists for all cases of MDR TB. The BTS should be funded to continue and enhance the National Advisory role given the small numbers being treated even within regional areas and provide overview and ratification of regimes.	of the recommendation is to improve systematic access to, and use of, the advisory service or other expertise for MDR TB.
Public Health England	Full	423	1	This section would benefit from a specific recommendation that Directors of public health should, in conjunction with the local housing authority housing and homelessness teams, should ensure that the local statutory homelessness review and assessment of housing needs recognise and reflects the relationship between homelessness, and other risk factors, and TB.	Thank you for your comment, We have included reference to the statutory homelessness review in the accommodation specific recommendations.
Public Health England	Full	423	3	'Is part of the JSNA' is not explicit enough to generate a JSNA that will inform commissioning for improved outcomes, just a description of the scale and nature. The addition of 'including barriers to identifying and treating TB eg, alcohol & drug, homelessness etc' or similar would be beneficial	Thank you for your comment. This recommendation leaves it open for local DPHs and health protection teams to advocate for the level of detail required. The GDG wished to strike an appropriate balance to ensure that where TB was a particular issue more detail could be included and that the DPH working with the local health protection would be in a position to decide this. Equally, where TB may not be such a high priority the committee wanted to ensure that the level of detail was not prohibitive to data being included in the JSNA.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					This certainly does not preclude your suggested information being included but that will be a matter for the DPH and health protection team to determine locally. There is reference to the discussion the committee had about JSNA and the need to enable proportionality of the TB related work for the JSNA based on local needs.
Public Health England	Full	424	6	It would benefit from identifying the 'at risk' groups or giving an example eg, 'homeless people' – this will provide a hook for those working in this sector to connect to/recognise the relationship	Thank you for your comment. High risk groups is defined in the glossary and incorporates the specific groups additionally classified as under-served which includes homeless people. It is not possible to cover each separate group each time they are relevant unless the recommendations are specific to that group alone.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	424	35	"equity proofed" is jargon and lacks clarity	Thank you for your comment. This term is defined in the glossary.
British Thoracic Society	Full	424	35	"equity proofed" is jargon and lacks clarity	Thank you for your comment. This term is defined in the glossary.
Homerton Hospital	Full	431	11	New recommendation for LTBI will require considerable investment. The role of outreach	Thank you for this comment. DOT for LTBI is not specifically recommended here. The committee

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Foundation Trust (HHFT)				workers for TB in preventing disease will be much less than the associated health and social care teams. Many would argue that specific DOT for LTBI cannot be instituted until we can use the once weekly regimens which have supporting evidence.	consider that DOT may form part of enhanced case management but this is not the only component of this intervention. As explained in the chapter the GDG wanted to include this to ensure that commissioners did not think that the previously incorporated recommendations were for LTBI, and that they consider the resource for case management in LTBI to be half of that for active cases which may or may not reflect whether DOT is provided. The recommendations where DOT is specifically covered is the adherence section which is focussed on active TB in specified groups.
British Thoracic Society	Full	431	11	New recommendation for LTBI will require considerable investment. The role of outreach workers for TB in preventing disease will be much less than the associated health and social care teams. Many would argue that specific DOT for LTBI cannot be instituted until we can use the once weekly regimens which have supporting evidence.	Thank you for this comment. DOT for LTBI is not specifically recommended here. The GDG consider that DOT may form part of enhanced case management but this is not the only component of this intervention. As explained in the chapter the GDG wanted to include this to ensure that commissioners did not think that the previously incorporated recommendations were for LTBI, and that they consider the resource for case management in LTBI to be half of that for active cases which may or may not reflect whether DOT is provided. The recommendations where DOT is specifically

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					covered is the adherence section which is focussed on active TB in specified groups.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	431	29	It is a sad indictment of the health service that this should be required in a list of recommendations!	Thank you for your comment.
British Thoracic Society	Full	431	29	It is a sad indictment of the health service that this should be required in a list of recommendations!	Thank you for your comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	439	1	A clear role for PHE! But having incidence teams may be an unnecessary expense.	Thank you for this comment. This recommendation is not about creating new teams of people or practitioners, but about harnessing the resources already available while ensuring an appropriate process and agreement is developed . This has been revised in the final guideline to make this clear.
British Thoracic Society	Full	439	1	The outbreak contact MDT approach is important and has clear role for PHE to deliver on. Theer needs to be an assessment of the cost effectiveness of there being a separate incidenct team.	Thank you for your comment.. It is not intended this is seen as a separate team but that resource should be drawn from the specialists already available this is intended to encourage agreements and pre-arranged contacts are set-up so that access and agreed process is established

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					to aid efficiency. This has been revised in the final guideline for clarity
Homerton Hospital NHS Foundation Trust (HHFT)	Full	451	24	This should be a target for public health overall, as housing the homeless significantly reduces mortality and morbidity per se.	Thank you for your comment. We do not disagree but this is a guideline focusing on TB. More generic recommendations are therefore not appropriate.
British Thoracic Society	Full	451	24	This should be a target for public health overall, as housing the homeless significantly reduces mortality and morbidity per se.	Thank you for your comment. We do not disagree but this is a guideline focusing on TB. More generic recommendations are therefore not appropriate.
Public Health England	Full	451	26	The addition of Homeless Link and SITRA as national umbrella bodies for the homelessness and supported housing sectors would be beneficial	Thank you for your comment. this had been added to the final guideline.
Public Health England	Full	451	28	'Considered a priority for housing'. This wording will not achieve change (and might not be possible from a legislative perspective) and needs to be revised to provide clarity on the following	Thank you for your comment. this has been clarified in the final guideline.

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				questions: - Priority: does this relate to homelessness 'priority need' status or 'priority for social housing'? - Which type of housing? Temporary? Supported? General needs social housing? We can suggest alternative wording depending on the intended outcome of this recommendation.	
Public Health England	Full	451	29	'Housing support' means different things to different people. Do you mean 'support from the housing sector to enable the right home environment for successful completion of TB treatment'?	Thank you for your comment. this has been clarified in the final guideline.
Public Health England	Full	452	27 29	An alternative which may have more impact would be 'This is to ensure that housing commissioners and front-line staff understand the importance of the home environment to successful TB treatment and recognise this in their day-to-day business of meeting housing needs'.	Thank you for your comment. The recommendation has been amended.
Homerton Hospital NHS	Full	454	5	Not sure where this information came from. Patients should be visited in their own homes shortly after diagnosis to see whether to obtain	Thank you for your comment. This text has now been deleted.

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation Trust (HHFT)				list of contacts and see environment. Tuberculin skin testing will probably not take place. So there are different aspects of contact tracing that occur.	
British Thoracic Society	Full	454	5	Patients should be visited in their own homes shortly after diagnosis to see whether to obtain list of contacts and see environment. Tuberculin skin testing will probably not take place. So there are different aspects of contact tracing that occur.	Thank you for your comment. This text has now been deleted.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	463	1	Explain how this differs from WHO advice. Perhaps a generalization to an area where air is re-circulated would be more sensible and could then include submarines (and their data) to give a better picture. This will also help to justify the duration of contact required for contact tracing in other settings.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Contact-tracing was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic	Full	463	1	Explain how this differs from WHO advice. Perhaps a generalization to an area where air is re-circulated would be more sensible and could	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this

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Society				then include submarines (and their data) to give a better picture. This will also help to justify the duration of contact required for contact tracing in other settings.	update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Contact-tracing was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	467	1	This section makes no concession to public opinion and the school's felt obligation to screen if there is an infectious case of TB. As many of the recommendations imply, this should be taken as an opportunity to educate about TB and its global significance.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Contact-tracing, including contact-tracing in schools, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.

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British Thoracic Society	Full	467	1	This section makes no concession to public opinion and the school's felt obligation to screen if there is an infectious case of TB. As many of the recommendations imply, this should be taken as an opportunity to educate about TB and its global significance.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Contact-tracing, including contact-tracing in schools, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	476	2	If you are going to give credence to this study, rather than considering that the infectious case may have been a relative of the index case, then this situation should be specifically included in the recommendation.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Contact-tracing, including contact-tracing among healthcare workers, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification

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					or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic Society	Full	476	2	If you are going to give credence to this study, rather than considering that the infectious case may have been a relative of the index case, then this situation should be specifically included in the recommendation.	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Contact-tracing, including contact-tracing among healthcare workers, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust	Full	478	1 287	This section should emphasize finding infectious cases, by sputum smear examination and/or Xpert MTB/RIF as there is unlikely to be a facility to give preventive treatment for LTBI until they are housed. The emphasis on radiographic screening has always overemphasized those who	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the

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(HHFT)			291	have self-healed or treated disease with scarring. Many individuals attend regularly for follow-up after such screening, as the screening itself has no "memory".	recommendations that have not been updated. Recommendations from PH37 – of which this is one – were to be incorporated into the new guidance without updating the evidence review. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic Society	Full	478	1 287 291	This section should emphasize finding infectious cases, by sputum smear examination and/or Xpert MTB/RIF as there is unlikely to be a facility to give preventive treatment for LTBI until they are housed. The emphasis on radiographic screening has always overemphasized those who have self-healed or treated disease with scarring. Many individuals attend regularly for follow-up after such screening, as the screening itself has no "memory".	Thank you for your comment. Although it is agreed that this may be useful, it has not been possible to update all sections and recommendations as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Recommendations from PH37 – of which this is one – were to be incorporated into the new guidance without updating the evidence review. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital	Full	483	12	As the Mantoux test in its current form has more false negatives and there is no correlation	Thank you for your comment**.** It has not been possible to update all sections and

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS Foundation Trust (HHFT)				between protection and the tuberculin response, the presence of a BCG scar should be sufficient evidence and an additional BCG vaccination not required for "Mantoux-negative".	recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination (except in terms of interventions to increase its uptake amongst high risk groups) was explicitly listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic Society	Full	483	12	As the Mantoux test in its current form has more false negatives and there is no correlation between protection and the tuberculin response, the presence of a BCG scar should be sufficient evidence and an additional BCG vaccination not required for "Mantoux-negative".	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination (except in terms of interventions to increase its uptake amongst high risk groups) was explicitly listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	491	308	6 months seems to be arbitrary. All those with symptoms should be screened again (see WHO collated evidence, e.g. X-ray screening in the Netherlands to indicate time from a normal CXR to massive disease can be as short as 3 months). Only 7% do not have symptoms.	Thank you for your comment. Although it is agreed that this may be useful, it has not been possible to update all sections and recommendations as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. Recommendations from PH37 – of which this is one – were to be incorporated into the new guidance without updating the evidence review. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
British Thoracic Society	Full	491	308	6 months seems to be arbitrary. All those with symptoms should be screened again (see WHO collated evidence, e.g. X-ray screening in the Netherlands to indicate time from a normal CXR to massive disease can be as short as 3 months). Only 7% do not have symptoms.	Thank you for your comment. Although it is agreed that this may be useful, it has not been possible to update all sections and recommendations as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that

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					have not been updated. Recommendations from PH37 – of which this is one – were to be incorporated into the new guidance without updating the evidence review. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	501	28	Enhanced case management should be defined at some stage (if there is indeed any difference between normal nursing care and this)	Thank you for your comment. The following definition has been added to the glossary: "Management of TB for someone with clinically or socially complex needs. It starts as soon as TB is suspected. As part of enhanced case management, the need for directly observed treatment is considered, along with a package of supportive care tailored to the person's needs."
British Thoracic Society	Full	501	28	Enhanced case management should be defined	Thank you for your comment. The following definition has been added to the glossary: "Management of TB for someone with clinically or socially complex needs. It starts as soon as TB is suspected. As part of enhanced case management, the need for directly observed treatment is considered, along with a package of supportive care tailored to the person's needs."

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Homerton Hospital NHS Foundation Trust (HHFT)	Full	504	20	Range of values and their implications should be given	Thank you for your comment. The abbreviation "NR" indicates that these values were not reported in the study.
British Thoracic Society	Full	504	20	Range of values and their implications should be given	Thank you for your comment. The abbreviation "NR" indicates that these values were not reported in the study.
Homerton Hospital NHS Foundation Trust (HHFT)	Full	505	20	Strictly this should include M. microti	Thank you for your comment. The stated definition was that defined within the scope for this guidance.
British Thoracic Society	Full	505	20	Strictly this should include M. microti	Thank you for your comment. The stated definition was that defined within the scope for this guidance.
Homerton Hospital NHS Foundation Trust	Full	507	6	Miller's definition of primary disease should be used, i.e. disease which develops in individuals with no prior anti-mycobacterial immunity. This includes a primary focus, mediastinal lymph nodes disease, pleural effusions, military TB, TB meningitis, renal TB, osteomyelitis, some forms of	Thank you for your comment. The definition has been updated to say: "The initial stage of **disease following** infection with TB bacteria **in individuals with no prior antimycobacterial immunity.** ~~, which~~It is often

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(HHFT)				abdominal TB and skin TB. It is NOT the same as latent tuberculosis infection.	asymptomatic, but can be detected by tuberculin skin tests or interferon-gamma release assays."
British Thoracic Society	Full	507	6	Miller's definition of primary disease should be used, i.e. disease which develops in individuals with no prior anti-mycobacterial immunity. This includes a primary focus, mediastinal lymph nodes disease, pleural effusions, military TB, TB meningitis, renal TB, osteomyelitis, some forms of abdominal TB and skin TB. It is NOT the same as latent tuberculosis infection.	Thank you for your comment. The definition has been updated to say: **"The initial stage of** disease following **infection with TB bacteria** in individuals with no prior antimycobacterial immunity. ~~, which~~It is often asymptomatic, but can be detected by tuberculin skin tests or interferon-gamma release assays."
Oxford Immunotec	Full	769 and 771	General	The cost of the IGRAs were obtained from one source (Pooran 2010). This publication was submitted in 2008 so this data is at least 7 years old. This publication obtained information from just one source for the QFT costs (Blackburn Royal Infirmary) and again one, but different source, (Royal Free Hospital, London) for the T-SPOT.TB test. Hence, a fundamental value used in the cost effectiveness model (the cost of the tests performed) is at least 7 years out of date, obtained from one source for each IGRA test and derived from different institutions. This data cannot be relevant in 2015 so again indicates a weakness in the model.	Thank you for your comment. The economic analysis is informed by a decision analytical model whereby information used to parameterise the model are obtained from various sources. It is unlikely in modelling to have all cost data, for example, from the same source. Cost parameters in the analysis were inflated using the Consumer Prices Index to bring the costs up to date. These were discussed at the GDG meetings. This cost parameter has also been subjected to additional sensitivity analysis in an addendum to Appendix H of the Full Guideline, with the cost of IGRA being reduced to £29and the cost of TST increased to £29. This had no impact on the base-case results

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British Infection Association	Full l	General	General	Throughout the section on diagnosis it is not clear at times if you are referring to the primary use of rapid diagnostic nucleic acid amplification tests on the initial samples, as opposed to the use of the tests once the organism has cultured.	Thank you for your comment. The table headings in this section have been amended to make this clearer. That is, the final column is now titled: "Additional tests on primary specimen (if it would alter management)"
George Eliot NHS Trust	Full l	31	13	If an adult is returning or moving back and forth to a high TB incidence country especially as a health care worker, should we still offer chemoprophylaxis?	Thank you for your comment. If they have tested positive following immune-based testing, yes.
Royal College of Surgeons	General	General	General	No comments	Thank you.
British Thoracic Society	Short	General	General	The guidance is inconsistent in approach with respect to TST/IGRA testing and also treatment in LTBI. The costings for the analysis appear to be based on older and more historic costings and the reality is that some centres have completely stopped doing TSTs in adults. This guidance in terms of standard contact tracing may unfortunately be irrelevant immediately and there should be consideration of local arrangements when making the	Thank you for your comment. The costings for both Mantoux and TST have since been given specific consideration in additional sensitivity analyses detailed in an addendum to appendix H of the Full Guideline. In addition, The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total

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				recommendations where some flexibility is allowed about the initial mode of testing. In addition the threshold of 5mm in all settings appears inconsistent across other national guidance (eg US which is situation dependent).	cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). The cost parameters have also been subjected to additional sensitivity analysis in an addendum to Appendix H of the Full Guideline, with the cost of IGRA being reduced to £29and the cost of TST increased to £29. This had no impact on the base-case results. All costing parameters were inflated to current prices using the Consumer Price Index.
British Thoracic Society	short			Spinal surgery if indicated refer to tertiary referral centre for orthopaedic or neurosurgical opinion, drainage of large paravertebral abscess should be done under CT guidance.	Thank you for your comment. The surgical recommendations have been amended so they are about *referring* for surgery.
TB Alert	Short	General	General	Is there enough of an emphasis (esp pgs. 10-24 and 64-71) about the two key issues most likely to impact on reducing TB rates: reducing diagnostic delay and improving treatment completion. Therefore TB Alert strongly agrees with the full version and pages 406 and 10.2.3.1 and the "relatively value of different outcomes" statement and would like to see this more explicit within the short guidance document which most	Thank you for this comment, this is not the kind of detail that is included in the recommendation sections of NICE guidelines.

