Appendix F:Health economics report (2015 work undertaken by NICE Internal Clinical Guidelines)

F.1 General

This appendix contains details of health economic analysis undertaken by the NICE Internal Clinical Guidelines team to support development of the guideline. It describes the original cost–utility model that was developed to inform the GDG's consideration of optimal duration of isolation for people with TB that is believed to be drug-sensitive (section F.2). It also provides evidence profiles for studies that were included in systematic reviews of published economic evaluations (see sections 3.3, 5.3 & 7.2 of the full guideline).

F.2 Duration of isolation

F.2.1 Decision problem

Table 1: Research questions

Section 6.2 of the full guideline	For people who have active TB, what duration of isolation is necessary to minimise the risk of infection to others

The GDG prioritised this area for original health economic analysis. Transmission of tuberculosis is a complex phenomenon, thought to be determined by a number of interacting factors: 1) the infectiousness of the source case; 2) the susceptibility of contacts; 3) the duration of exposure and closeness of contact; 4) the environment in which the exposure takes place and 5) natural history factors. The GDG felt that a health economic model might provide a framework for exploring the relationships between these factors and how they might contribute to the decision problem of how long a patient should be isolated for. There are also significant cost and quality of life considerations: Isolation beds are more expensive than regular inpatient beds, and few studies have considered the quality of life implications of inpatient isolation (none with specific reference to TB). The clinical effectiveness of inpatient isolation practices has been largely inferred from studies of TB outbreaks and animal infection. Therefore, the GDG were keen to explore the benefits, harms and costs of isolating patients with infectious TB.

Table 2: PICO

Population	Patients (who are not considered to be at risk of drug resistance) with infectious TB (pulmonary) who are either being discharged home or back onto a hospital ward
Intervention	A short duration of isolation (7 days) with appropriate drug therapy
Comparator	14 days isolation with appropriate drug therapy
Outcomes	A cost-utility analysis was constructed based on the quality of life (in quality adjusted life years[QALYs]) and costs of isolation and TB morbidity & treatment

F.2.2 Systematic review of published cost–utility analyses

F.2.2.1 Methods

We conducted a systematic literature search in order to obtain published cost–utility analyses that provide evidence of the cost effectiveness of the interventions in question.

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of inpatient isolation methods (e.g. side-room isolation, negative-pressure isolation and home isolation) and durations. The GDG believed that these are the 2 factors which most determine the cost of isolation for infection control and the relative impact on the isolated patient's quality of life during the isolation period. These 2 factors are in turn dependent on the risk the patient poses to contacts that are potentially susceptible to TB. Therefore, we also searched for studies which included reference to the isolation methods and durations appropriate for patients with clinical features that may elevate or reduce their relative infectiousness.

Search strategy

The search strategy was based on that used to identify clinical evidence for this question, with the RCT filter removed and a standard economic filter applied (see appendix C).

F.2.2.2 Results

Study identification

2177 studies were identified and after title and abstract screening, the full text was ordered for 5 studies. On perusal of the retrieved papers, no cost–utility analyses were identified which considered the relative benefits, harms and costs of isolation methods and durations. However, useful non-health economic evidence that did not meet the formal inclusion criteria was presented to the GDG, as part of development of the original health economic model (see F.2.4, below).

9 studies, although outside the formal inclusion criteria, contained information of relevance to the question and were therefore presented to the GDG.

F.2.2.3 Discussion

No evidence was obtained to provide guidance to answer the review question.

The GDG felt that clinical prediction rules might be a useful component of the diagnostic work-up for patients for whom isolation is indicated, as some prognostic markers could potentially guide the expected duration of isolation particularly if they could be correlated with infectivity. Therefore, the GDG was presented with a number of studies in addition to the clinical review which described natural history and diagnostic factors which could be used to guide isolation practices. These studies are described in the table below, along with their reasons for exclusion which were based on review and presentation to the GDG.