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				practitioners will be most regularly referring to	
TB Alert	Short	General	General	Sometimes there is a tendency for the short version to mention more around those who are primarily homeless or who have substance misuse issues, rather than migrant communities who maybe well settled within the community and who require a different approach for building rapport in order to discuss TB and promote testing – LTBI or active. The latter group still experience health inequalities and fall into NICE PH37's definition of hard-to-reach.	Thank you for your comment. Only those classified as hard to reach (under-served in this guideline) migrants were included in the PH37 definition – established migrant communities were excluded from that definition.
Our life	Short	General	General	Our Life have been commissioned by PHE to enable access to the right home environment for treatment completion. This work will be completed in early July. The findings from this work so far provide compelling evidence that insecure and unsuitable housing has a significant impact on the spread and effective treatment of TB, and costs to the health system, impacts include: • Extended hospital stays due to housing rather than medical need • Increased likelihood of being lost to follow up • Increased risk of infecting others • Increased risk of developing multi-drug	Thank you for this comment. The GDG received expert testimony on accommodation to support TB service delivery. However, at that time it did not consider they had received enough evidence to make any further recommendations than they have done. As the evidence you discuss has not been made available for the GDG we have been unable to take it into account when finalising the guideline.

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				resistant TB • Significantly increased burden on TB Teams to locate patients for DOT, and to address their housing and support needs, with particular challenges around patients with No Recourse to Public Funds. There is also clear evidence that there are opportunities through closer working with Local Authority Housing and Environmental Health Teams in the delivery of their duties to prevent homelessness and tackle overcrowding and manage Houses in Multiple Occupation to reduce the spread of the disease, and enable earlier diagnosis and more efficient active case finding.	
Health Protection Scotland	Short	General	General	Section on BCG vaccination considers children to 16 years, screening considers children to 17 years, and section 1.3.1.8 children 15 years and younger and then young people 16-18 years - does there need to consistency in the definition for children. The definition on page 105 for children and young people refers to people aged 17 or younger.	Thank you for your comment. The age cut-offs used in the recommendations reflect those used in or derived from the update reviews, which were in turn determined by those used in CG117. 'Children and young people' are those aged 17 or younger, with 'young people' specifically being those aged 16 or 17, 'older.
Public Health	Short	General	General	There is inconsistent use of "under-served groups" and "other high risk groups" e.g. p11 & 12	Thank you for your comment. Both of these are defined in the glossary and have different

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England				and elsewhere, we would suggest careful review of these phrases and consistent use	meanings. The GDG used them to reflect different, though at times overlapping circumstances. This is why sometimes the committee would refer to both groups within a recommendation, whereas at other times they referred to just one of these groups. Under-served is used in this guideline to mean groups of adults, young people and children from any ethnic background, regardless of migration status. They are 'under-served' if their social circumstances, language, culture or lifestyle (or those of their parents or carers) make it difficult to: • recognise the clinical onset of TB • access diagnostic and treatment services • self-administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer) • attend regular appointments for clinical follow-up. The groups classified as under-served in this guideline are: • people who are homeless • people who misuse substances • prisoners

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					• vulnerable migrants. 'High-risk groups' is used in this guideline to mean adults, young people and children from any ethnic background, regardless of migration status, who are at increased risk of having or contracting TB. This includes people classified as under-served, people identified as contacts according to the case finding recommendations, new entrants from high-incidence countries and people who are immunocompromised.
Public Health England	Short	General	General	There is inconsistent use of the age cut-off e.g. p33 L27 which talks about children 15 or less and then on p23 adults age >18, we would suggest careful review of these age cut-offs and consistent use	Thank you for your comment. The age cut-offs used in the recommendations reflect those used in or derived from the update reviews, which were in turn determined by those used in CG117. 'Children and young people' are those aged 17 or younger, with 'young people' specifically being those aged 16 or 17. This is now explicitly stated in the glossary.
Calderdale and Huddersfeld FT]	Short	General	General	Section 1.2.1.11 says, New Entrants with Mx reading of 5mm or greater, regardless of BCG history, should be considered for LTBI treatment once active disease is excluded, yet . . .Section 1.6.2.1 says to consider the effect of BCG history, We need clarity!!	Thank you for your comment. Owing to a lack of reporting, the relationship between BCG status in these populations and the diagnostic accuracy of the tests could not be quantitatively established from the evidence considered. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose

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					LTBI. In contrast, blood tests are unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses. However, given the uncertainty present the GDG concluded it was important, as part of the regular workup of these patients, to consider their BCG history when making the decision to offer LTBI therapy.
TB Alert	Full	1.5		Recommendation 172 This paragraph does not come out strongly enough in the short guidance and therefore we suggest it be added in there under 1.1.2.3	Thank you for your comment. The recommendations in the Short and Full versions of the guideline are now identical.

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TB Alert	Full	1.5		Recommendation 235 Again, this paragraph is not reflected strongly enough in the short guidance and we feel it needs to be, in section 1.6.4.3	Thank you for your comment. The recommendations in the Short and Full versions of the guideline are now identical.
TB Alert	Full	1.6	General	We would like to see a recommendation for research to be done around the most effective methods to encourage people to present for TB testing e.g. via support from a TB Link Worker, a third sector org, a local authority social/housing support worker etc and what is needed to best support that individual, such as home visits, outreach, mobile phone calls, attending clinic with the patient, contact with a person who has had TB in the past etc. Such insights around particular ethnic or community groups would be valuable in the event of outbreak or for improving treatment completion rates etc. The research considered by NICE (mainly as the mentioned body is missing) is more focused on prison or homeless groups and not all groups affected by TB. Although 9.1.6.1 includes appraising awareness raising research considered by the GDG, it is clear that the quality and quantity of this needs increasing.	Thank you for your comment. There is a research recommendation around peer support, which is detailed in the full guideline.
Royal College of	Short	1.3.2.1	41	There is mention here of nurses for adult patients. Some commentators feel that there should be	Thank you for your suggestion. The

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Paediatrics and Child Health				specific paediatric nursing expertise, although others feel that it is better for nurses to be able to look after entire families.	recommendation has been amended to say: "…TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised clinician, and by paediatric trained nursing staff, where possible…"
CHIVA	Short	1.3.2.1	41	Paediatric nursing guidance (RCN) in the UK states clearly that children should be looked after by paediatric trained nursing staff. With adherence a major factor in the completion of treatment adult nurses looking after children should at least receive some extra training. CHIVA group is working with HIV infected children as such we understand the importance of adherence and the support required for children and their families.	Thank you for your suggestion. The recommendation has been amended to say: "…TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised clinician, and by paediatric trained nursing staff, where possible…"
Birmingham & Solihull TB Service	Short	1.3.2.1	41	There is mention here of nurses for adult patients. Some commentators feel that there should be specific paediatric nursing expertise, although others feel that it is better for nurses to be able to look after entire families	Thank you for your suggestion. The recommendation has been amended to say: "…TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised clinician, and by paediatric trained nursing staff, where possible…"
TB Alert	Short	3	26	Suggest that a definition of what is meant by the term under-served groups goes in here, along	Thank you for this comment.

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				with at-risk groups so it is clear they are two distinct groups and each is clearly defined at the outset.	The GDG received expert testimony on accommodation to support TB service delivery. However, at that time it did not consider they had received enough evidence to make any further recommendations than they have done. As the evidence you discuss has not been made available for the committee we have been unable to take it into account when finalising the guideline.
TB Alert	Short	3	27 28	Implies that only the 'NHS and PHE have been working on TB' at this should be updated to include local authority PH teams and many third sector organisations.	Thank you for your comment. Text now says: "The NHS and Public Health England**, as well as a local authority public health teams and many third sector organisations,** have been working to reduce the harm caused by TB to many individuals and communities. TB is a notifiable disease, meaning that clinicians have a statutory duty to notify local authorities or a local Public Health England centre of suspected cases, and efforts have been made to strengthen services and ensure clear lines of accountability and responsibility. However, a stronger approach to TB control is now needed to build on this work. Indicators of TB incidence and TB treatment outcomes have been included in the Public Health Outcomes Framework. In addition, Public Health England and NHS England have designed a collaborative tuberculosis strategy for England

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					that brings together best practice in clinical care, social support and public health. Agencies at all levels – including national and local government, clinical commissioning groups and third sector partners – are committed to working in partnership to decrease the incidence of TB, fight the spread of drug-resistant forms of the disease, reduce current health inequality and, ultimately, eliminate TB as a public health problem in England."
TB Alert	Short	3	31	Suggest that a clearer term than 'strengthen' be used at it is not clear what this means – does it mean put in additional financial resources for example.	Thank you for your comment. This is the terminology used within Public Health England's Collaborative tuberculosis strategy for England: 2015 to 2020. For more information, please read the strategy in full: https://www.gov.uk/government/publications/collaborative-tuberculosis-strategy-for-england
TB Alert	Short	4	1	Suggest word 'stronger' is replaced by multi agency or collective – as TB is not merely a medical issue and the involvement of additional parties and services beyond the NHS is needed. It would be helpful for NICE to clearly state, that public health aspects of TB include those social issues that affect people's perception of TB and their interaction with health services. There is a risk, otherwise, of some readers viewing public health through a narrower lens of BCG, new	Thank you for your comment. This is the terminology used within Public Health England's Collaborative tuberculosis strategy for England: 2015 to 2020. For more information, please read the strategy in full: https://www.gov.uk/government/publications/collaborative-tuberculosis-strategy-for-england

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				entrant screening etc. To ensure the correct perspective is taken, the terminology used could be "clinical, social and public health interventions".	
London TB workforce Group	Short	10	8	We believe that there should be a change of focus in the phrasing so that it should read "Public health teams ….in collaboration with multi-disciplinary TB teams…" We believe that it should be the remit of Public health to lead on raising and sustaining awareness of TB rather than the onus being on the TB teams. Please note, awareness raising and targeted activities in under-served and other high-risk groups by MDT TB teams are not usually commissioned nor workload impact recognised. We would recommend to mentoin third sector organisation ets her.	Thank you for your comment. NICE consider Public Health teams to be an integral element of multi-disciplinary TB teams as are the voluntary sector. The glossary item specifies a broad mix of professionals to meet the needs of those with complex physical and social issues including a consultant in communicable disease control or health protection and the voluntary sector. The decision about which element(s) of the MDTB team leads on particular interventions should be a matter for local agreement.
NHS England	Short	10 12 276	13 47	We are concerned that the specific reference to Emergency Departments may mean that referrals and work with other departments in hospitals leads to decreased prioritisation and reduced education opportunities across other hospital departments, especially Radiology and ENT.	Thank you for your comment**.** These are examples only and not intended to be exhaustive. This has not been altered from the previous published guideline which has been incorporated here.
TB Alert	Short	10	18	Page 380 in the full version states that such TB awareness training should be CPD accredited	Thank you for your comment. This information forms part of the synthesis of

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				and that it meets a national minimum standard – this is not mentioned and we feel it should be included in the short version to ensure this is prioritised and auctioned. In addition, we feel that this section would benefit from being clearer on which professional groups the contents of the proposed training programme are aimed at, for example would the content be the same for A&E staff in the NHS or social/housing support workers in a local authority?! This is an important recommendation and therefore we believe the more specific this section could be, would mean greater buy-in and subsequent action.	recommendations across multiple NICE guidelines, but does not form a recommendation. The recommendations do say what topics need covering and all should be covered for each group, however, the breadth and depth of training may differ across groups. The implementation of recommendations is left open for local decision making and to enable its design to meet local needs it is not possible for NICE to make detailed recommendations for every scenario or group whom may receive training or how this training may be modified for different groups they need to be adaptable to local needs, service delivery structures, models or agreements.
TB Alert	Short	11	20	There are some important topics missing, especially: incentives / ways of providing practical support to encourage people to attend TB services and complete treatment effectively. In addition, a line on how to make services more accessible would be useful and there to specify things like longer appointment times, mobile outreach, home visits etc.	Thank you for your comment. These elements are covered elsewhere in the guideline for example the adherence section amongst others.
Our life	Short	13	8	It would be beneficial to include a specific reference to housing and homelessness teams as organisations that multi-disciplinary teams should work in partnership with. The peers will also be more effective if they have representation from	Thank you for this comment. The voluntary sector, social workers and local housing representatives are included as team members in the glossary item on multi-disciplinary TB teams. The glossary item on peers includes the fact they

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				different higher risk groups including homelessness.	are people who may have experienced TB. and that they may be recruited from specific populations, this could include homeless people or others in high risk or under-served groups.
TB Alert	Short	13	13	Suggest the widely accepted PH term of 'information, education and communication' be added when referring to templates for leaflets, posters etc, as this term reflects the three key areas which any piece of marketing or material should include.	Thank you for this comment. The GDG did not review evidence on marketing terms or processes to inform these recommendations.
TB Alert	Short	13	21	We feel that the first thing to be included should be a statement that TB treatment is free and confidential – this is missing, plus is another stating that TB treatment is effective (in the majority of cases)	Thank you for this comment. The recommendation on the content of the materials does not state the specific topics to cover for example ' that TB treatment is free' but offers recommendations on the key issues to consider including. However the fact TB treatment is free is highlighted in other elements of the guideline including the recommendations on awareness raising and adherence recommendations therefore NICE do not feel they need to repeat this detail here.
TB Alert	Short	14	8	No mention of the potential need to produce materials in community languages in order to accommodate the needs of new entrants.	Thank you for your comment.. The second bullet in 1.1.2.3 includes language as a consideration and third bullet includes tailoring to a populations needs. Therefore we consider this is covered.

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TB Alert	Short	14	13	No mention of using social media as an effective way to provide information on TB – suggest Facebook, Twitter, and podcasts are mentioned.	Thank you for your comment. A range of formats is recommended in 1.1.2.4 including electronic and podcasts, this recommendation also suggests they should be published online. NICE guidelines do not endorse specific social media sites.
Public Health England	Short	14	17 24	Should this not also include mention of the value of opportunistic (identification of the need) at secondary care or tertiary care	Thank you for your comment. The list is not intended to be exhaustive, however, the recommendation has been revised following consideration by the GDG
NHS England	Short	15 325	5 2	We would like to bring to the attention of the GDG that BCG for neonates is now included in the maternity tariff payment and that it should therefore be easier for commissioners to ensure that it is offered as soon as possible after birth. To support commissioners in the commissioning of neonatal BCG a statement on this in the BCG section should be included.	Thank you for your comment, this has been clarified in the full guideline.
Health Protection Scotland	Short	16 188	7 13	Would be helpful to ensure consistency with the Green Book chapter on TB which includes • previously unvaccinated tuberculin-negative individuals under 16 years of age who are contacts of cases of respiratory TB"	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated.

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					BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.
Kent Community Health NHS Foundation Trust: TB team	Short	16	13	This recommendation from 2006 is too vague and causes no end of issues in areas of low incidence where BCG is not a universal vaccination. On page 15 (line 6) it states we should vaccinate eligible babies in line with Green Book but this recommendation is not in line with the green book. For low incidence areas the guidance needs to be much more specific about what "family history of TB" is because we have a huge amount of very angry parents whose children are not entitled to the BCG who tell us they have a distant relative who had TB so that they can get the vaccine. We have therefore made it our policy to only offer BCG to those who fit the Green Book criteria, however there are times when we feel this approach does not cover babies who do not fit the criteria but where TB has been an issue. Much clearer clarification of	Thank you for your comment. It has not been possible to update all sections and recommendations from CG117 as part of this update. Areas for review and update were identified, prioritised and agreed through the scoping process, but it means that some of the recommendations that have not been updated. BCG vaccination, except in terms of encouraging uptake of BCG among people at increased risk of TB, was listed in the scope under 'Areas from the original guideline that will not be updated by an evidence review'. Changes have only been made for the purposes of clarification or, for example, because of equalities duties or a change in the availability of medicines or services. These recommendations are not, therefore, open for comment.

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				this would be much appreciated.	
British Thoracic Society	Short	17	13 22 23	This section does make clear who will provide these resources and should be clarified: P17 1.1.3.14 line 13 the access to BCG for infants and New Entrants is clear but who will deliver to older children? P17 1.1.3.14 line 22-23 where will GPs refer older children for testing and BCG?	Thank you for this comment. This recommendation is for primary care as they should deliver the testing and vaccination in line with the green book for all eligible populations irrespective of age. Regarding incentives, this is for CCGs to consider, the rationale for including this is explained in the full guideline linking evidence to recommendations table..
British Thoracic Society	Short	18	5	P18 1.1.3.15 line 5 To clarify statements, it would be helpful to have a definition of disadvantaged	Thank you for this comment. A glossary item has been added as follows: "People in unfavourable circumstances, especially with regard to financial or social opportunities."
NHS England	Short	18 337	19 30	There is inconsistency of wording around Mantoux and IGRA. The two phrases 'Mantoux negative' and 'Mantoux negative (or IGRA negative)' are used inconsistently across a number of sections. We would advise that where the phrase 'Mantoux negative' is used '.and/or IGRA negative' is added to avoid confusion.	Thank you for your comment. We have now been through to ensure that this is now consistent across all the recommendations.
George Eliot NHS Trust	Short	19	11	One month or three, its three in the Green Book?	Thank you for your comment. The recommendation has now been amended to be

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					consistent with the Green Book.
NHS England	Short	20	4	The footnote on BCG test threshold does not make clear whether the 'new recommendations' are international or national. We would appreciate clarity on this point.	Thank you for your comment. This refers to the new recommendations on diagnosing latent TB. The reference to international guidance has been removed as the driving factor was internal consistency for this guidance.
London TB workforce Group	Short	23	General	This recommendation will be a challenging change in practice because it will increase the number of children especially who will be eligible for LTBI rx and clinics (and possibly other services needed to support the work –up activity) will need to be able to manage the increase in referrals and workload.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline. This part of the guideline was prioritised for original health economic work, which considered the optimal testing strategy for children. The model suggested that TST ≥5 mm, being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). Given the lack of existing substantive evidence on which to recommend a 6 mm induration cut off, the GDG felt that the evidence review undertaken by Warwick, and the accompanying original health economic analysis provided sufficient basis to recommend that 5 mm and not 6 mm was an appropriate threshold.

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					There was a strong desire to bring this recommendation into line with current international (evidence-based) guidance, which specifies a 5 mm threshold. Furthermore, the group noted that reliably measuring the difference between 5 mm and 6 mm in practice was extremely difficult. In addressing concerns of extra costs and volume of patients: The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7).
London TB workforce Group	Short	23	General	The TB nursing team at St Mary's Imperial College have had experience of implementing this approach and would be willing to submit its experiences to the NICE shared learning database. Contact Marie O'Donoghue, Lead TB Nurse marie.odonoghue@imperial.nhs.uk	Thank you for your comment. We have passed it to the NICE implementation support team to inform their support activities for this guideline.

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George Eliot NHS Trust	Short	23	4	We are concerned about mantoux being an unlicensed product in the UK so requires a patient specific Direction or individual prescription which can only be written by an independent nurse prescriber for that nurse to supply or a doctor who is willing to sign without seeing the patient – is there a way around this ?	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
NHS England	Short	23 25	4 7 5	Contact tracing for non-pulmonary TB is an opportunity to assess other people in possibly high risk communities for either active TB disease or latent TB infection. We would prefer that the recommendation 'to screen contacts of pulmonary disease' is extended to non-pulmonary disease particularly in high risk communities and where children and young people are involved.	Thank you for your comment. The GDG discussed this issue but concluded that, due to the resource implications of contact-tracing and the relatively few cases identified by tracing contacts of people with extrapulmonary TB, contact-tracing should be limited to those index cases who are infectious (those with pulmonary TB).
Public Health England	Short	23	4 5 11 12	Recommendations in 1.2.1 (affects all LTBI testing recommendations), including the respective ones in the long version – increase the age limit for testing to 65 years We think more robust evidence is required to ensure that extending the age limit is safe and beneficial for the patients. *Rationale:* The GDG has taken the decision to increase the cut-off age for LTBI testing and treatment to 65	Thank you for this comment. Our systematic review, network meta-analysis, and original economic analysis (conducted by Imperial College) suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a greater relative risk of death from TB in older people. The model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to

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				years of age. The GDG stated the following reason for extending age limits: "Although evidence on contact tracing in adults of different ages was not reviewed as part of the 2015 update, the age threshold for testing is directly dependent on evidence of the benefits, harms and costs of treating latent TB. The Committee has reviewed this evidence and concluded that people should be offered treatment up to the age of 65 years." The decision to extend the age limit appears to have been taken based on the trade off between higher hepatotoxicity in older age groups ('about 5.5x higher') and a higher mortality risk (4x higher, full guideline p319). In the UK, we observed a higher TB incidence rate and slightly higher mortality due to TB in older age groups (21), but unfortunately we were unable to find a detailed age-stratified clinical and cost effectiveness analysis which would be required to support above conclusion and recommendation. The single most important adverse event of preventative chemotherapy for LTBI is hepatotoxicity. Fortunately, whilst it can be serious, this is a rare event (about 0.3-0.4%(22)). However, the increase of hepatotoxicity with age has been demonstrated in a range of observational studies(23–25) and in at least one RCT(26). Because hepatotoxicity is rare, any	die of active TB, if they develop it (and their chance of doing so increase with age), than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages. In its deterministic base case, the model suggested that treating all people under the age of 65 with 6H or 3HR would lead to net health gain at a cost of less than £20,000 per QALY gained, compared with no treatment. The balance of benefits, harms and costs was less favourable in people over the age of 65: although the model still suggested that treatment would result in QALY gains (i.e. greater benefit than harm), ICERs exceeded £20,000 per QALY for all regimens other than 2RPz, which the GDG thought would be inappropriate to prescribe to asymptomatic people, especially those in an older age-group. For this reason, the GDG concluded the most appropriate recommendation would be to offer treatment with 6H or 3HR to all people with LTBI under the age of 65. Please see Section 7.2.2 of the full guideline for more detail.

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				robust age-stratified analysis of hepatotoxicity would require a very large sample size, and to detect a doubling of risk with a simple stratification of a population under and over 35 years of age with 80% power would require a sample size of more than 10,000. To appropriately estimate risk by more granular stratification (e.g. 3 strata) would take the sample size up to 20,000. Similarly, decreasing the risk ratio to, say 1.5 would increase sample sizes significantly (personal correspondence). Whilst we agree that the current age stratification at 35 years of age is somewhat artificial and arbitrary, we do not know of large enough studies that would provide robust enough estimates of age-stratified risk to provide enough assurance that the increase of clinical risk is acceptable. References 21. Public Health England. Tuberculosis in the UK. 2014 report. [Internet]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/360335/TB_Annual_report__4_0_300914.pdf 22. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev Online. 2000;(2):CD001363.	

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				23. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest. 2005 Jul;128(1):116–23. 24. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med. 2003 Aug 15;168(4):443–7. 25. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999 Mar 17;281(11):1014–8. 26. IUAT. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. Bull World Health Organ. 1982;60(4):555–64.	
Kent Community Health NHS Foundation Trust: TB team	Short	23	4 12	Although we are happy with this new approach (mantoux up to age of 65) we are a bit surprised that it doesn't seem to fit in at all with the TB Strategy 2015-2020 which advises IGRA for all new entrants from high incidence areas 16-35. Why use IGRA for them and Mantoux for others and why only screen up to 35 while extending	Thank you for your comment. Although the scope and methodology for the Public Health England guidance overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the PHE guidance centred upon a population-level screening programme for new migrants, whereas

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				screening and TB treatment to 65 for everyone else?	the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
London TB workforce Group	Short	23	5	We suggest review of the age 65 year cut off for LTBI treatment, particularly in high risk groups given that those age >65 are given anti TNF and those with HIV infection have a longer life expectancy.	Thank you for this comment. Our systematic review, network meta-analysis, and original economic analysis (conducted by Imperial College) suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a greater relative risk of death from TB in older people. The model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it (and their chance of doing so increase with age), than people aged 15–44. This proved to be an

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					important consideration in balancing the risks and benefits of treatment in people of different ages. In its deterministic base case, the model suggested that treating all people under the age of 65 with 6H or 3HR would lead to net health gain at a cost of less than £20,000 per QALY gained, compared with no treatment. The balance of benefits, harms and costs was less favourable in people over the age of 65: although the model still suggested that treatment would result in QALY gains (i.e. greater benefit than harm), ICERs exceeded £20,000 per QALY for all regimens other than 2RPz, which the GDG thought would be inappropriate to prescribe to asymptomatic people, especially those in an older age-group. For this reason, the GDG concluded the most appropriate recommendation would be to offer treatment with 6H or 3HR to all people with LTBI under the age of 65. Please see Section 7.2.2 of the full guideline for more detail.
British Thoracic Society	Short	23	9	The evidence for regarding ≥5 mm induration as a positive Mantoux regardless of BCG status needs to be described in detail not because using 5 mm rather than 6 mm will make any tangible difference but because disregarding BCG status would be a major departure with greater	Thank you for this comment. The evidence is discussed in detail in the full guideline and in Appendix H. The GDG discussed the possibility that previous BCG vaccination can raise the likelihood of false-positive results when using TST to diagnose LTBI. In contrast, blood tests are

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				implications. The ATS recommended 3 cut-offs (5, 10 and 15 mm) to improve the sensitivity and specificity of the test in different population settings. The argument for regarding a 5 mm as an all or nothing reaction (e.g. Al Zahrani et al, 2000, AJRCCM 162:1419) is strongest in children as tuberculin reactions wane much quicker after BCG given in the neonatal period than later in life. (Menzies 2000 Clin Infectious Dis 31(Suppl 3):S71-4.	unlikely to be affected by BCG history. Where BCG status was reported in the evidence, the studies that suggested that there was no strong evidence of an association between BCG vaccination history and TST positivity (see appendix H, sections 4.3.3.2.3, 4.4.3.2.2 and 4.5.4.1.3). The group also noted that, in the analysis for children, 91.6% of participants in the studies from which diagnostic accuracy had been estimated had previously undergone BCG. In this population, a strategy that classified people as positive if their TST exceeded a threshold of 5 mm was most likely to be optimal. Therefore, there is no evidence that using a low threshold in a population with a high prevalence of BCG vaccination leads to an excess of false-positive diagnoses that outweighs the benefit of minimising false-negative diagnoses.
Public Health England	Short	23	9 12	Recommendations in 1.2.1 (affects all LTBI testing recommendations), including the respective ones in the long version – decrease in positivity threshold level for TST reading to 5 mm. We disagree with the decision to ignore previous BCG vaccination with respect to defining TST positivity. Rationale: The decision to decrease the threshold for a	Thank you for your comments. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated,

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				positive TST to 5mm (regardless of BCG) is based on practice in other countries, not on a new evidence review. It is worth noting that the validity of using one cut off for all depends on the likelihood that TST positivity is influenced by other factors, such as the level of BCG vaccination or environmental mycobacterial contamination. It is worth noting that even the CDC has different cut off levels for different risk groups, and that they recommend IGRA testing for TST positives that had BCG previously. NB – vaccination histories and scars are not always reliable markers for migrants from less developed countries. The impact of BCG vaccination on false positive results had apparently been discussed by the GDG, which concluded that "The magnitude of the impact BCG status has on the diagnostic accuracies and cost effectiveness of the tests examined could not be established quantitatively due to poor reporting of BCG vaccination in the evidence." Whilst we agree that evidence for using different cut-off levels for TST is limited, there is some evidence of its effect on TST reading(16) and of course these observations are inherent in the mechanism of TST and thus biologically plausible. It is also worth pointing out, that many other countries, including the USA(17), Canada(18) and Australia(19) stratify the reading results for TST (usually by risk groups). It is also	it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). The GDG agreed that the impact of BCG vaccination could not be established from the data extracted for the review and highlighted their concerns in the Evidence the Recommendations section (see section 3.1.3.5 of the Full Guideline). In addition, further work undertaken by Warwick Evidence to examine the relative benefits and harms of false-positives and treatment exposure has been included in Appendix H and discussed in the full guideline. The model for children suggested that TST ≥5 mm, being the most sensitive strategy, should be used as the preferred first-line test but that, to improve sensitivity further, IGRA testing should be undertaken in children who are negative on TST. This approach was estimated to maximise QALY gains at an acceptable cost (around £19,000 per QALY gained, compared with TST [≥5 mm] alone). The model for recent arrivals from countries with a high incidence of TB also found that TST (≥5 mm), being the most sensitive strategy, should be used as the preferred first-line test. In this instance, using IGRAs as a second-line test to identify people who are TST-negative but still have latent infection that may progress to active TB would marginally increase the cohort's

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				worth noting that reading thresholds will vary with different products and different concentrations(20), this is particularly important in view of on-going supply issues, which may well prompt the need to procure another TST product with a different concentration. Whilst a 5mm threshold level for BCG negative individuals would bring the UK in line with other countries and may seem appropriate, a 'one size fits all' approach for a uniform reading threshold of 5mm would not appear suitable, given the absence of robust studies unambiguously proving the absence of impact of BCG on TST reading and the evidence and practice to support different reading levels described above. References 16. Bierrenbach AL, Cunha SS, Barreto ML, Pereira SM, Dourado I, Ichihara MY, et al. Tuberculin reactivity in a population of schoolchildren with high BCG vaccination coverage. Rev Panam Salud Pública Pan Am J Public Health. 2003 May;13(5):285–93. 17. Centers for Disease Control and Prevention (CDC. Targeted Tuberculin Testing and Interpreting Tuberculin Skin Test Results [Internet]. [cited 2015 Jun 21]. Available from: http://www.cdc.gov/tb/publications/factsheets/testi	expected QALYs, but this gain would come at a cost that could not be considered a good use of NHS resources (ICER of just under £60,000 per QALY gained, compared with TST [≥5 mm] alone). The model for immunocompromised people relied on data that showed a different pattern of diagnostic accuracy: IGRAs appeared to be the most sensitive option, in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).change in threshold

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				ng/skintestresults.htm 18. Public Health Agency of Canada. Canadian Tuberculosis Standards. Diagnosis of latent Tuberculosis Infection. [Internet]. Available from: http://www.respiratoryguidelines.ca/sites/all/files/CTB_Standards_EN_Chapter%204.pdf 19. NSW Government. Tuberculin Skin Testing. Policy Directive. [Internet]. Available from: http://www0.health.nsw.gov.au/policies/pd/2009/pdf/PD2009_005.pdf 20. Stuart RL, Bennett N, Forbes A, Grayson ML. A paired comparison of tuberculin skin test results in health care workers using 5 TU and 10 TU tuberculin. Thorax. 2000 Aug;55(8):693–5.	
British Thoracic Society	Short	23	11	This is mantoux dependent and the assumptions on which this is based are seriously methodologically flawed. a) A 90% mantoux reading rate is only achievable if the TB Nurse does home placement and reading, which requires/costs 2 visits. In practice only 2/3 to ¾ return for readings in a clinic. b) The IGRA costs are 10 years out of date	Thank you. Warwick Evidence have undertaken a further analysis, detailed in an addendum to Appendix H, to determine what value of TST return has an impact/changes the results of the analysis. The recommendations of this guideline are not intended to apply to formal screening programme(s). Rather, they are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised

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				and more than 40% greater than current unit costs. c) Also operationally dependent on mantoux availability – which is seriously under threat. We strongly suggest that wherever the mantoux is mentioned, an option for single IGRA should be given unless this recommendation is overturned on the basis of a more appropriate economic appraisal. Additionally why not household contacts of non-respiratory disease as well as opportunistically looking for LTBI, and they may have the same respiratory source. This is essential for children as looking for adult source.	document, The model's base-case assumption of a 94% return rate was drawn from a UK study in a setting that was directly applicable to this decision problem (Pareek et al.'s 2013 analysis of case-finding among people registered with primary care practices). In addition, these return rates are consistent with what was used in CG117. In that guideline, proportion of TST results read (at first or second attempt) was 90%. The sources used for this input were Diel et al., 2006; Bothamley et al.,2002 and GDG consensus). For these reasons, the GDG was satisfied that the parameter used was an accurate reflection of reality. However, in view of stakeholders' suggestion that the figure might be optimistic, additional sensitivity analysis was undertaken to explore the model's sensitivity to this parameter. This showed that TST (≥5 mm) remains the most cost-effective strategy as long as the probability of the TST result being read is 76% or higher. The GDG agreed that return rates could be assumed to exceed this figure with a very high degree of confidence. The sensitivity analyses are detailed in an addendum to Appendix H of the full guideline, and the GDG's consideration of the

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					issue has been expanded in the relevant LETR table (section 3.1.4.5). The cost parameter were obtained from published sources and inflated to current prices. Warwick Evidence have amended these costs in a sensitivity analysis to assess the impact on the results. This is detailed in an addendum to Appendix H of the full guideline. In that analysis the cost of IGRA was reduced to £29 and the cost of TST increased to £29. This had no impact on the base-case results. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7). It is also important to note that this work was limited in scope to the opportunistic screening of patients (for whom there is suspicion of LTBI at the point of presenting to care and does not extend to contact tracing or larger screening initiatives.