Table 3: Supplementary evidence discussed by GDG

Study	Setting	Notes	Reason for exclusion
Fortún et al. (2007)	Respiratory disease clinic in Madrd	Time to smear (AFB) and culture conversion during therapy in patients with pulmonary TB related to cavitation on CXR, AFB load and drug resistance	Since all patients were isolated, and caused no transmission, no information on the relative infectivity of disease characteristics could be ascertained.
Telzak, (1997)	Acute care centre, Bronx, New York	Time to smear and culture conversion related to gender, ethnicity, HIV status, TB history, AFB load (high/low), CXR and Drug resistance.	Assumes that smear-negative and culture-negative patients are not infectious. Does not detail onward transmission rates relating to clinical covariates of smear and culture conversion time.
Lim et al. (2010)	2,100 bed, tertiary-care referral centre in northern Taiwan and an 800 bed local teaching hospital in southern Taiwan	Relationship between culture status after two months of therapy to initial smear grade, clinical response to treatment, and drug regimen	As above, and setting may not be applicable to the NHS context.
Olaru et al. (2014)	TB referral centre, Germany	Time to smear and culture conversion, and changes to smear grade in patients on TB therapy.	Details the impact of therapy on smear grade, but does not explore how smear grade relates to infectivity risk
Gutierrez (2011)	Lima, Peru	Correlation of cough frequency with treatment efficacy in pulmonary TB patients	Uses composite outcome measures which combine treatment adherence, transmission and resolution of symptoms into “favourable” and “unfavourable” dichotomous classification. The data does not allow the disaggregation of infections from this and relationship to cough frequency
Craft et al. (2000)	Washington hospital, USA	Potential infections as a result of reducing the number of negative smears needed to discharge patients from isolation	Small sample size (42 patients over 4 years). Use of negative pressure for drug susceptible cases, and TB costs used do not represent UK practice.

Study	Setting	Notes	Reason for exclusion
Ritchie et al. (2007)	Acute care hospital, New Zealand	Defining duration of isolation based on relationship between smear grade and time to detect TB in liquid culture.	The current processing time for culture is longer than the minimum isolation for drug-susceptible patients. The sample size in this retrospective study is small, and the GDG felt that the correlation between smear grade and TTD-TB may not provide sufficient grounds to discontinue isolation in the absence of other factors determining infectivity.
O'Shea et al. (2014)	NHS hospital, Birmingham UK	Predicting risk of transmission based on time to detect TB in liquid culture.	as above
Millman et al. (2013)	U.S Hospital	Selecting isolation method and duration based on smear microscopy or Gene-Xpert diagnostics	The addition of a molecular test may minimise the risk of incorrectly discharging MDR patients early, but would not provide a basis for assessing the relative infectivity of different patients and how long they should be isolated for.

F.2.3 Original cost–utility model – methods

Given the absence of relevant evidence in the published literature, we developed an original cost–utility model to explore the benefits, harms and costs of different approaches to isolation.

F.2.3.1 Overview of the model

Modelled populations and interventions

The starting point for this analysis was the existing recommendation that patients with suspected infectious TB, who are deemed to be at low risk of drug resistance should be isolated in a side-room and given appropriate drug therapy. Assuming that treatment is adhered to, and clinical improvement occurs, patients with drug susceptible disease may be released from isolation after 14 days. We limited our analysis to drug-sensitive TB for a number of reasons. Firstly it accounts for the majority of TB cases in England and Wales. Secondly, the literature used to parameterise our analysis is concerned with the transmission of drug-susceptible TB and did not provide information on the relative infectivity of drug-resistant strains, or explore how drug resistance might be correlated with prognostic markers

such as smear grade. We did not identify any other evidence that would enable us to perform informative analysis for people who are suspected of drug-resistant TB. Thirdly, the GDG advised us that minimising transmission of drug-resistant TB constitutes a high priority for infectious disease control; therefore, it is unlikely that any analysis balancing risks, benefit and costs of infection control in this population would be considered helpful, when the overriding imperative is to reduce onward transmission to zero.

In our model, we assume that the 14-day period of isolation and therapy is 100% effective at preventing onward transmission of TB regardless of whether a patient is being discharged home, to a congregate setting such as a school, or back to a hospital ward. Given the expense of isolation compared to a regular inpatient bed, and the limited number of side-rooms available on wards, an evidence-based assessment of the optimum duration of isolation is desirable. The decision problem in light of the initial assumptions is therefore what are the marginal costs, benefits and harms of reducing the duration of isolation compared with current practice?

We undertook 2 separate analyses: 1 for people who have no reason other than prevention of disease transmission for continued inpatient admission (so can be discharged to their usual residence when isolation is discontinued) and 1 for people with a continuing clinical need for inpatient treatment (who would need to be cared for on a shared ward if isolation were discontinued). See Table 4 for details of the decision problems addressed.

Table 4: Economic model PICO

Population	Patients with active infectious TB that is not suspected to be drug resistant (and their potentially susceptible contacts)
Intervention	Initiation of appropriate drug therapy and inpatient isolation in a side room (meeting NHS estates specifications) for 7 days, then discharge to either a. The patient's usual residence; or b. A shared inpatient ward
Comparator	Initiation of appropriate drug therapy and inpatient isolation in a side room (meeting NHS estates specifications) for 14 days
Outcomes	Transmission of TB (LTBI and active disease) and associated costs and QALY losses.

The model uses a patient perspective for outcomes and an NHS and PSS perspective for costs, in line with the Guidelines Manual (2012).

Model structure

The analysis is based on a simple mathematical model, which estimates the infectious potential of a person with TB and calculates the impact of consequent infections (in terms of QALY loss and treatment costs incurred by the people infected). We assume that isolation is 100% effective in preventing onward transmission of TB; therefore, secondary cases can only be caused in any portion of the 14 days during which the patient is not isolated.

The model is parameterised from the cohort of patients described in Lohmann et al. (2012). This retrospective study describes a series of contact investigations performed over a period of 5 years in a Dutch Municipal Health Service. Contacts of index cases with active TB were assessed using tuberculin skin test (TST) and chest radiography, and then retrospectively matched to contact with index cases on whom a sputum smear microscopy grading was performed at the point of diagnosis. For all index cases, the self-reported onset of symptoms was recorded and a duration of potential infectivity was inferred from this.

Crucially this paper allows the relationship between duration of TB, initial smear grade, and contact setting to be explored. Because the relative proportion of subsequent latent and

active TB cases caused by each index case can be derived, the relative infectiousness of index cases can be used to calculate the expected number of infections caused given smear grade and setting.

As far as the index case is concerned, the model is limited to a 14-day time horizon (that is, we assume that isolation during the first 14 days following diagnosis will have no impact on the person's management or quality of life beyond that period). However, in order to estimate the consequences of secondary infections, the model needs to calculate the lifetime costs and QALYs of people who come into contact with the index case and become infected with either immediately active TB or latent TB (that may become active at some point in the future).

For active TB, the model applies a fixed average cost of treatment, and calculates QALY losses taking account of disease- and treatment-related morbidity as well as the probability of acute TB-related death.

For latent TB infection, a submodel was used to estimate the discounted costs and QALYs associated with each case. This was a Markov model with a 3-month cycle length, and a lifetime time horizon. The Markov structure allows costs and utilities to be accrued for each cycle spent in a series of health states. The model describes the progression of a cohort of patients with LTBI, some of whom progress to active disease and accrue costs and QALY decrements as a result. QALYs are also lost through TB-related mortality. Given that patients infected with LTBI will carry a progression risk for the remainder of their life-expectancy, it is appropriate that the model is run over that timescale. Costs and QALYs were discounted at 3.5% per annum.

Table 5 gives a description of the health states considered, and the possible transitions between them.

Table 5: Submodel of latent TB infection: health states and transitions

Name	Description
Health states	
Latent infection	100% of the cohort starts with LTBI infection
Previous active TB	A state reflecting the history of treated active TB
Dead	Includes TB-related and background mortality
Transitions	
Does not progress to active TB	Patients with LTBI remain with LTBI for another cycle
Progress to active TB	Patients with LTBI progress from latent to active disease
Die of TB	Mortality from active TB
Recover	Patients who develop active disease are treated and recover
Death (not TB)	Life-expectancy-related mortality
Remain alive	Patients with previous active TB who remain alive for another cycle, who will re-enter the "previous active TB" state in the next cycle.

Figure 1provides a schematic depiction of the model structure.