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British Thoracic Society	Short	24	7 10	This statement is contradicted by subsequent recommendations and perhaps it meant to say "*only consider doing IFN-gamma assays WITHOUTdoing a Mantoux if Mantoux is unavailable or impractical.*"	Thank you for your comment**.** Amended to: "Only consider using interferon-gamma release assays **alone** in children and young people if Mantoux testing is not available or is impractical. This includes for example, situations in which large numbers need to be tested."
British Thoracic Society	Short	24 25	11 23 1 20	I have never understood why for a neonatal contact we should wait for 3 months before doing a Mantoux (1.2.1.5) whereas in a 5 week old close contact immediate Mantoux testing would be recommended and then if negative, repeated in 6 weeks (1.2.1.6). Immune responses may differ in early infancy but if close contact has occurred at birth tuberculin conversion ought to have occurred by 6 weeks. The guidelines would then have us wait a further 6 weeks before testing. Would it not be more logical to recommend doing the initial Mantoux at 6 weeks (not 3 months) or 6 weeks after the known contact and if negative, repeating 6 weeks later?	Thank you for your comment. The GDG agreed with this approach and the recommendation has now been updated.
British Thoracic Society	Short	24 25 26	11 23	These recommendations ought to be presented additionally as algorithms to ease understanding and usage. Sadly unless I have missed them, these	Thank you for your comment. The third population noted (children born to a mother who is diagnosed with any form of TB soon after delivery) would be covered by the current recommendation for neonates. No evidence was

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			1 30 1 9	guidelines again fail to give any specific recommendations on what to do: a. if a child is born to a mother who has started treatment for TB at least 2 weeks before delivery b. if a child is born to a mother who has started treatment for TB less than 2 weeks before delivery c. if a child is born to a mother who is diagnosed with any form of TB soon after delivery Recommendations on the need for separation, breastfeeding, etc should be made. True congenital TB acquired prenatally *in utero* is vanishingly rare (I have never seen it) and would present with an ill infant with disseminated disease. However, in my experience, a neonate can develop primary TB without any possibility of postnatal transmission (and thus fulfil the revised Cantwell criteria for congenital TB) by perinatal transmission in a mother with active disease. Presumably this is due to aspiration or ingestion of infected amniotic fluid from the maternal genital tract. I believe a significant proportion of pregnant women with active TB may have evidence of placental infection. If latent TB infection is confirmed on a Mantoux	identified for the first 2 populations mentioned (children born to a mother who has started treatment for TB at least 2 weeks before delivery or to a mother who has started treatment for TB less than 2 weeks before delivery). With regards the presentation of recommendations as algorithms to ease understanding and usage, the NICE pathway will also be published alongside the Short and Full versions of the guideline (as well as the costing and implementation tools and the Information for the Public). NICE pathways are an online resource for healthcare professionals to use on a day-to-day basis, which presents recommendations from a guideline (as well as linking them to relevant guidelines) in a set of interactive topic-based diagrams.

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				test in a child aged less than 2 years presumably adding rifampicin to the isoniazid to shorten the treatment to a further 3 months rather than continuing isoniazid alone for 6 months is an option which should be specified.	
British Thoracic Society	Short	24 25 26	11 23 1 30 1 9	If latent TB infection is confirmed on a Mantoux test in a child aged less than 2 years presumably adding rifampicin to the isoniazid to shorten the treatment to a further 3 months rather than continuing isoniazid alone for 6 months is an option which should be specified.	Thank you for your comment. The GDG discussed this concern and concluded the following: 6 months of isoniazid is recommended in neonates, and for children and young people over the age of 4 weeks either of the recommended regimens (6 months of isoniazid or 3 months of isoniazid and rifampicin) may be used, though selection should be based on the parameters outlined in the recommendation below: "Base the choice of regimen on the person's clinical circumstances. Offer: • 3 months of isoniazid (with pyridoxine) and rifampicin to people aged younger than 35 years if hepatotoxicity is a concern; this would include both liver function (including transaminase) tests and assessment of risk factors • 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant." The following text has now been added to the

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					Evidence to Recommendations table: "Given that there was a lack of evidence regarding which regimens should be used for chemoprophylaxis and the treatment of latent TB in children, the recommendations were predominantly based on paediatric expert opinion. Isoniazid should be started on its own in neonates and started in the absence of evidence of infection as a precaution. It was decided that to add rifampicin would be inappropriately exposing non-infected neonates to drugs. For children older than 4 weeks the choice should be isoniazid for 6 months or isoniazid and rifampicin for 3 months. While one is waiting for the second TST isoniazid alone is justified to avoid unnecessary exposure to a second drug in uninfected children."
British Thoracic Society	Short	24	12	Should read "…TB who have not had…" and not "…TB and has not had…"	Thank you for highlighting this. It has now been amended.
British Thoracic Society	Short	25	21 24	Referral of children under 2 years of age who are close contacts to an appropriate paediatric specialist is excellent and presumably intended as a recommendation for TB nurses doing contact tracing. The testing strategy to be followed ought to be described in the guideline.	Thank you for your comment. This recommendation is specifically concerned with contacts with a smear-negative index case. The referral to an expert rather than specification of a testing strategy reflects the lack of evidence seen for this population. Evidence to Recommendations text: "The GDG

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					noted that they had not seen evidence relating to the management under 2 who are contacts of smear-negative index cases. Diagnosis of latent infection in these individuals can be complex, and should be considered by an expert on a case-by-case basis. As with the diagnosis of latent TB for individual, diagnosis should include a risk assessment based on the duration and intensity of effective contact (the exposure) and the presence of other factors that may increase susceptibility to infection."
London TB workforce Group	Short	26	6 9	Is it correct that the only group that have a 6 week re-screen are children age 2-17? We suggest that adult contact of sputum smear positive TB should also have a 6 week re-screen if initial screening is complete < 6 weeks post exposure and results are negative.	Thank you for your comment. Re-screening after 6 weeks is also recommended in children aged between 4 weeks and 2 years: "If a child aged between 4 weeks and 2 years has been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment: • Assess for active TB. • Start treatment for latent TB and carry out a Mantoux test. • If the Mantoux test is inconclusive, refer the child to a TB specialist. This should be a specialist in paediatric TB or, as a minimum, a paediatrician with experience in TB.

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					• If the Mantoux test is positive (5 mm or larger, regardless of BCG history), reassess for active TB; if this assessment is negative, complete treatment for latent TB (see section 1.2.2). • If the Mantoux test is negative, continue treatment for latent TB, reassess for active TB **after 6 weeks and repeat the Mantoux test:** o if the Mantoux test is negative, consider an interferon-gamma release assay o if the interferon-gamma release assay is negative, treatment for latent TB may be stopped; give a BCG vaccination if the child has not already had one o if either test is positive, reassess for active TB; if this assessment is negative, complete treatment for latent TB" In the case of adults, the diagnosis of latent TB in this population was out of scope, changes could only be made to the wording in order to ensure consistency with other recommendations (e.g. treatment for LTBI is now recommended up to the age of 65 – in order for this to be achieved, we need to test up to the age of 65), for clarity of the recommendation, or, for example, because of equalities duties or a change in the availability of medicines. It was not possible to review the use of repeat testing in this population. Areas that

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					have not been reviewed in this update may be taken into consideration when NICE next reviews this guideline. NICE may undertake a more rapid update of discrete areas of the guideline if new and relevant evidence is published.
NHS England	Short	26 137	10 29	We are concerned that the GDG has recommended that Mantoux is used in preference to IGRA for latent TB testing in new entrants from high risk countries. This refers to statements not just at the defined pages and lines, but also at various other sections of the documents. Again it does not take into account more recent evidence that supports the use of IGRA in preference to Mantoux. The NICE guidance recommendation is different to the process as outlined in the 'Latent TB testing and treatment for migrants, a practical guide for commissioners and practitioners' which has been developed as one of the actions of the Strategy and was written using the most up to date and peer reviewed evidence NHS England (https://www.gov.uk/government/publications/latent-tb-infection-ltbi-testing-and-treatment). Issues that should also be considered that have not been defined in the evidence include the costs of training staff in Mantoux and staff turnover. Experience in pilots and schemes where	Thank you for your comment. Although the scope and methodology for the TB strategy overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the TB strategy centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas. Many thanks for the references for current evidence. However, this evidence does not reflect our three high risk populations of interest.

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				Mantoux has been used is that the process fails when staff who have been trained leave the organisation and it takes time to build up the expertise. The benefit of IGRA is it requires the taking of a blood sample which can be done in a variety of health care settings by a number of appropriately trained staff – it does not require such a specialist skill as Mantoux does. Using a blood sample for IGRA means that the patient does not require a return visit within a set time period for the reading of the Mantoux. The economic analysis is not explicit on these aspects of Mantoux versus IGRA including the risks and costs of patients attending for a second visits and the ability for IGRA to be offered in a wider range of settings.	Hence, Warwick Evidence were unable to incorporate this into the analyses. Warwick Evidence costed Mantoux test and staff time required for administering the test and reading the results using a bottom-up costing approach but couldn't obtain a cost for the Mantoux test. For this reason, Warwick used data from published sources and adjusted to current prices. The cost for TST in the models include having the test administered and having the result read.
Kent Community Health NHS Foundation Trust: TB team	Short	26	10 19	As above. This contradicts TB strategy.	Thank you for your comment. Although the scope and methodology for the TB strategy overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the TB strategy centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that

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					should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
British Thoracic Society	Short	26	11	Will using tuberculin skin tests (TST) in new entrants (even outside of a national test and treat programme) lead to DNA's compared to one step IGRA? I would be concerned that asking for patients to come back may lead to loss of patients. (MD)	Thank you for your comment. Additional sensitivity analysis has examined the impact of lowering the TST return rate on the cost-effectiveness results and is described in an addendum to Appendix H of the Full Guideline. The recommendations of this guideline are not intended to apply to formal screening programme(s). Rather, they are explicitly focused on the identification of cases among people who are already known to healthcare services. This distinction has been emphasised in the revised document, The model's base-case assumption of a 94% return rate was drawn from a UK study in a setting that was directly applicable to this decision problem (Pareek et al.'s 2013 analysis of case-finding among people registered with primary care practices). In addition, these return rates are consistent with what was used in CG117. In that guideline,

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					proportion of TST results read (at first or second attempt) was 90%. The sources used for this input were Diel et al., 2006; Bothamley et al.,2002 and GDG consensus). For these reasons, the GDG was satisfied that the parameter used was an accurate reflection of reality. However, in view of stakeholders' suggestion that the figure might be optimistic, additional sensitivity analysis was undertaken to explore the model's sensitivity to this parameter. This showed that TST (≥5 mm) remains the most cost-effective strategy as long as the probability of the TST result being read is 76% or higher. The GDG agreed that return rates could be assumed to exceed this figure with a very high degree of confidence. The sensitivity analyses are detailed in an addendum to Appendix H of the full guideline, and the GDG's consideration of the issue has been expanded in the relevant LETR table (section 3.1.4.5).
TB Alert	Short	26	11	This does not differentiate between patients who are tested for latent TB as individual cases (for example opportunistically tested when seeing a GP for another reason) from people who are tested as part of a comprehensive programme of new entrant testing. It is not practical to use	Thank you for your comment. With regards to the differing advice provided by the TB strategy, there are key differences with the scope and methodology of this guidance. Foremost among these is the fact that the TB strategy centred upon a population-level screening programme for new

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				Mantoux for large scale screening programmes in primary care. From an administrative perspective, it is not practical to provide Mantoux training for sufficient numbers of nurses in primary care. Additionally, the suggested 5mm threshold was lead to many false positives. From a patient perspective there are several barriers: the patient is required to attend clinic twice and there will be significant DNAs for the second appointment; instead of having an extra blood test as part of a new patient screening, the patient has to have a test specifically for TB which they might resist due to stigma in certain communities – the distinction between latent and active TB will not necessarily overcome this. This recommendation also directly contradicts PHE/NHSE's new guidance documents for implementing the Collaborative TB Strategy for England, which recommends IGRA for new entrant LTBI testing.	migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas. Additional sensitivity analysis has examined the impact of lowering the TST return rate on the cost-effectiveness results and is described in an addendum to Appendix H of the Full Guideline. .
Royal College of Nursing	Short	26	11	Our members have indicated that this does not correlate with the TB strategy, as by using tuberculin skin tests (TST) in new entrants may lead to increase DNAs compared to one appointment for IGRA.	Thank you for your comment. Although the scope and methodology for the TB strategy overlaps with that for this guidance to some degree, there were key differences. Foremost among these is the fact that the TB strategy centred upon a population-level screening programme for new

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					migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas.
London TB workforce Group	Short	26	11	This recommendation will be a challenge in practice because there will be training issues if mantoux is recommended as the main screening tool. Issues include having to set up PSD's to administer mantoux, ensuring ongoing training for staff, currently mantoux is not frequently used outside of TB services, mantoux availability has been problematic which will may cause delays and backlogs for services to deal with. There is also the issue of the patient having to make to two visits if mantoux is used, high possibility of DNA's.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
London TB	Short	26	11	If new entrant screening is at a population level	Thank you for your comment. This guidance only

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workforce Group				we question the advised two pronged approach development it would be more suitable for services to offer IGRA – particularly in light that it is recommended to consider a single interferon-gamma release assay for other large groups of people.	covered diagnosis of latent TB in new entrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. The screening of new entrants as part of a formalised screening programme was explicitly excluded from the scope.
London TB workforce Group	Short	26	11	Also – has anyone looked at person acceptability to either test?	Thank you for your comment. The acceptability of the tests was included as an outcome of interest in the review protocols for these reviews. The Guidelines Manual (2012) states that 'Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them. Thus, if the evidence suggests that an intervention or service provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population' (chapter 7).
British Thoracic Society	Short	26	24 28	P26 1.2.1.10 6-9 is it correct that the only group that have a 6 week re-screen are children age 2-17? Again inconsistent as indicated in prior comments	Thank you for your comment. Re-screening after 6 weeks is also recommended in children aged between 4 weeks and 2 years: "If a child aged between 4 weeks and 2 years has

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				with respect to retesting times.	been in close contact with people with smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment: • Assess for active TB. • Start treatment for latent TB and carry out a Mantoux test. • If the Mantoux test is inconclusive, refer the child to a TB specialist. This should be a specialist in paediatric TB or, as a minimum, a paediatrician with experience in TB. • If the Mantoux test is positive (5 mm or larger, regardless of BCG history), reassess for active TB; if this assessment is negative, complete treatment for latent TB. • If the Mantoux test is negative, continue treatment for latent TB, reassess for active TB **after 6 weeks and repeat the Mantoux test:** o if the Mantoux test is negative, consider an interferon-gamma release assay o if the interferon-gamma release assay is negative, treatment for latent TB may be stopped; give a BCG vaccination if the child has not already had one o if either test is positive, reassess for active TB; if this assessment is negative,

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					complete treatment for latent TB" In the case of adults, although it is agreed that the update of the recommendations may be useful, the content of the guideline is restricted to the areas detailed within the scope. Because the diagnosis of latent TB in this population was out of scope, changes could only be made to the wording in order to ensure consistency with other recommendations (e.g. treatment for LTBI is now recommended up to the age of 65 – in order for this to be achieved, we need to test up to the age of 65), for clarity of the recommendation, or, for example, because of equalities duties or a change in the availability of medicines. It was not possible to review the use of repeat testing in this population. Areas that have not been reviewed in this update may be addressed 2 years after publication, when NICE next considers updating this guideline. NICE may undertake a more rapid update of discrete areas of the guideline if new and relevant evidence is published.
British Thoracic Society	Short	27	4 12	P27 1.2.1.14 lines 4-12 please note this is inconsistent with BHIVA guidelines (British HIV Association guidelines for the treatment of TB/HIV coinfection 2011): ''In patients with AIDS or CD4 counts < 200 cells/mL, the sensitivity of the test is only 0–20%.	Thank you for your comment. The recommendations for diagnosis latent TB in people who are immunocompromised are based on updated clinical- and cost-effectiveness reviews. As stated in the Evidence to Recommendations table, these found IGRAs to be the most sensitive option in this patient group.

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				False positives occur after BCG immunization. Some data suggest that combining IGRAs and tuberculin testing improves sensitivity [1,24]. We do not recommend the routine use of TSTs In an HIV-infected individual with a positive IGRA, the risk of developing active TB, and therefore the need for chemo-preventative therapy, are based on (see Table 9 and Flow Chart 1): _ region of origin; _ current blood CD4 cell count; _ duration of time on HAART. HIV-positive patients at increased risk fall into the following groups for countries of origin: _ sub-Saharan Africa – if duration of current antiretroviral therapy is < 2 years, whatever the current blood CD4 cell count; _ medium TB incidence countries – if duration of current antiretroviral therapy is o2 years and current CD4 count is <500 cells/mL; _ low-incidence countries, for example the United Kingdom (for Caucasians) – if not on antiretrovirals, or if duration of current antiretroviral therapy is < 6 months and current CD4 count is < 350 cells/mL.	For this reason, the economic model suggested that TST-led strategies are dominated (are more expensive and less effective) by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).

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				Patients should be offered screening with IGRA if (and only if) they are in one of these groups and would benefit from chemoprophylaxis [BII].''	
London TB workforce Group	Short	27	4 12	Please note this is inconsistent with BHIVA guidelines: In patients with AIDS or CD4 counts o200 cells/mL, the sensitivity of the test is only 0–20%. False positives occur after BCG immunization. Some data suggest that combining IGRAs and tuberculin testing improves sensitivity [1,24]. We do not recommend the routine use of TSTs In an HIV-infected individual with a positive IGRA, the risk of developing active TB, and therefore the need for chemo-preventative therapy, are based on (see Table 9 and Flow Chart 1): _ region of origin; _ current blood CD4 cell count;	Thank you for your comment. The recommendations for diagnosis latent TB in people who are immunocompromised are based on updated clinical- and cost-effectiveness reviews. As stated in the Evidence to Recommendations table, these found IGRAs to be the most sensitive option in this patient group. For this reason, the economic model suggested that TST-led strategies are dominated (are more expensive and less effective) by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone).