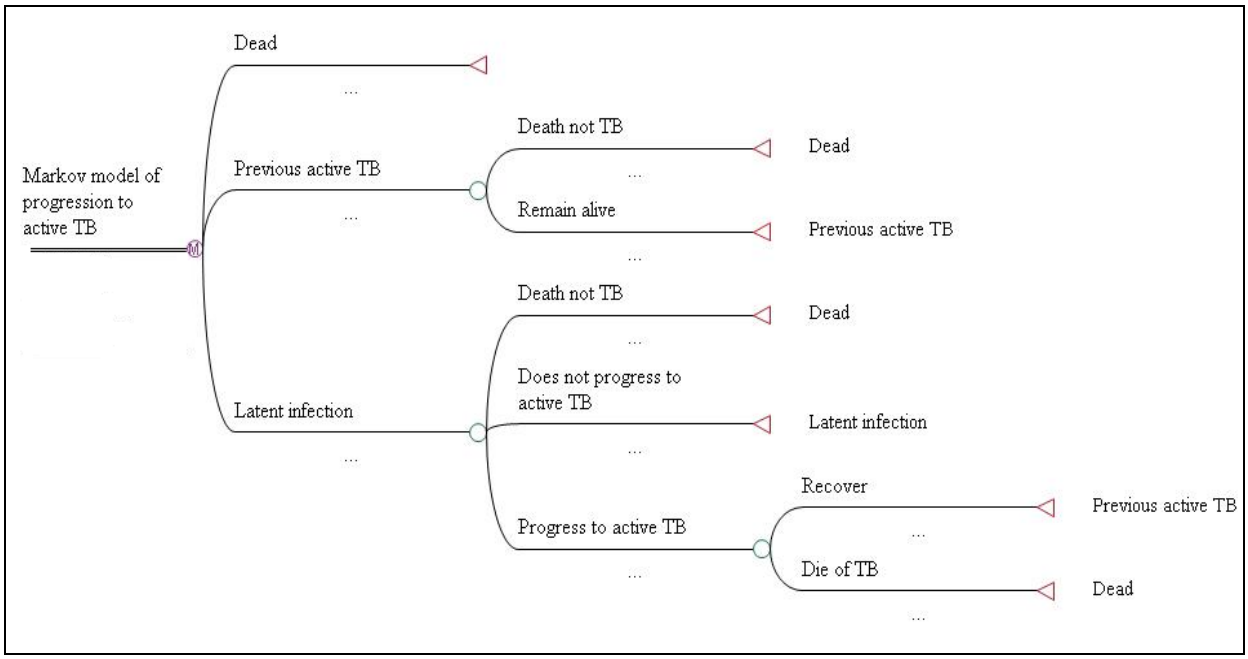

Figure 1: Submodel of latent TB infection – structure

Key assumptions

There are a number of assumptions built into the economic model which need to be considered when analysing the results generated. These are summarised in Table 6.

Table 6: Key assumptions of original cost–utility model

- The de-novo health economic model relies heavily on a single paper for its inputs (Lohmann et al. 2012), which was selected after an exhaustive literature search. This study was used because it provides its results in a helpful level of detail, rather than because it was believed to be especially relevant to the decision context.
- The relative infectivity of patients with given smear grades was taken from this single study and are therefore assumed to be representative of the relative frequency of smear grades in the general TB infected population
- The model assumes that 14 days on appropriate chemotherapy reduces the probability of infecting others to zero on day 14. This is because the true relationship between treatment and infectiousness has not been quantified directly in humans (only indirectly in guinea pig studies) and current guidance is based on the largely expert-opinion based assumption that 14 days' treatment is sufficient in drug susceptible patients to reduce their infectiousness to practically zero. Our assumptions are therefore in line with this long-held belief.
- In the base case, the model assumes that, until 14 days' treatment has been completed, the probability of infection is the same as for an untreated case.
- The Gammaitoni and Nucci (1997) equations for the probability of TB infection on a ward are temporally explicit, but we assume the input parameters remain static over the timeframe being modelled. Therefore mean values of quanta, air changes, and numbers of susceptibles over time are used.
- The number of air changes, which is the key variable other than the index patient in determining the number of quanta in the atmosphere (seeing as the volumetric characteristics of the room are fixed), were assumed to follow those observed by (Gilkeson et al. 2014) on Nightingale wards in an NHS hospital. As with the mean number of susceptibles present, the air changes were assumed to be a fixed rate over the duration of

stay as the mathematical complexity of modelling airflow changes, and the associated change in quanta, is beyond the plausible scope of this analysis.

- Quanta numbers are in themselves not verifiable, but are a mathematical representation of infectiousness. Because of the assumptions that variables influencing quanta are held static, the quanta production rate is also held static. Authors such as Nardell et al. (1991) have illustrated the heterogeneity of quanta production rates both at an individual patient level and between different patients with clinically very similar disease. However, the prognostic factors which can cause some patients to produce unusually large numbers of quanta (so-called 'super producers') are too poorly defined to model with reasonable accuracy.
- We assume that no onward transmission of TB occurs beyond the contacts of the index case.
- The model assumes that all patients are drug susceptible, and are all correctly diagnosed as having TB. There is an implicit assumption therefore that no patients are incorrectly isolated, and the potential costs and harms of this possibility are not considered.
- We assume that there is no health loss associated with side-room isolation.

F.2.4 Parameters

F.2.4.1 General approach

Identifying sources of parameters

With the exception of the rate at which people with latent TB progress to active TB which was drawn from the systematic review conducted for section 7.2.4, of the main guideline. parameters were identified through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

When searching for quality of life, resource use and cost parameters in particular searches were conducted in specific databases designed for this purpose, the CEA (Cost-Effectiveness Analysis) Registry and the NHS Economic Evaluation Database (NHS EED) for example.