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				_ duration of time on HAART. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011 e11 r 2011 British HIV Association HIV Medicine (2011) 12, e1–e26 HIV 954 HIV-positive patients at increased risk fall into the following groups for countries of origin: _ sub-Saharan Africa – if duration of current antiretroviral therapy is o2 years, whatever the current blood CD4 cell count; _ medium TB incidence countries – if duration of current antiretroviral therapy is o2 years and current CD4 count is o500 cells/mL; _ low-incidence countries, for example the United Kingdom (for Caucasians) – if not on antiretrovirals, or if duration of current antiretroviral therapy is o6	

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				months and current CD4 count is o350 cells/mL. Patients should be offered screening with IGRA if (and only if) they are in one of these groups and would benefit from chemoprophylaxis [BII].	
Public Health England	Short	27	21 22	"Outbreak" should be changed to "incident" and it would be helpful if the "incident" were clearly defined in the text not just the glossary. Consideration should also be given to adapting the glossary definition. A "TB Incident" definition currently used in London is: When a case of infectious TB is identified in a congregational setting, e.g. workplace, school, university, etc. where following a risk assessment, contact tracing and screening may be required.	Thank you for your comment. The terminology has now been amended to 'incident'.
London TB workforce Group	Short	27	21	We are concerned that the term "outbreak" is not appropriate – should be incident management	Thank you for your comment. The terminology has now been amended to 'incident'.

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George Eliot NHS Trust	Short	27	22	Should this say Incident not outbreak	Thank you for your comment. The terminology has now been amended to 'incident'.
London TB workforce Group	Short	27	22	We are concerned that this recommendation only covers incidents affecting 18 – 65 year olds. Incidents and screening can affect all ages and can occur in nursery, junior schools etc.	Thank you for your comment. The recommendation has been amended to cover all ages as follows: "In an incident situation when large numbers of people may need to be screened, consider a single interferon-gamma release assay for people aged 18–65 years. **For children and young people, follow recommendations 1.2.1.1 to 1.2.2.6.**"
London TB workforce Group	Short	28	7	We recommend that it is made clear what is meant by a high incident country - Suggest hyperlink to explanation	Thank you for your comment. This is defined in the glossary as follows: "A high-incidence country or area has more than 40 cases of TB per 100,000 people per year."
Health Protection Scotland	Short	28 188	8	"recently arrived" Is there is a definition for recently as open to different local definitions of "recently"	Thank you for your comment. Health professionals should use their judgement to interpret the term 'recently arrived'. This may be useful in cases, for example, where people have arrived from countries with a particularly high incidence of disease, or where there may be high rates of comorbidities – such as HIV – which may increase the likelihood that the individual is infected. Both of these may lead a health professional to employ a more permissive

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					definition of 'recently arrived'.
London TB workforce Group	Short	28	16	Offer an interferon-gamma release assay test to new NHS 16 employees who have had contact with patients in settings where TB is highly prevalent. We recommend that *patients in settings where TB is highly prevalent* is clarified. Hyperlink to explain?	Thank you for your comment. Unlike 'high incidence', high prevalence is not defined numerically, rather it is defined by risk factors. There are two ways in which settings may be considered 'high prevalence' in this guidance. One is where there are people at a high risk of TB, which is described in section 1.2 of the 'short version' of the guideline: • contacts of people with infectious disease • new entrants from high incidence countries • people who are immunocompromised • healthcare workers in contact with TB patients or clinical materials • people from underserved groups, including people who are homeless, people who misuse substances, prisoners and other detainees and vulnerable migrants. A second is due to a high risk of progressing to active disease once infected – specified in recommendation 1.2.2.1 as people who: • are HIV positive; • are children younger than 5 years; • have excessive alcohol intake;

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					• are injecting drug users; • have had solid organ transplantation; • have a haematological malignancy; • are having chemotherapy; • have had a jejunoileal bypass; • have diabetes; • have chronic renal failure or are receiving haemodialysis; • have had a gastrectomy; • are having anti-tumour necrosis factor-alpha treatment or other biologic agents; or • have silicosis.
British Thoracic Society	Short	28	19	Does this include pre TNF treatment assessment? If so this should be explicitly stated or no guidance on this important area is given.	Thank you for your comment. Yes. The definition of 'immunocompromised' is provided in the glossary as follows: "In this guideline, immunocompromised refers to a person who has a significantly impaired immune system. For instance, this may be because of prolonged corticosteroid use, tumour necrosis factor-alpha antagonists, antirejection therapy, immunosuppression-causing medication or comorbid states that affect the immune system, for example, HIV, chronic renal disease, many haematological and solid cancers, and diabetes."

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NHS England	Short	29 139	1 10 23	The advice to offer IGRA in the settings described in this section conflicts with advice elsewhere in the draft guidance i.e. migrants, contact tracing, healthcare workers (section 1.2, short version) regarding the use of IGRA and we question the rationale for its use with this population (the prison population) but not in the general population.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment. .
London TB workforce Group	Short	29	1	This recommendation will have cost implications for substance misuse services – also need clarity are they to do this independently of their local TB service?	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment.
London TB workforce Group	Short	29	4	We recommend that it is made clear what is meant by a high incident area - Suggest hyperlink to explanation	Thank you for your comment. This is defined in the glossary as follows: "A high-incidence country or area has more than 40 cases of TB per 100,000 people per year."
London TB workforce	Short	29	10	This recommendation may be a challenging change in practice for prison services and there	Thank you for your comment. This is a recommendation from PH37. As per the scope for

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Group			14	should be some clear framework to support this otherwise it is not practical suggesting that they do this in isolation of TB services.	this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment.
London TB workforce Group	Short	29	17	Routine testing and treatment for those in prison and attending substance misuse services will require education, pathways and funding. Implications for TB services to deliver this training.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment.
Oxleas NHS Foundation Trust	Short	30	1.2.2.1	People with low Vit D may need to be added to the groups of people with latent tb at increased risk of tb activation..There is extensive evidence to this based on previous studies conducted ie Experiment done in Mongolia in 2012, Vit D study in Pakinstan 2010 etc.	Thank you for your comment. The GDG discussed the inclusion of low vitamin D amongst the groups at increased risk of progression from latent to active TB but did not feel that it was a useful indicator. Further work would be required to define what is meant by 'low'.
British Thoracic	Short	30	4	There is no mention of giving 6 months rifampicin for latent TB assumed to be isoniazid-resistant in the section on Managing latent TB (1.2.2) nor of	Thank you for your comment. Although searched for, no evidence was identified that examined the treatment of latent TB exclusively in people in

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Society		31 32	31 1 29 1 11	what to do if a close contact of MDR TB is diagnosed with latent TB. This may be hidden somewhere else in the guideline but ought to appear here.	whom the infection was suspected to be drug resistant (for example, because the index case had drug resistant tuberculosis). The GDG did not, therefore, feel able to make recommendations on which regimen should be used in this population. Contact-tracing for index cases with MDR-TB with should be as for drug susceptible disease, though it is considered more urgent. The LTBI treatment regimen may be designed based on the resistance pattern of the isolate from the index case, though chemoprophylaxis is not always given. Patients should be referred to a specialist or, as a minimum, their management should be discussed with the specialist advisory services through the regional multidrug-resistant TB network. Although it is agreed that further MDR-specific recommendations would be useful, the Committee were prevented from this by both the rarity and case-specific nature of MDR management, as well as a paucity of evidence.
Our life	Short	30	5	It would be beneficial to add a bullet point stating 'in insecure or unsuitable housing or are homeless	Thank you for your comment. It has been shared with the GDG. However, because no evidence was seen in support of its inclusion, it was not included in the recommendation.
London TB workforce	Short	30	8	We suggest that pregnancy and post-partum period is added to this list of people at increased	Thank you for your comment. It has been shared with the Committee. However, because no

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Group			19	risk of developing active TB (we are not advocating treatment for LTBI, rather raising awareness of the risk). The incidence of TB diagnosis is significantly increased postpartum. Although we did not find an increase during pregnancy, the postpartum incidence may reflect an increase during pregnancy given diagnostic, immunological and administrative delays. Clinicians' awareness should be improved and the effectiveness of public health policy measures such as targeted screening of pregnant and postpartum women in high-risk groups should be evaluated Ref: Risk of tuberculosis in pregnancy: a national, primary care based cohort and self-controlled case series study. http://www.atsjournals.org/doi/pdf/10.1164/rccm.201106-1083OC	evidence was seen in support of its inclusion, it was not included i the recommendation.
George Eliot NHS Trust	Short	30	20	When shall we take CXR? 3 months from when then 12 months from the first CXR?	Thank you for your comment. The guidance for managing people with latent TB who are at increased risk of going on to develop active TB but who choose not to undergo treatment for latent TB has changed. Chest X-rays are no longer recommended after 3 and 12 months due to a lack of clinical- and cost-effectiveness evidence. People "should be advised of the risks

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					and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise' information."
British Thoracic Society	Short	30	25 26	Needs clarification –Is this 3 month/12 month xrays for PTB contacts only OR routine testing for LTBI in which case (confusing ref to all groups in 1.2.2.2 – 1.2.2.9). If it is all groups, there is no rationale for 3 and 12 month CXR for those with a long term condition and likely remotely acquired LTBI.	Thank you for your comment. The guidance for managing people with latent TB who are at increased risk of going on to develop active TB but who choose not to undergo treatment for latent TB has changed. Chest X-rays are no longer recommended after 3 and 12 months due to a lack of clinical- and cost-effectiveness evidence. People "should be advised of the risks and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise' information."
London TB workforce Group	Short	30	25	Needs clarification –Is this 3 month/12 month x-rays for PTB contacts only or routine testing for LTBI?	Thank you for your comment. The guidance for managing people with latent TB who are at increased risk of going on to develop active TB but who choose not to undergo treatment for latent TB has changed. Chest X-rays are no longer recommended after 3 and 12 months due to a lack of clinical- and cost-effectiveness evidence. People "should be advised of the risks and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise'

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					information."
London TB workforce Group	Short	30	25	What is the rationale for 3 and 12 month CXR for those with a long term condition and likely remotely acquired LTBI	Thank you for your comment. The guidance for managing people with latent TB who are at increased risk of going on to develop active TB but who choose not to undergo treatment for latent TB has changed. Chest X-rays are no longer recommended after 3 and 12 months due to a lack of clinical- and cost-effectiveness evidence. People "should be advised of the risks and symptoms of TB (on the basis of an individual risk assessment), usually in a standard letter of the type referred to as 'Inform and advise' information."
British Thoracic Society	Short	30 31	27 1 2	The omission of the rifapentine/isonaizid and also rifampicin alone regimes for LTBI are significant and need consideration and inclusion. Was the evidence considered especially the impact weekly versus daily latent TB treatment may have on the completion rates amongst vulnerable groups e.g. prisoners, homeless etc.	Thank you for your comment. As rifapentine is not currently licensed in the UK, the Committee was unable to make recommendations on its use. It was, however, included in the evidence base as a comparator. There was only limited evidence identified for rifampicin-alone regimens. These did not perform well compared to the 2 recommended regimens. Adherence is one of the outcomes for which data are reported in our review; however, we did not perform separate analyses for vulnerable groups. Please see the separate review question on Adherence and treatment completion (section

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					9.2).
Public Health England	Short	31	1 2	The recommendation of Rifinah or Isoniazid for treatment of LTBI. This appears based on a network meta-analysis (appendix L) and cost effectiveness analysis performed by Imperial (appendix i). It is unclear why the network analysis (similar to one we published last year in Annals) omits 3-4 months Rifampicin monotherapy from its analysis of effectiveness, which was favoured in our review(2) and elsewhere(3). It is also unclear why the scarce evidence for 1RZ (based on a single study (0 events of n=80) still featured as the most effective regimen in the review. References 1. World Health Organization. Guidelines on the management of latent tuberculosis infection [Internet]. 2014. Available from: http://www.who.int/tb/publications/ltbi_document_page/en/ 2. Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of Latent Tuberculosis Infection: A Network Meta-analysis. Ann Intern Med. 2014 Sep 16;161(6):419–28. 3. Sharma SK, Sharma A, Kadhiravan T,	Thank you for your comment. The review undertaken for this question did not identify any RCTs of rifampicin monotherapy that reported activation of TB as an outcome. An important difference between the review protocol for this guideline question and the methods adopted in the published reviews cited is that the GDG chose to include RCTs only if they had been conducted in populations with diagnostic evidence of LTBI (in practice, this meant participants had to be TST-positive, as this was the test used by all identified studies). In contrast, Stagg et al. and Sharma et al. include studies in which contacts of known cases (and other people at high risk of TB) have received chemoprophylaxis, without any investigation of markers of LTBI. For this reason, our review and NMA contain fewer studies than those publications. The GDG discussed this issue in detail at the time the review protocol was finalised and concluded that the advantages of concentrating on a setting that directly reflects the decision problem (i.e. people with LTBI) outweighed any benefit that would be gained from including a broader range of evidence.

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				Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013;7:CD07545.	It is correct that the evidence for 1RZ is sparse; however, this uncertainty is appropriately reflected in the wide credible intervals around estimated treatment effects. This treatment did not have sufficient relevant data to be included in the original health economic model. For this and other reasons (including licensing), no recommendation is made supporting the use of pyrazinamide-containing regimens.
British Thoracic Society	Short	31	3	"Concerns about hepatotoxicity" is very vague you could argue that the concern is being aged over 35 – should the risks be spelt out?	Thank you for your comment. Concerns might include abnormal pre-treatment liver function tests, liver disease, alcoholism or drug use. This has now been stated in the Evidence to Recommendations table.
London TB workforce Group	Short	31	5	There is no recommendation for the use once weekly Isoniazid and Rifapentine 3 month regimen. This will aid in adherence and DOT. We recognise cannot recommend unlicensed drugs in the UK, however, given the emphasis to increase LTBI testing and treatment and complexities of supporting these groups once weekly Isoniazid and Rifapentine 3 month regimen would very much support adherence and DOT. http://www.cdc.gov/tb/topic/treatment/ltbi.htm	Thank you for your comment. However, as rifapentine is not currently licensed in the UK, the Committee was unable to make recommendations on its use. It was, however, included in the evidence base as a comparator.

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British Thoracic Society	Short	31	16	Checking liver function before starting treatment for latent TB particularly if using both isoniazid and rifampicin should also be specified although it is implied by 1.2.2.8	Thank you for your comment. Although investigation of liver function is important before undertaking treatment, it is not within the scope of this guideline to define what constitutes 'normal' or 'appropriate' liver function – this is an issue that goes beyond TB. However, following review of the SPCs for isoniazid and rifampicin, the following text has been added to the Evidence to Recommendations table: "The group concluded that the evidence overall, in conjunction with their own clinical experience, supported their recommendation that liver function should be assessed before treatment is initiated, as specified in the British National Formulary. **Isoniazid, especially if given with rifampicin, may induce abnormalities in liver function, particularly in patients with pre-existing liver disorders, the elderly, the very young and the malnourished. The Summary of Product Characteristics for isoniazid and rifampicin (the drugs recommended by this guideline for the treatment of latent infection) recommend that transaminase measurements – especially glutamic pyruvic transaminase and glutamic oxaloacetic transaminase – be obtained at baseline.**

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					Furthermore, those with abnormal liver function before treatment initiation should undergo more cautious management of their regimen, including careful clinical **monitoring – the Summary of Product Characteristics for isoniazid and rifampicin recommend that this be undertaken monthly**. They did not feel that it was strong enough to recommend that people with abnormal liver function not be eligible for treatment."
NHS England	Short	31 28 40	16 45 19	We note that the cost implications for extended screening for HIV, Hep B&C to those tested for latent TB infection have not been included in these documents. While we recognise the approach of a 'one stop shop' to target people at high risk of other infectious diseases but recognition needs to be made of the financial impact.	Thank you for your comment. This was discussed with the GDG and the recommendation has been amended as follows: New text in the Evidence to Recommendations table The group noted the increased risk of hepatotoxicity during treatment during latent tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore concluded that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment

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					and that treatment could be carefully managed and monitored if undertaken. **They concluded that the reduced risk of hepatitis B or C coinfection in children, and the impact this would have on the cost-effectiveness of testing, meant that only a weak recommendation for testing could be made.** They also stated that health economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing those at increased risk of coinfection would have been useful to their decision-making. New recommendations *Offer testing for HIV before starting treatment for latent TB. See NICE guidelines on increasing the uptake of HIV testing among black Africans in England and increasing the uptake of HIV testing among men who have sex with men.* *Offer testing for hepatitis B and C before starting treatment for latent TB in adults. Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and*

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					management of chronic hepatitis B in children, young people and adults.
Public Health England	Short	31	16 24	This is a very good recommendation – could it be made more clear that it does also relate to children in general (if that is the intention)	Thank you for your comment. All adults about to undergo treatment for latent TB should be offered hepatitis B and C testing (strong recommendation), whereas it should only be considered in children (weak recommendation). This was in recognition of stakeholder concerns regarding the cost-effectiveness of testing children for hepatitis B and C. It was still concluded that testing should be an option in children, however, in recognition of the potential for increased hepatotoxicity of treatment for latent TB in children who had hepatitis B and C, and the impact that this would have on the choice of treatment. Testing would therefore offered on the basis of a risk assessment. New text in the Evidence to Recommendations table: "The group noted the increased risk of hepatotoxicity during treatment during latent tuberculosis infection. Although the evidence was limited, it is also the experience of the GDG that those at increased risk of tuberculosis infection are at an increased risk of hepatitis B and C, and that this carries an increased risk of drug-induced hepatotoxicity. The group therefore concluded

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					that testing those at increased risk of hepatitis coinfection was important, such that informed decisions could be made with regards treatment and that treatment could be carefully managed and monitored if undertaken. **They concluded that the reduced risk of hepatitis B or C coinfection in children, and the impact this would have on the cost-effectiveness of testing, meant that only a weak recommendation for testing could be made.** They also stated that health economic evidence on the testing of all patients with latent tuberculosis infection for hepatitis (and other blood borne viruses) against just testing those at increased risk of coinfection would have been useful to their decision-making." Updated recommendations: "Offer testing for hepatitis B and C before starting treatment for latent TB in adults. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults." "Consider testing for hepatitis B and C before starting treatment for latent TB in children and young people. See NICE guidelines on hepatitis B and C: ways to promote and offer testing to

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					people at increased risk of infection and hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults."
London TB workforce Group	Short	31	16	Have hepatology services been consulted/ contributed to this guidance/ impact on their service considered?	Thank you for your comment. Hepatology services were welcome to register as a stakeholder, and through this take part in the consultation process. With regard the impact on their service, hepatotoxicity of antituberculosis drugs was integrated into a number of reviews (including diagnosis and treatment of latent infection). Furthermore, this comment has been shared with the NICE implementation support team to inform their support activities for this guideline.
London TB workforce Group	Short	32	6	This recommendation will have implications for services as will increase enhanced case management and require adequate resources to administer DOT and other workload activity - again the use of a once weekly prophylaxis regimen should be considered?	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline. Studies on the use of a once weekly prophylaxis regimen that met the inclusion/exclusion criteria for the reviews conducted on the treatment of latent TB infection would have been included in the evidence base.
London TB workforce	Short	32	20	It would be useful to have some information on the drug regimen, there is an assumption that	Thank you for your comment. A cross reference to the relevant recommendations has now been

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Group				staff reading the guidance will be aware of what the drug regimens are – suggest hyperlink to the information	inserted.
British Thoracic Society	Short	33 34	6 7 6 1	Obtaining confirmatory positive TB cultures from children who usually have primary pulmonary TB often only manifest by enlarged mediastinal lymph nodes is notoriously difficult. This is acknowledged in the discussion in the full version of the guidelines which I think also mention that using a combination of methods may increase the chances of diagnostic yield. I also recall that it states that the chances of a positive culture from BAL may be higher when there is evidence of lung parenchymal involvement and presumably if the lavage were directed to the affected lung segment. It is therefore surprising that although bronchoscopic lavage is included as a diagnostic investigation for adults, it is omitted for young people and children. The role of bronchoscopy in paediatric TB is controversial but it should not be ignored altogether. Studies comparing different diagnostic investigations in children are small and often flawed. It may be preferable to state: "Bronchoscopic lavage is not the preferred diagnostic investigation in children and young people but may be considered particularly if there are focal parenchymal abnormalities on the chest X-ray"	Thank you for your comment**.** Only limited evidence was available for bronchoalveolar lavage, such that the GDG concluded that there was insufficient evidence to suggest that it should be used in place of sputum induction or gastric aspiration. They noted the invasiveness of this procedure, which requires highly skilled personnel and significant sedation and analgesia. The use of general anaesthesia reduces the distress of the child involved but carries inherent risks, whereas intramuscular injections of local anaesthesia can be very painful and upsetting for the child, as well as their parents or carers and the clinician administering the intervention. These points are noted in the Evidence to Recommendations table.

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London TB workforce Group	Short	33	6 7	We welcome this, however there is service implications here as there are areas/ services that do not have access to sputum induction facilities and there will be training needs to be met.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
NHS England	Short	33 29	16 31	The developments in diagnostics for identification of what TB mycobacterium the patient has changed rapidly over the last few years and this document does not make any reference to Whole Genome Sequencing (WGS), which is either in place or being put into place for a range of diseases including TB. The document is very specific about what tests should be used and we would like to see a statement that includes either WGS or 'advances in identification' to ensure that the TB patient and their treatment is not adversely affected by lack of use of the latest diagnostic tests.	Thank you for your comment. It has been shared with the GDG However, because no evidence was seen in support of its inclusion, it was not included in the recommendations.
British Thoracic Society	Short	33	27 31	Offering a NAAT automatically for all children and young people with suspected TB is generous but very welcome if it would help to improve diagnostic yields.	Thank you for your comment.
London TB workforce Group	Short	35 41	General	We are aware that no clear evidence exist – some direction on diagnostic approaches and length of active treatment for those presenting	Thank you for your comment. For the diagnosis of uveitis/ocular TB, see the following recommendation:

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				with uveitis/ocular TB should be included.	"Refer to an expert for sites not listed here, including TB of the eye and other rare sites of disease." For the treatment of uveitis/ocular TB, see the following recommendations: "For people with active TB without central nervous system involvement, offer: • isoniazid (with pyridoxine), rifampicin, pyrazinamide and ethambutol for 2 months, then • isoniazid (with pyridoxine) and rifampicin for a further 4 months. Modify the treatment regimen according to drug susceptibility testing." "For people with active TB of the central nervous system, offer: • isoniazid (with pyridoxine), rifampicin, pyrazinamide and ethambutol for 2 months, then • isoniazid (with pyridoxine) and rifampicin for a further 10 months. Modify the treatment regimen according to drug susceptibility testing."
Public Health	Short	36	General	The information in tables 2-11 is helpful but to aid assimilation of this we would recommend that the	Thank you for your suggestion. It was felt that a further table would not be a useful addition to the

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England		41		individual tables 2-11 are brought together into one table	Short or Full versions of the guideline. However, your comment has been shared with the NICE implementation support team to inform their support activities for this guideline.
George Eliot NHS Trust	Short	42	25 27	There is a statement on the need to treat people who have had a lymph node surgically removed. There is no similar comment on cases where a tuberculoma in the lung has been surgically removed. This happens with reasonable regularity when an indeterminate pulmonary nodule is excised for diagnostic and therapeutic purpose.	Thank you for your comment. It has been shared with the GDG. However, it was not considered necessary to include this in the recommendations.
British Thoracic Society	Short	43	5 6	Dosing regimen recommendations for children have been omitted. Some mention should be made of the need for relative increased dosing in children indicated by pharmacokinetic studies. Adult recommendations for fixed-dose combination tablets in the UK based on weight do not necessarily give the doses required in children. However fixed-dose combinations can help to reduce the pill burden if the doses are supplemented with single drug tablets. Thus the following recommendation could be made: "*Fixed-dose combination tablets can be used for children and young people who can swallow tablets but may require additional single drug supplementation to achieve the relatively higher per kg doses recommended by WHO for*	Thank you for your comment. For drug dosing in children, clinicians should refer to the British National Formulary for Children.

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				children". These would be: • Isoniazid: 10 mg/kg/day (10-15 mg/kg/day) • Rifampicin: 15 mg/kg/day (10-20 mg/kg/day) • Pyrazinamide: 35 mg/kg/day (30-40 mg/kg/day) • Ethambutol: 20 mg/kg/day (15-25 mg/kg/day)	
British Thoracic Society	Short	44	13	There is no mention in the recommendations that the bioavailability of adjunctive corticosteroids would be reduced by concurrent rifampicin. A recommendation for the use of adjunctive corticosteroids for reducing extrinsic bronchial compression from massive mediastinal lymph nodes should be included.	Thank you for your comment. However, the GDG did not feel that the evidence identified supported such a recommendation.
British Thoracic Society	Short	45	8	Is the evidence for the use of steroids in pericardial TB still considered robust in view of recent trial evidence?	Thank you for your comment. Although not extensive, the GDG noted that there was some evidence to show that corticosteroids decreased mortality, although this effect was not statistically significant. Overall, the GDG concluded that the evidence supported the use of corticosteroids in patients with pericardial tuberculosis. Although the meta-analysis did not provide strong evidence in terms

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					of corticosteroid use reducing mortality, this meta-analysis was unable to include the long term survival data from the Strang paper due to the format in which it was reported. When viewed in isolation, the survival analysis in this paper showed a clear protective effect.
British Thoracic Society	Short	45	8	Should the risks versus benefits of high dose steroids be mentioned especially in HIV infected patients. N Engl J Med. 2014 Sep 18;371(12):1121-30. doi: 10.1056/NEJMoa1407380. Epub 2014 Sep 1.Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis.	Thank you for your comment. However, the GDG were unable to make such recommendations as they had not seen any relevant evidence on this subject (dosing of steroids was not covered in the review protocols).
TB Alert	Short	46	4 5	Suggest that a statement be included which captures the fact that A&E could be the first point of presentation to NHS services by some with suspected TB and therefore it is vital that they are supported and treated effectively with clear referral routes etc	Thank you for your comment. This forms part of the rationale for developing these recommendations and is included in the FULL guideline. This level of detail is however, not relevant for the recommendations.
London TB workforce Group	Short	46	13	Same can be done in primary care so same recommendation please.	Thank you for your comment. The GDG did not consider any evidence on primary care referral specifically. However, recommendation 1.8.9.5 recommends all healthcare professionals ensure first line diagnostic tests are available.

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British Thoracic Society	short	47	3	CNS adjunctive surgery should also be considered if tuberculous brain abscess	Thank you for your comment. The GDG were unable to make such recommendations as they had not seen any relevant evidence on this subject.
London TB workforce Group	Short	47	24	Wording is poor – and if resistance suspected then need for infection control measures should have started before getting the Rif probe	Thank you for your comment. The recommendations have been amended as follows: "For people with clinically suspected TB, a TB specialist should request rapid diagnostic nucleic acid amplification tests for rifampicin resistance on primary specimens if a risk assessment for multidrug resistance identifies any of the following risk factors: • history of previous TB drug treatment, particularly if there was known to be poor adherence to that treatment • contact with a known case of multidrug-resistant TB • birth or residence in a country in which the World Health Organization reports that a high proportion (5% or more) of new TB cases are multidrug-resistant. **Start infection control measures.**" "If the rapid diagnostic nucleic acid amplification test for rifampicin resistance is positive:

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					• ~~start infection control measures and~~ continue infection control measures until pulmonary disease has been excluded • manage treatment along with a multidisciplinary team with experience of managing multidrug-resistant TB • offer a treatment regimen involving at least 6 drugs to which the mycobacterium is likely to be sensitive • test for resistance to second-line drugs."
Abbott Molecular	Short	47	12 to 15	Resistance to one of the two most commonly used drugs in the current four-drug (or first-line) regimen, isoniazid and rifampin define multidrug-resistant TB (MDR-TB). The instructions do only mention resistance to Rifampicin so we will recommend also to include that TB specialists should request rapid diagnostic nucleic acid amplification tests for INH resistance on primary specimens	Thank you for your comment**.** These recommendations are concerned with multidrug resistance, which rifampicin resistance is considered a proxy for. This is why no other resistances are mentioned.
Abbott Molecular	Short	48	2 to 4	Resistance to one of the two most commonly used drugs in the current four-drug (or first-line) regimen, isoniazid and rifampin define multidrug-resistant TB (MDR-TB). We would recommend the TB specialist to access INH resistance before treating as drug-	Thank you for your comment. Recommendations 1.3.7.2 and 1.3.7.3 state that clinicians should "modify the treatment regimen according to drug susceptibility testing." Treatment should be started without waiting for culture results if there are clinical signs and symptoms consistent with a diagnosis of TB, as per recommendation 1.3.1.2,

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				susceptible TB with the standard regimen	in order to reduce the risk of morbidity or mortality in the patient.
British Thoracic Society	short	49	13	With respect to isoniazid resistance, Rifampicin and ethambutol for 7 months (up to 10 months for extensive disease) as a recommendation appears poor. The evidence to give treatment for just 9 months is lacking and we feel that INH resistant TB should always be treated for one year.	Thank you for your comment. The GDG discussed this but expressed concerns regarding treatment periods that may be unnecessarily long and the impact that they have on the patient.
George Eliot NHS Trust	Short	51	23	Definition of grading needed such as scanty, moderate or profuse?	Thank you for your comment**.** The GDG were unable to make such recommendations as they had not seen any relevant evidence on this subject. However, the GDG did state that "laboratory practices should be in accordance with the UK's Public Health England's Standards for Microbiology Investigations" (see recommendation 1.3.2.2).
London TB workforce Group	Short	52	12	The guidance is suggesting respiratory precautions for those with pulmonary TB for the first 2 weeks regardless of smear status. Patients (without risk of MDR and not on wards with immunocompromised patients) with no cough and / or x3 smear negative sputa or BAL smear negative would usually be de-isolated and not wait for completion of 2 weeks of treatment.	We agree with your comment. The Committee concluded that there was insufficient evidence to shorten the duration of isolation from the previously recommended 14 days whilst on chemotherapy, but did agree that following 14 days of treatment that it was appropriate to consider discharging the patient from isolation based on a risk assessment and consideration of the discharge destination. This is noted in the

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					Evidence to Recommendations table.
TB Alert	Short	52	25	TB Alert would like to see stronger wording/emphasis here as the LA does have a legal responsibility to accommodate vulnerable people with TB (as a PH risk) even if they do not have legal status. This is a loophole which has affected TB teams being able to support and encourage such individuals to complete their treatment	Thank you for your comment. This has been amended to: "Work with the local public health team and the local authority to ensure accommodation for people with TB"
Janssen	Short	53	11	There is lacking detail with regards to the treatment options available in the management of MDR-TB. Given MDR-TB is a complex and challenging disease to treat, it would be beneficial to tabulate the current treatment options available in the NHS, as stratified by class. Specific reference to page viii) in the "Companion handbook to the World Health Organisation guidelines for the programmatic management of drug-resistant tuberculosis", details this respective information. This would ensure that the updated guidelines reflect recent advances in MDR-TB treatment through acknowledging novel agents available in class 5. This would provide clarification for respective formulary listings and commissioner requests, therefore supporting a more rapid application of	Thank you for your comment. Although it is agreed that more detailed and MDR-specific recommendations would be useful, the GDG were prevented from this by both the rarity and case-specific nature of MDR management, as well as a paucity of evidence. Patients should be referred to a specialist or, as a minimum, their management should be discussed with the specialist advisory services through the regional multidrug-resistant TB network.

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				the guidelines in clinical practice.	
London TB workforce Group	Short	53	21	We suggest remove the word ideally. We advocate that patients with MDR TB should have x3 negative cultures (Vs smears)	Thank you for your comment. It has been shared with the GDG; however, they did not decide to change the recommendation.
George Eliot NHS Trust	Short	56	1	Please confirm you mean we just screen close contacts of pulmonary cases, not extra-pulmonary cases?	Thank you for your comment. Yes. The GDG concluded that, due to the resource implications of contact-tracing and the relatively few cases identified by tracing contacts of people with extrapulmonary TB, contact-tracing should be limited to those index cases who are infectious (those with pulmonary TB).
Public Health England	Short	57	20 23	We would recommend adding: Consider on-site/community screening to improve uptake of screening This should also be added to screening at other settings, such as childcare or workplace Reference 1. London LTB Extended contact tracing (LTBEx) team; unpublished data 2. http://www.ncbi.nlm.nih.gov/pubmed/22236846 Duarte R, Neto M, Carvalho A, Barros H. Improving tuberculosis contact tracing: the role of evaluations in the home and workplace. Int J Tuberc Lung Dis 2012; 16:	Thank you for your comment. This recommendation was incorporated from CG117 and was not part of the draft guideline consultation. Please also see section 1.6.1 which has more recommendations around contact tracing where reference is given to appropriate settings for contact tracing under different situations.