It is unlikely a randomised control trial of isolation methods and durations will ever be undertaken because of the obvious ethical implications of such work. However, this means that the effectiveness of isolation remains unquantified in direct, empirical terms and has to be inferred. This gap in the clinical effectiveness data meant that a more pragmatic search strategy was employed.

We asked the GDG to identify papers of relevance. We reviewed the sources of parameters used in the other de-novo health economic work produced for this guideline by Warwick Evidence (see appendix H) and Imperial College (see appendix I). During our systematic review (see F.2.2, above), we retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

We asked the GDG to identify papers of relevance. We reviewed the sources of parameters used in the published CUAs identified in our systematic review (see F.2.2.2, above); during the review, we also retrieved articles that did not meet the formal inclusion criteria, but

appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

The subsections below detail the parameters included in the model and their derivation, sources and uncertainty.

F.2.4.2 Estimating infectivity of index cases

The ideal source of evidence for a model like this would be one in which people who are known to have active, infectious TB are observed interacting with a population of susceptible people, with the resulting disease transmission recorded and analysed. For evident reasons, no such studies exist. Therefore, the model relies on the significant assumption that people who are being treated for active TB have patterns of **relative** infectivity that are identical to people who have undiagnosed, untreated TB. By looking at characteristics that, in retrospective studies, are shown to be associated with the transmission of disease in people who did not know they had it, it was inferred that similar factors will influence the spread of disease in people whose TB has been identified. In particular, smear grade and exposure to congregate settings (estimated using attendance or employment at a school as a proxy indicator) were considered to be important predictors of transmission risk. The GDG confirmed that this was a reasonable assumption that enabled a potentially informative analysis to be undertaken.

Different methods were used to estimate the **absolute** infectivity of index cases for the 2 scenarios considered (discharge to the community and discharge to an inpatient ward).

People discharged to the community

We estimated the **absolute** infectivity of people discharged from hospital to their normal residence in a 2-stage process. Firstly, we estimated how infectious the average patient is at the point of diagnosis (day 0). Secondly, we simulated the amount of transmission that would be expected during the 14-day period (so we could calculate how many secondary cases might be caused if isolation were discontinued after 7 days).

To estimate infectivity at day 0, the model again relied on data from Lohmann et al. (2012). From this study, we know what the probability of disease transmission was over the pre-diagnosis period, and we know how long that period was (for the average index case). However, how the probability of infection might have varied over that period is unknown. Therefore, 3 simple alternative assumptions were explored. In all 3 of these scenarios, the cumulative probability of infection over 136 days (denoted *P* in the equations below), is the same; however, the different assumptions lead to different profiles of infectivity over time and

– critically, for the purposes of this analysis – different estimates of infectious potential at the moment of diagnosis.

Under the assumption of **uniform** infectivity, we wish to derive the daily probability of infection, *q*, that, over the course of 136 days, would lead to the observed probability of infection, *P*:

$$P = 1 - \prod_{i=1}^{136} 1 - q \quad \textbf{(1)}$$

Under the assumption of **linearly increasing** infectivity, we wish to derive the amount the daily probability of infection would have to increase, *r*, such that, over the course of 136 days, the observed probability of infection, *P*, would be expected:

$$P = 1 - \prod_{i=1}^{136} 1 - r\frac{i}{136} \quad \textbf{(2)}$$

Under the assumption of **exponentially increasing** infectivity, we wish to derive the factor by which the daily probability of infection would have to increase, *s*, such that, over the course of 136 days, the observed probability of infection, *P*, would be expected:

$$P = 1 - \prod_{i=1}^{136} 1 - p_1(1+s)^{i-1} \quad \textbf{(3)}$$

In this formulation, it is necessary to specify p_1, the probability of infection on day 1 from which subsequent exponential growth proceeds. We assumed that, for the first day only, this probability would be the same as that calculated under the assumption on linearly increasing infectivity.

For uniform infectivity, equation (1) may be solved for *q* using the standard formula for rescaling probabilities over time:

$$q = 1 - (1 - P)^{1/136} \quad \textbf{(4)}$$

Equations (2) and (3) have no straightforward analytical solution, but *r* and *s* may be estimated using numerical optimisation (we used the generalised reduced gradient nonlinear algorithm used by the Solver add-in in Excel).

For example, in the cohort reported by Lohmann et al. (2012), the probability that the average person with TB would have caused 1 or more cases of active TB over a mean of 136 days of potential infectivity prior to diagnosis, was 0.140. If we assume that such a

person experienced uniform infectivity over that period then, per equation (4), that person's daily probability of causing 1 or more case of active TB was 0.0011 (and this is also the daily infection probability at the point of diagnosis). If we adopt an assumption of linearly increasing infectivity, then *r* in equation (2) is estimated to be 0.0022. Under the assumption of exponentially increasing infectivity, *s* is estimated to be 0.0455, which implies a daily probability of infection, at the time of diagnosis, of 0.00658.

Figure 2 illustrates these 3 different scenarios.

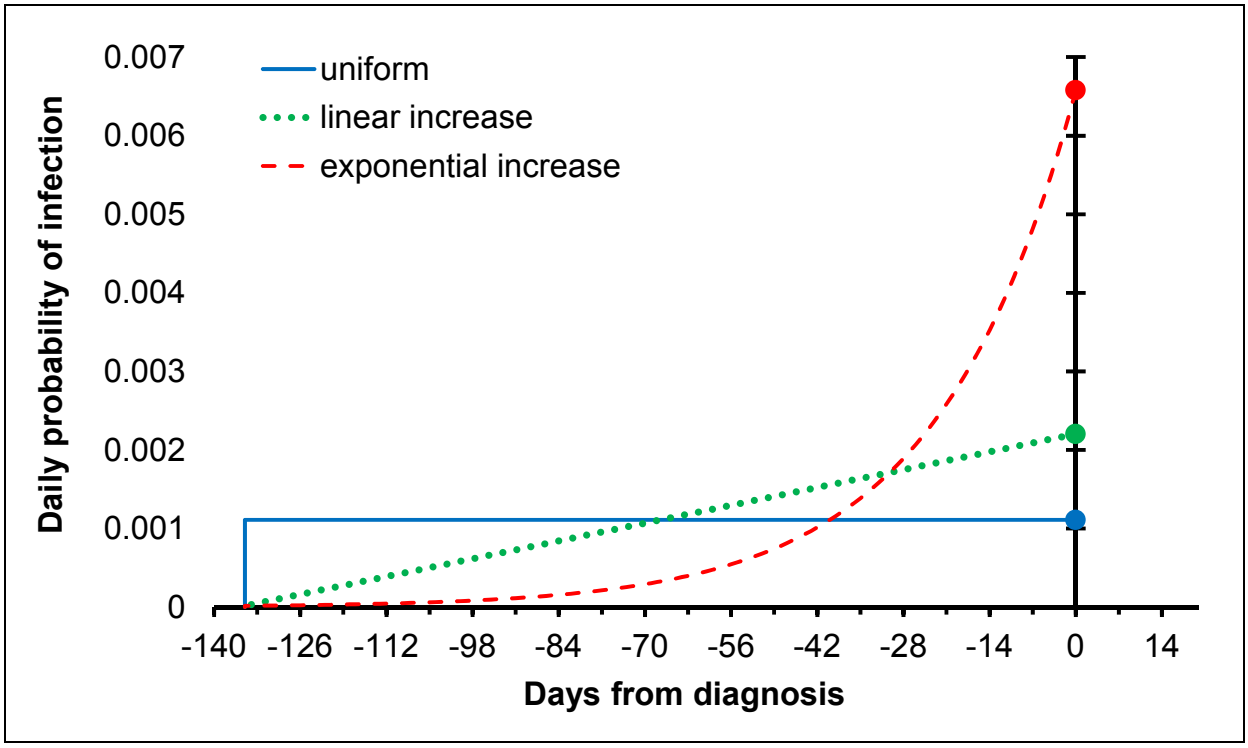

Figure 2: Alternative scenarios for estimating infectivity of index cases

Having estimated infectiousness at the point of diagnosis, the model proceeds to project the probability of transmission over the 14-day treatment period. The model was configured to simulate 3 profiles that were directly analogous to the pre-diagnosis scenarios: that is, either uniform infectivity (maintaining the level of infectiousness calculated at day 0), or decreasing infectivity with a linear or an exponential shape. These scenarios are illustrated in Figure 3.