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				55–59.	
George Eliot NHS Trust	Short	58	24 28	This and the next point are ambiguous as household contacts are over 8hrs – so we need a definition of immunosuppressed as that's most in-patients and who should identify who they are	Thank you for your comment. In this guideline, immunocompromised refers to a person who has a significantly impaired immune system. For instance, this may be because of prolonged corticosteroid use, tumour necrosis factor-alpha antagonists, antirejection therapy, immunosuppression-causing medication or comorbid states that affect the immune system, for example, HIV, chronic kidney disease, many haematological and solid cancers, and diabetes. This definition is provided in the glossary.
George Eliot NHS Trust	Short	59	1-6	As above - This and the next point are ambiguous as household contacts are over 8hrs – so we need a definition of immunosuppressed as that's most in-patients and who should identify who they are	Thank you for your comment. In this guideline, immunocompromised refers to a person who has a significantly impaired immune system. For instance, this may be because of prolonged corticosteroid use, tumour necrosis factor-alpha antagonists, antirejection therapy, immunosuppression-causing medication or comorbid states that affect the immune system, for example, HIV, chronic kidney disease, many haematological and solid cancers, and diabetes. This definition is provided in the glossary.
Kent Community Health NHS	Short	59	16 29	As above. Offering treatment for latent to new entrants 65 and younger contradicts TB strategy.	Thank you for your comment. Although the scope and methodology for the TB strategy overlaps with that for this guidance to some degree, there

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Foundation Trust: TB team					were key differences. Foremost among these is the fact that the TB strategy centred upon a population-level screening programme for new migrants, whereas the NICE guidance explicitly excludes this. The NICE guidance only covered diagnosis of latent TB in new migrants from high incidence countries who were identified 'opportunistically', not as part of a formalised screening programme. It details the tests that should be ordered if a new migrant from a high incidence country who has not yet been tested is identified, for example, by a GP or in the course of a hospital visit for other reasons. This means that the decision-making and recommendations, and the evidence reviews and health economic modelling that underpinned these, are focused on different areas. Our systematic review, network meta-analysis, and original economic analysis (conducted by Imperial College) suggests that the risk of hepatotoxicity remains low in older age groups and should be considered in the context of a greater relative risk of death from TB in older people. The model reflects that people aged 51–65 are approximately 5½ times more likely to develop hepatotoxicity when receiving antituberculosis drugs than people aged less than 35. However, people aged 45–64 are also 4 times more likely to die of active TB, if they develop it

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					(and their chance of doing so increase with age), than people aged 15–44. This proved to be an important consideration in balancing the risks and benefits of treatment in people of different ages. Please see Section 7.2.2 of the full guideline for more detail.
TB Alert	Short	60	12	Would like to see the addition of 'help community cased and voluntary orgs to successfully address TB-related associated myths and stigma' adding to 1.6.2.2 as we feel it is crucial that such workers who are regularly client facing with people who maybe at greater risk of TB have the skills and knowledge to remove any misconception or myth around TB as part of their discussion around registering with primary care etc.	Thank you for your comment. This is a recommendation from PH37. As per the scope for this guideline, such recommendations were not reviewed for the 2015 update. Changes have only been made for the purposes of clarification or, for example, because of a change in the availability of medicines. These recommendations are not, therefore, open for comment.
TB Alert	Short	63	General	Include in the incident team, additional personnel as needed such as TB Link Workers, Peer Educators, workers from relevant third sector organisations who work with the community in question to assist in building trust and rapport with the individual/group in question. Also suggest referring the reader to 1.8.11.1-3 to make it clear that there may be a need to provide accommodation in the event of an outbreak and who has responsibility for this. This could save valuable time when dealing with the incident.	Thank you for this comment. Peer educators and voluntary sector workers are members of the multi-disciplinary TB team as described in the glossary and, they are therefore implicitly included in these recommendations.

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Public Health England	Short	63	1.6.4.3	We would recommend adding another bullet point: • on-site screening should be encouraged wherever possible to improve uptake Reference: 1. London LTB Extended contact tracing (LTBEx) team; unpublished data 2. http://www.ncbi.nlm.nih.gov/pubmed/22236846 Duarte R, Neto M, Carvalho A, Barros H. Improving tuberculosis contact tracing: the role of evaluations in the home and workplace. Int J Tuberc Lung Dis 2012; 16: 55–59.	Thank you for your comment. The recommendation states "coordinate incident or outbreak contact investigations at places where the person with TB spends significant amounts of time" this could include on-site testing if this was considered appropriate by the incident team. NICE do not consider it is necessary to provide this level of detail as it is for local decision making on an incident by incident basis.
Public Health England	Short	63	11	We are concerned that section 1.6.4 is not very clear. It would be helpful to have a clear definition of an 'incident' and an 'outbreak' and also when a 'response' to these is warranted. Additionally in this section it would be good to state when extended workplace / other screening should take place in relation to close house-hold screening	Thank you for this comment. Incident in a congregate setting, incident risk assessment and outbreak are covered in glossary items in the guideline. NICE did not consider evidence on specific thresholds to trigger action and the committee concluded this is for discussion and agreement at a local level by communicable disease experts. The decision to extend the contact investigation is also a local decision dependent on the data collected as part of the incident response – see bullet 4 in 1.6.4.3.

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Public Health England	Short	63	13	We are concerned that section 1.6.4 is not very clear. It would be helpful to state if this section refers specifically to 'pulmonary TB' rather than just 'TB' as appears in L13	Thank you for your comment. This has been clarified in the final guideline
Public Health England	Short	63	21	We would recommend removal of the phrase "they should tell the TBCB a referral has been made" as it is unclear why this is helpful and in some areas of the country this could result in a substantial increase in correspondence when the action to respond sits with the PHE Health Protection team in conjunction with the NHS	Thank you for your comment the guideline has been updated.
London TB workforce Group	Short	63	21	This is suggesting that the TB Control Board should be routinely informed of cases in congregate settings. Is this correct? In areas like London, this is a regular occurrence and the rationale for doing this routinely is not clear.	Thank you for this comment the guideline has been updated.
Public Health England	Short	63	23	Whilst we agree that TBCBs should *consider* setting up a local 'incident team' to deal with incident and outbreak management we feel the way this is written is quite prescriptive and would be better phrased as: 'TB control boards working with local health protection teams should consider setting up or	Thank you this recommendation has been revised.

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				having access to an 'incident' team that will:'	
London TB workforce Group	Short	63	23 24	We suggest rewording – consider: TB control boards should ensure the timely coordination of the management of TB incidents and outbreaks and oversee, support and monitor the activities and impact of the incident team e.g. LTBEx team.	Thank you for this comment. We have clarified the role of TB control boards in this recommendation.
Public Health England	Short	63	26	We recommend that the phrase "Support or undertake contact investigations" could be more explicit about contact screening, e.g. "support or undertake contact screening, e.g. performing Mantoux tests or taking blood for IGRA"	Thank you for your comment. There is a glossary item for contact investigations which makes it clear this means diagnostic testing of people having been identified as having significant exposure risk. The types of diagnostic test to use are covered elsewhere in the guideline.
TB Alert	Short	65	General	Suggest making it clear that the patient in question may fit under one or all of the scenarios on the given list.	Thank you for your comment. NICE do not consider it necessary to make this distinction; any one of the scenarios should result in DOT being offered.
British Thoracic Society	Short	65	6	P65 1.7.1.2 Offer an incident risk assessment to every person with TB, to identify their needs and whether they	Thank you for your comment. We agree this should say adherence risk assessment and this has been updated.

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				should have enhanced case management. Suggest: This should be adherence risk assessment not incident	
London TB workforce Group	Short	65	6	Offer an incident risk assessment to every person with TB, to identify their needs and whether they should have enhanced case management. Suggest: This should be adherence risk assessment not incident	Thank you for your comment. We agree this should say adherence risk assessment and this has been updated.
TB Alert	Short	66	1.7.1.6	Suggest including 'an assessment on the level of isolation (if any) the patient in question has, as this could mean the need to provide additional support to those who feel they are alone and isolated.	Thank you for your comment. There was no indication either in the evidence reviewed or from the expert perspective of the committee that feeling alone and isolated would impact on adherence.
TB Alert	Short	67	1.7.1.6	Additional bullet is needed to include active consideration be given to whether the individual has access to or presents to third sector / community / faith based services and could additional support be provided through them to help treatment adherence etc.	Thank you for your comment. NICE believe these are covered with all the options listed. Third sector and other support routes should be covered through the MDTB team as this team should be made up of the wider support mechanisms you suggest.
TB Alert	Short	67	1.7.1.7	Additional bullet needed which includes capturing who the lead local commissioning lead is in relation to treatment costs, housing or social care needs, funding any incentives/enablers	Thank you for your comment**.** This is covered in the service organisation section of the guideline. NICE recommend commissioners consider an end to end pathways from prevention to cure and

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					all relevant support mechanisms.
Our life	Short	68	7	It would be beneficial to add a bullet point stating 'ensuring they are living in suitable accommodation'	Thank you for your comment. This is covered specifically in the service organisation element of the guideline, and covered under the broad heading of social and psychological support
British Thoracic Society	Short	70	1	P70 1.7.3.7 line 1 Multidisciplinary TB teams should ensure accommodation is available for the duration of TB treatment after the prisoner or detainees release Suggest: Multidisciplinary TB teams should work with commissioners and CCG to ensure accommodation is available for the duration of TB treatment after the prisoner or detainees release	Thank you for your comment. As the recommendation in question is not contained within the 'service organisation' section NICE methodology does not allow the GDG to specify 'commissioners' in the recommendation.
London TB workforce Group	Short	70	1	Multidisciplinary TB teams should ensure accommodation is available for the duration of TB treatment after the prisoner or detainees release We recommend rewording to: Commissioners and CCG should work with Multidisciplinary TB teams to ensure accommodation is available for the duration of TB treatment after the prisoner or detainees release.	Thank you for your comment. As the recommendation in question is not contained with the 'service organisation' NICE methodology does not allow the GDG to specify 'commissioners' I the recommendation.

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Oxleas NHS Foundation Trust	short	70	1.7.4.1	Re-establishing tb treatment is becoming very popular with our practice after interruptions due to adverse events AND it might be helpful if the protocol is tabulated or in a graphic form for easy following/implementation by the practitioners.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
TB Alert	Short	70	1.7.3.7	Typo – should state: 1.8.11	Thank you for highlighting this.
Our life	Short	71	26	It would be beneficial to add a bullet point stating 'ensuring suitable accommodation for patients with no recourse to public funds, or meet the accommodation needs of extremely complex cases'	Thank you for your comment. This is covered elsewhere in the guideline.
TB Alert	Short	72	1.8.1.3	Additional bullet needed which states 'findings from any TB service or local cohort review'	Thank you for your comment. This is a list of examples and not intended to be exhaustive. Cohort review is specifically mentioned in the next section of recommendations and further detail is added in the specific section of recommendations about the cohort review process and reporting.
Public Health England	Short	72	9	We suggest a change in phrasing would be helpful here. Changing "the need to share services, such as mobile X-ray facilities, across different geographical areas" to "the need to share services, such as mobile X-ray facilities and outreach incident screening teams across	Thank you for your comment, this has now been revised.

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				different geographical areas"	
TB Alert	Short	73	1.8.1.8	Additional bullet needed: 'regular updates/progress on workforce development TB training.' This would capture updates on TB awareness training across all relevant sectors: NHS, local authority and third sector.	Thank you for your comment. this list is not considered to be exhaustive and every suggestion cannot be captured here, awareness raising activities are mentioned in the first set of recommendations in the guideline.
TB Alert	Short	74	1	Why are asylum seekers and refugees only mentioned? Suggest adding in new entrants as a more inclusive term. In addition, people with mental health problems are more mentioned on the list provided.	Thank you for your comment. This is incorporated from PH37 the evidence reviewed for that guideline was focused on specific groups as per the glossary item linked to in the recommendation. All new entrants were not part of the evidence base or the focus of the original guideline as not all new entrants are from under-served groups.
TB Alert	Short	74	19	We would like to see added that TB control boards would also monitor associated collaborative commissioning arrangements around all aspects of TB prevention and control as without this oversight, delays could occur.	Thank you for this comment. NICE do not include rationales within their recommendations this level of detail is included in the Full guideline when linking evidence to recommendations.
Our life	Short	74	22	It would be beneficial to add an additional bullet point stating 'Agree pathways to appropriate accommodation to ensure housing needs are addressed promptly (including for those with NRPF)	Thank you for your comment This is covered in the section on housing – the evidence in this area is limited therefore the strength of the recommendations must be appropriate

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Public Health England	Short	75	4	Cohort review is a useful way to improve local TB control. Whilst we agree with the text in general we would like to suggest a slight change in the wording to strengthen and clarify it to help implementation "TB control boards should ensure cohort review is undertaken at least quarterly (see section 1.8.6), and that the results, actions taken and issues identified are fed back to local clinical and TB networks in addition to being ~~These should be~~ reviewed~~agreed~~ by accountable bodies such as clinical commissioning groups, trust management, TB control boards, Public Health England Centre directors and local authority directors of public health~~as agreed~~, ~~all of whom 9 should make sure~~ so that appropriate action is taken."	Thank you for your comment this however does not alter the intent or meaning of the recommendations. The recommendation is edited in NICE style.
British Thoracic Society	Short	75	6	P75 1.8.2.4 line 6 …. Cohort review …… results are fed back to local clinical and TB networks. and the TB control board Suggest: …. Cohort review …… results are fed back to local clinical and TB networks <u>and the TB control board</u>	Thank you for your comment – but this seems tautological as the TB control board are ensuring results are fed back, it is not clear why they would feed back to themselves.
TB Alert	Short	77	1.8.2.12	Please include: 'Incorporating the news and experiences of local people who have been	Thank you for your comment. If local networks consider this important they can agree to include

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				affected by TB, their carers and the services working to support them'	this information as part of their partnership working and agreements. The recommendation does not preclude that happening.
British Thoracic Society	Short	78	General	The BTS view is that given that the actual number per region is still small. all cases of MDR should also be registered and discussed in a national manner within the National MDR Advisory Service and this mechanism will also ensure all novel and high cost medication will be peer reviewed externally	Thank you for your comment. The recommendation already suggests accessing information via this service and recording the consideration of the advice from the advisory service. The committee did not consider evidence on mechanisms to monitor or peer review high cost medications in relation to the advisory service and therefore cannot make such recommendations.
TB Alert	Short	79	1.8.5.1	Please include that although the JSNA is important, DPHs should also be considering how this contributes to the TB related sections of PHOF	Thank you for your comment. These recommendations are specifically about needs assessment and how that feeds into commissioning decisions. The PHOF may be considered separate to this, if that is not the case we anticipate that local DPHs will ensure it is incorporated as required.
TB Alert	Short	79	1.8.5.2	Please be aware that although PHE houses TB related clinical data, it would be the local authority who has qualitative data concerning valuable insight into the culture, health beliefs and behaviours of migrant and settled ethnic communities and that this is important for a	Thank you for your comment This recommendation is not meant to preclude local data. The list of sources included in recommendation 1.8.5.4 includes multiple factors in addition to the indicators from PHE including Indices of social deprivation, local education and awareness raising programmes and the views

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				detailed local needs assessment.	and experiences of people with TB, carers and services working with them amongst other things.
Our life	Short	79	12	It would be beneficial to add 'and the barriers to identification and treatment through risk factors such as homelessness, alcohol and drug use' This section could also refer to the statutory duty of local authorities to carry out a homelessness review and assessment of housing needs which should align with JSNA priorities.	Thank you for your comment. This section is specifically about local needs assessment via the JSNA. One aspect mentioned in the long list of information that might be considered includes the "views and experiences of people with TB, carers and services working with them" it is anticipated therefore these issues may be covered through this. NICE believes that issues around the statutory duty regarding homelessness it better in the section on accommodation.
Our life	Short	80	2	It would be beneficial to add 'e.g. homelessness'	Thank you for your comment. There is a specific section on accommodation in the guideline where it is recommended MDTB teams assess persons' living conditions and work with relevant commissioners and others to agree a process for identifying and providing accommodation for homeless people diagnosed with TB.
Our life	Short	81	14	It would be beneficial to include a section suggesting the Cohort Review should on occasions take a thematic approach to explore issues relating to under-served and high-risk groups, for example homelessness.	Thank you for your comment The GDG received no evidence to support your suggestion. The recommendations as written do not preclude this and each area is free to agree that this would be a useful way to deliver cohort review for their area.

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Public Health England	Short	81	22 26	Rather than state case managers should present standardised information on each case should this say – should present information that includes demographic etc.… (standardised means different things to different people) and the main thing is to include the relevant information ..	Thank you for your comment. This element of the guideline was not open for comment as it was previously published in PH37 the only aspect that has changed is the added example of HIV test results, pre-treatment and on-going status to provide a greater level of clarification on what data may be presented.
Public Health England	Short	82	3 9	Chairs could also include from "PHE national infection service"	Thank you for your comment. this was not intended to be an exhaustive nor prescriptive list there are many other options available too, this can be agreed locally.
Public Health England	Short	82	11	We would like to suggest that the new text "and the TB control boards" is removed as cohort review is a local activity and collation of data and outcomes does not involve the 'TB control boards'. As indicated earlier TBCBs do need to receive the outputs of cohort review but are not directly involved in the data or presentation of this.	Thank you for your comment. . This has been removed.
TB Alert	Short	83	1.8.7.1	We suggest adding the following: "having the necessary resources to engage in proactive IGRA based LTBI testing programmes" (as unless a quiet TB service, additional resources would be needed to undertake proactive screening, as this does place additional strain on existing services	Thank you for your comment NICE are not recommending a pro-active LTBI screening programme this is not one of the recommendations in this guideline and is out of scope for this guideline.