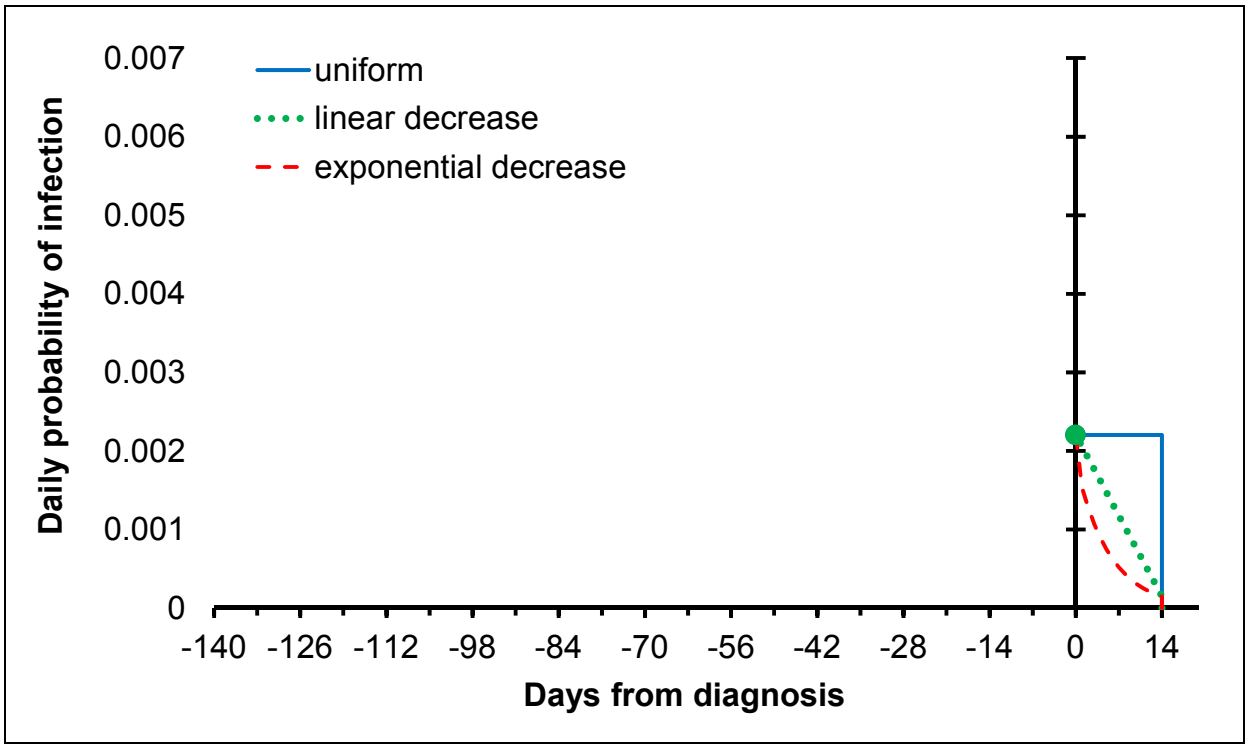

Figure 3: Alternative scenarios for estimating infectivity of index cases

Although the models for pre- and post-diagnosis infectivity are the inverse of each other, there is no particular reason to limit the model to scenarios in which the same shape is used for both estimates. Therefore, a total of 9 combinations of profiles were possible (see Figure 4).

For our base-case analysis, we relied on the simplest possible assumption: that infectivity both before and after diagnosis is uniform. Other scenarios were investigated in sensitivity analysis (see below).