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				dealing with active cases otherwise). In addition to the same point, please also add "have access to relevant third or community sector organisations who can provide support, engagement, or outreach services to either under served or high risk TB groups as part of either pro active LTBI testing programmes or enhanced case management of active cases."	
Royal College of Nursing	Short	83	8	*One whole-time equivalent case manager is recommended per 20 incident cases needing enhanced case management.* Our members commented that not having these patients shared could have an impact on nurse's skills as some patients that require enhanced case management can be due to the patients having other health problems, on poly pharmacy, or even have intolerance to drugs. It will also not be practical to implement this in some geographical areas, through community service and having to visit patients with complex needs over a large geographical stretch, it will be challenging. Nurses not looking after cases with complex needs will not be able to utilise their skills. It is suggested that where increased numbers of complex cases is high, the total number of cases should be 35.	Thank you for your comment. The responsibility for providing advice on setting staffing levels has now transferred to NHS Improvement. The recommendations have been revised to take account of this. An additional recommendation has also been included stating that "Commissioners should ensure NHS Improvement's principles of safe staffing are applied when commissioning TB services".

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London TB workforce Group	Short	83	16	The workforce would strongly suggests that once it is established that a patient requires ECM e.g. DOT, substance misuse, no recourse to public funds etc the workload for LTBI ECM is equivalent to the workload for active cases that require ECM. The workload required to establish a support plan is equivalent and not related to length of treatment course. Suggest: ECM for LTBI case management is the same as for active cases i.e. 1:20 not 1:40	Thank you for your comment. This has been discussed with the committee who believe that as the course of treatment is shorter, the overall WTE is less on a per annual basis.
British Thoracic Society	Short	84	5	P84 1.8.7.1 line 5 Provide dedicated administration support - A ratio would be helpful e.g. 1 dedicated admin : 100 active cases 1 dedicated admin:200 LTBI cases	Thank you for your comment. No evidence to provide this level of detail or specificity was available this was a consensus recommendation supported by expert testimony. The expertise on the committee did not extend to being able to estimate this ratio. The committee were however clear that administration support should not diminish clinical staffing. This change to the recommendation may have an opportunity cost that would impact directly on clinical staff numbers.
British Thoracic Society	Short	85	3	P85 1.8.8.1 line 3 A ratio would be helpful e.g. 1 TB support worker: 40 cases that require ECM	Thank you for your comment. The recommendations on TB support workers do not specify which activities should be considered part of the remit of this role and would thus make it very difficult to make these types of estimates. Additionally, there is no evidence available on

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					which to make this estimate. This level of decision making is left to commissioners working with control boards based on local needs, this allows greater flexibility when considering implementation of this set of recommendations.
London TB workforce Group	Short	85	3	A ratio would be helpful e.g. 1 TB support worker:40 cases that require ECM	Thank you for your comment. The recommendations on TB support workers do not specify which activities should be considered part of the remit of this role and would thus make it very difficult to make these types of estimates. Additionally, there is no evidence available on which to make this estimate. This level of decision making is left to commissioners working with control boards based on local needs, this allows greater flexibility when considering implementation of this set of recommendations.
London TB workforce Group	Short	85	24 28	We strongly support guidance advocating cross boundary working	Thank you for your comment
London TB workforce Group	Short	86	20 21	We suggest re-wording emergency departments should refer suspected TB cases direct to TB clinics	Thank you for this comment. The detailed recommendations regarding referral by emergency departments are captured in the hyper-linked recommendations in parentheses. The recommendations in this section are about rapid access therefore the appropriate actor is the

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					multi-disciplinary TB team.
British Thoracic Society	Short	87	8	P87 1.8.9.1 line 8 The referral pathway should include a single point of referral with facilities to accept e- referrals secure for PII to promote prompt referral / rapid access	Thank you for your comment. The committee did not consider any evidence on this. The recommendations are designed to support TB services nationally, it is not clear how wide spread or accessible this form of referral is.
Our life	Short	88	28	Experience has shown that this process is extremely difficult to put in place promptly when cases arise, resulting in lengthy delays to patients receiving accommodation, and either staying unnecessarily in hospital, or risking infecting others through rough sleeping and 'sofa surfing'. Stating that Local Government and CCG's should fund accommodation carries the additional risk of delays to decisions being reached. It would be beneficial to state that they must work together to agree a clear process for this in advance of cases arising. An effective example of this include a Service Level Agreement between Public Health, the CCG and the Local Authority in Hackney (Homerton Hospital)	Thank you for your comment. Recommendation 1.8.11.2 covers the need to agree a process for identifying and providing accommodation. It is at the discretion of local partnerships to determine whether this is set up as a service level agreement. It would be beneficial if this kind of evidence was submitted to the NICE Into Practice database as this can subsequently be considered in future guidelines and users of the guideline can learn from case studies.
British Thoracic Society	Short	89	6 7	P 89 1.8.11.4 line 6-7 Changes to benefits etc may mean that some patients are not eligible for housing support on completion of treatment. Actions here may	Thank you for your comment, the recommendation covers an action to ensure plans are made to continue housing people once treatment is completed. It is at the discretion of

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				include referral to services that can support this group on completion of treatment e.g. hostels managed by faith organisation and services that provide a Voluntary Assisted Return and Reintegration Programme (VARRP).	local services to determine how this is implemented which could be via the route you suggest or other mechanisms.
Our life	Short	89	6	It is unlikely that multi-disciplinary teams will be successful in ensuring plans are made to continue housing people once their TB treatment is completed. This would fit better in the section above.	Thank you for your comment. Given the wide breadth of professionals that should form MDTB teams including housing support, the voluntary sector and social workers in addition to healthcare professionals (see glossary item) it was concluded that the skill mix should enable delivery of the recommendation.
Our life	Short	89	8	The inclusion of Homeless Link and Sitra would be beneficial.	Thank you for your comment. the recommendation has been updated.
Our life	Short	89	8 15	An alternative suggested by Gill Leng which would have more impact would be "This is to ensure that housing commissioners and front line staff understand the importance of the home environment to successful TB treatment and recognise this in their day to day business of meeting housing needs"	Thank you for your comment. the recommendation has been updated following GDG discussion.
British Thoracic Society	Short	89	16	Barriers to implementation – complex screening protocols and reliance on two stage tests for latent TB may impact on implementation.	Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.

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TB Alert	Short	89	16	Our response to both questions: • TB seen as a social, rather than purely a medical issue and therefore a broader view taken on what is needed to effectively reduce rates through a whole systems approach that includes stakeholders beyond the NHS. • Proactive work on myth busting is badly needed however, consideration needs to be made (and additional funding prioritised) as such work will have an impact on services, many who are already stretched to capacity and under-resourced. This will assist in reducing diagnostic delay and encouraging treatment completion. • Having patient incentives/enablers in place to assist and support people on treatment to be able to effectively comply and engage effectively with services. • Local accommodation arrangements in place for the vulnerable who have active TB-rather than it be at local housing department discretion as to whether this would be funded or not.	Thank you for your comments. We agree with this and it is why stakeholders broader than the NHS are encouraged in service recommendations and in the glossary item on multidisciplinary TB teams and TB Control Boards. This is included in the awareness raising recommendations. Patient enablers are included in adherence and service recommendations. This is outside the remit of NICE. It is housing provider's responsibility.
British Thoracic	Short	89	26	Would another useful research topic include looking at increasing treatment completion rates	Thank you for your comment. This is included

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Society				for latent TB?	under the following research recommendation: "Strategies to improve treatment completion in those infected with latent TB infection and at risk of non-adherence. Is Directly Observed Preventative Therapy (DOPT) and other support strategies effective and cost effective compared self-administered therapy in promoting the uptake of and adherence to treatment in those populations who should be offered DOT as part of enhanced case management for latent TB?"
TB Alert	Short	10.2.3.1 409	General	The expert witness statement captured under the theme of strategic oversight and commissioning: "...the need to consider TB prevention and control services from and perspective of an end to end pathway, that is from prevention to cure and follow up where relevant," is something TB Alert strongly supports and therefore you maybe interested to see this insert from our response to the national TB strategy: *"An integrated commissioning service needs to ensure that local planning for TB takes a whole system perspective, covering all aspects of Prevention, Access, Diagnosis, Treatment & Care, and Control. The local control board needs to include stakeholders with the knowledge, commissioning responsibilities and delivery*	Thank you for your comment. NICE recommend 'local strategy and service commissioning focuses on an end-to-end pathway' . End to end pathway is defined in the glossary

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				responsibilities for all parts of the whole system pathway, or people at the appropriate level who are authorised to represent them. *Since the board is likely to operate across CCG and local authority boundaries, there must be agreed channels of representation and communication to ensure decisions reflect each area's input and that commissioning and delivery decisions are followed through across the board's footprint."* TB Alert would recommend incorporating this theme within the short guidance document under section 1.8.7.1.	
Royal College of Surgeons	General	General	General	No comments	Thank you
NHS England	General	General	General	No comments	Thank you
The Royal College of Pathologists	General	General	General	No comments	Thank you
RCGP	Full	General	General	The College welcomes these updated guidelines however, feels there are considerable issues that	Thank you for your comments. We have responded to each specific comment below

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				should be addressed. 1. Overall responsibility and co-ordination of TB services. Recommendation 181 does not make it clear whether it is PHE or NHS England's overall responsibility for management of Tuberculosis in England. A single TB control board with overall responsibility is required to co-ordinate geographical areas and standardise data collection particularly for patients crossing geographical boundaries and are hard to reach. 2. A single point of contact for GPs is essential. Currently there are at least 4 local services for most GP to contact: 1. Paediatric and children services 2. Adult services 3. Screening services 4. TB prevention clinics See this example from Bristol: http://briscomhealth.org.uk/wp-content/uploads/2015/02/TB-Care-Pathway-2-TB-Screening-in-Primary-Care.pdf 3. Tuberculin skin testing requires 2 hospital clinic appoints which are likely to be difficult for hard to	1. The guideline makes clear that the 2 organisations should work in partnership to take responsibility. It is beyond the remit of this guideline to determine who, if either, should have overall responsibility for TB prevention and control activities as both have a key role to play. 2. Due to different local arrangements for how TB services are commissioned and provided it would be difficult to specify a single point of contact. Recommendation 1.1.1.2 does recommend a role for multidisciplinary TB teams to provide local referral pathways, including details of who to refer and how. 3. Although it is agreed that this may be a useful area for review, it was not one identified in the course of scoping and therefore has not been

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				reach groups. Have alternatives been valuated such as follow up by mobile phone with a standard paper measure? 4. The role of the GP The guidelines do not recognise that TB often co-exists with other conditions other than HIV such as diabetes and pregnancy. Considerable GP input may be required to managing these co-existing conditions.	addressed within this guidance. 4. The guidance attempted to address the comanagement of TB and these comorbidities or coexisting conditions in the following review questions (see chapter 4.9 of the full guideline document): *In people co-infected with drug susceptible, active TB and HIV receiving drug treatment for both infections, what are the key pharmacological considerations that should be taken into account when selecting a treatment regimen for treating active or latent TB?* *How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active pulmonary and extrapulmonary TB?* In this review, the key comorbidities or co-existing conditions identified were HIV, liver disease, renal disease, diabetes, substance misuse, vision impairment / eye disease and pregnancy / breastfeeding. These reviews were conducted in recognition of the fact that TB often co-exists with other conditions other than HIV, such as those noted by the stakeholder. Following consideration of these reviews, the

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					Lack of evidence available meant that the Committee did not feel able to make specific recommendations for the co-management of these conditions. Instead, they discussed who should be involved in management decisions and decided that clinicians work with a specialist multidisciplinary team with experience of managing TB and the comorbidity or coexisting condition. The GP may be involved in care, but it was concluded that with the specialist multidisciplinary team with appropriate experience was the most important element in ensuring good management of both conditions.
British Thoracic Society	Full	80	11	The seven priorities are not obvious at start of publication (check summary)	The seven priorities for implementation are no longer included as part of the Full guideline.
NB: The following stakeholder comments were submitted as part of the consultation on the draft recommendations for tuberculosis but were omitted from the table due to an administrative error. Whilst the comment was not considered by the guideline development group (GDG), the points that were raised were also identified by stakeholders which were duly considered by the GDG.					
Plymouth Hospitals NHS Trust	General	NA	NA	Significant omission: Lack of guidance for screening prior to use of anti-TNFa biological agents (unless I missed it) The BTS guidance (Thorax 2005;60:800) predates the widespread use of IGRAs. NPSA recommends we assess all for TB risk prior	Thank you for your comment. The guideline committee made recommendations 11, 12, 13 & 14 (see page 131 in the Full Guideline) for people who are anticipated to be, or are currently immunocompromised – a subgroup defined in the guideline as:

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				to anti-TNF Rx, but does not state how. Various specialist societies (Derm/Rheum/Gastro) have issued differing guidance. BTS declined to update their 2005 guidelines as stated it would fall within the scope of this 2015 NICE guidance. While it may be appropriate to screen all with IGRAs +/- TST in addition to exposure history/demographics/CXR, such an approach is not necessary cost effective in areas with low TB incidence. My estimate for our typical patient starting anti-TNF agents (Caucasian, UK born, middle aged) is that the cost of screening with IGRAs is >£150k per case TB prevented. Without specific NICE guidance many colleagues in similar low incidence areas are already practising defensively (particularly when recommended by some specialist societies) and are screening all with IGRAs, regardless of cost, rather than risk having a case of miliary TB. I don't know what the correct answer is, but I think national advice from NICE is this area is essential.	"..people (both genders, any age) who are immunocompromised or at risk from immunosuppression (e.g. transplant recipients or those with HIV, renal disease, diabetes, liver disease, haematological disease, cancer, autoimmune disease, or who are on or about to start anti-TNF-α treatment, steroids, or cyclosporins" (P.134 of the Full Guideline) Recommendations 13 and 14 relate specifically to testing strategies: 13. For adults who are severely immunocompromised, such as those with HIV and CD4 counts of fewer than 200 cells/mm3, or after solid organ or allogeneic stem cell transplant, offer an interferon-gamma release assay and a concurrent Mantoux test. • If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history), assess for active TB. • If this assessment is negative, offer them treatment for latent TB infection. [new 2016] 14. For other adults who are immunocompromised, consider an interferon-gamma release assay alone or an interferon-gamma release assay with a concurrent Mantoux test.

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					1. If either test is positive (for Mantoux, this is an induration of 5 mm or larger, regardless of BCG history), assess for active TB 2. If this assessment is negative, offer them treatment for latent TB infection. [new 2016] These recommendations were based on the evidence contained in the report produced by Warwick Evidence (Appendix H of the Full Guideline) which examined the cost-effectiveness of different testing strategies to diagnose latent TB in immunocompromised patients .The evidence synthesis included 9 studies comparing IGRA with TST tests prior to initiation of TNF-alpha therapy in patients with immune mediated inflammatory diseases. All studies were from low incidence hospital settings in Europe or the USA (see Table 11 of appendix H for full details).The context for this work is the opportunistic screening at the point of care of people for whom there is clinical suspicion of being at risk of TB, which is likely to be less common in areas of low TB prevalence. It is also important to distinguish between the NPSA recommendation that all patients be screened prior to anti-TNF therapy, and the recommendations from this guideline which are not intended to inform large-scale screening programs for latent TB in all patients undergoing anti-TNF or other

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					immunocompromising treatments. Population-level screening is explicitly out of scope for this clinical guideline. The analysis suggested that for immunocompromised people IGRAs appeared to be the most sensitive test. For this reason, the economic model suggested that TST-led strategies are dominated by those that use IGRAs as the first or only option. The optimal strategy was to offer an IGRA as a first-line test and then use TST (≥5 mm) as a second-line test in IGRA-negative cases (ICER of approximately £19,000 per QALY gained, compared with IGRA alone). This analysis did not consider the development of active miliary disease. As discussed in the Linking Evidence to Recommendations table on page 142 of the Full Guideline, the GDG emphasised that the question here is about providing guidance in situations where a decision to offer a test has already been made and evidence-based recommendations on what tests to perform are needed. The GDG concluded that the harms associated with underdiagnosis of LTBI substantially outweighed those of overdiagnosis. Therefore, it was appropriate to make recommendations that gave priority to high-sensitivity strategies (those that minimise false negatives), even if they were associated with a greater probability of false-positive diagnoses. It was stressed that these

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					numbers are sensitive to the underlying prevalence of LTBI and that, at lower prevalence, a higher-specificity strategy is likely to be more important.
Plymouth Hospitals NHS Trust	Short	NA	NA	1.1.3.18 – although not officially for comment, as "in grey". The DH Green Book was updated in 2011; the 2015 NICE guidance needs to be updated to reflect this – eg that those who are working for 3/12 need BCG (rather than 1/12 stated in this draft)	Thank you for your comment. The recommendation has been amended to reflect the updated Green Book: "… people going to live or work with local people for more than *3 months* in a high incidence country."