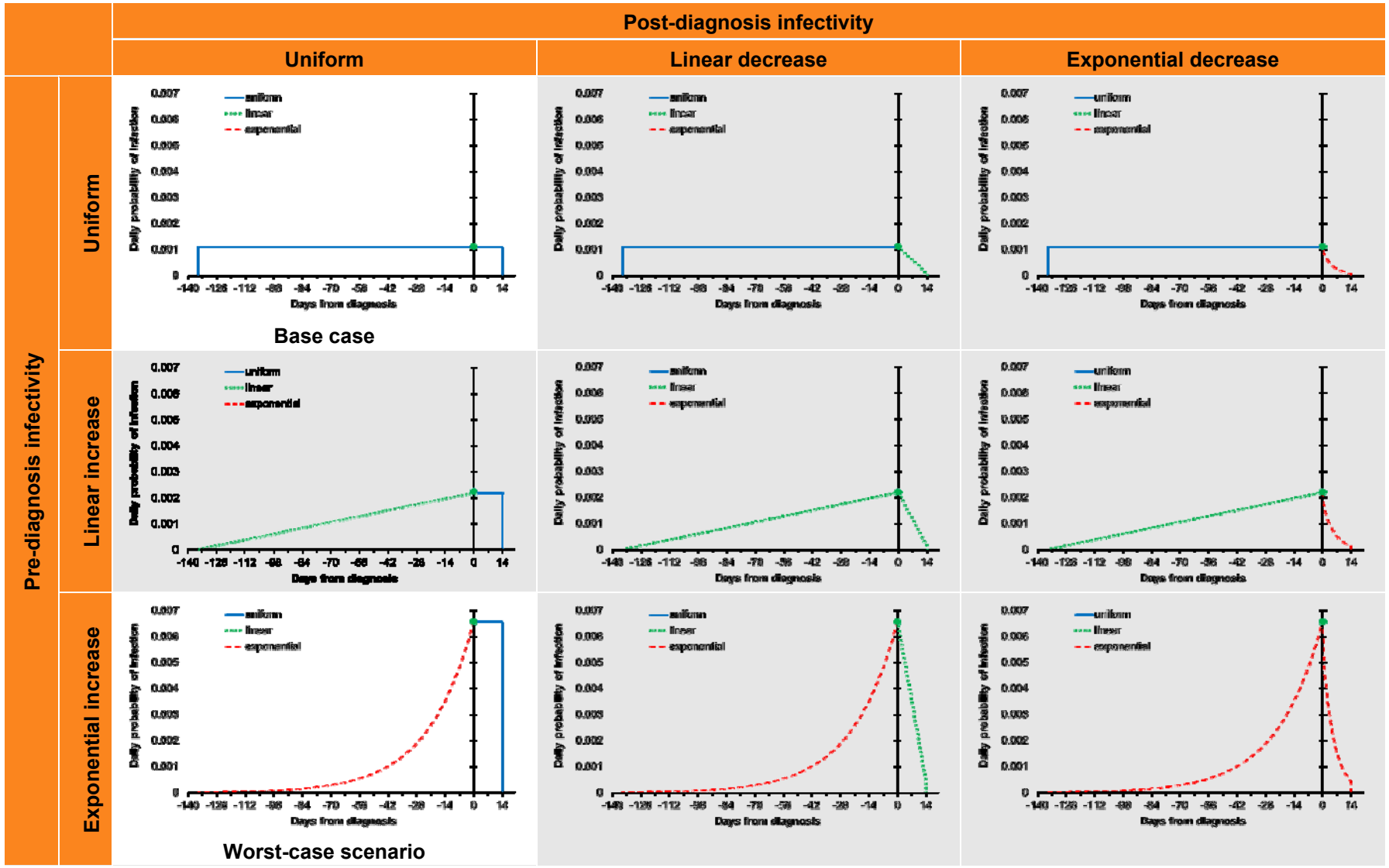

Figure 4: Full range of possible scenarios for estimating infectivity of index cases

People discharged to an inpatient ward

We took a different approach to estimating transmission probability in an inpatient setting. This is because, in the context of a single, enclosed environment, it becomes plausible to adopt an airborne infection dispersal model. This was done to examine the costs and consequences of discharging a patient with potentially infectious TB back onto a hospital ward after their stay in isolation. The GDG felt that this scenario was potentially where the biggest cost and health impacts would be felt, as the probability of transmission was higher given the potential for prolonged exposure to a case and the immunocompromised (relative to the general population) status of the susceptible patients.

An informal review of potential dispersal models was undertaken, and the approach described by Gammaitoni and Nucci (1997) was selected based on published application to TB infection modelling where the index case was an untreated individual in contact with susceptible persons over a defined period of time in a well described setting.

The model describes the probability of infection as:

$$P = 1 - e^{\left[-\frac{pI\phi}{V}\left(\frac{Nt+e^{-Nt}-1}{N^2}\right)\right]}, \quad \textbf{(5)}$$

where:

V = the volume of the room (m^3)
N = the room ventilation rate (air changes per hour)
S = the mean number of susceptible patients in the room
I = the mean number of infectors
P = the mean pulmonary ventilation rate of the susceptibles (m^3 per hour)
t = the mean exposure time (hrs)
ϕ = the mean quanta production rate

The equation is then used to calculate the number of susceptible patients who become infected, C, thus:

$$C = S\left(1 - e^{\left[-\frac{pI\phi}{V}\left(\frac{Nt+e^{-Nt}-1}{N^2}\right)\right]}\right). \quad \textbf{(6)}$$

We used these equations to calculate the probability of TB infection in the circumstance of a patient with infectious TB being discharged onto a 6 bed NHS hospital bay with known dimensions and assumed airflow, pulmonary ventilation and quanta production rates. We assumed that the relative infectivity of different smear grades and the relative proportions of latent and active TB caused by smear grade detailed by Lohmann (2012) were generally applicable in this context. We combined these conditional probabilities with the probability of infection calculated from the G&N equation to determine the possible transmission of latent and active infection on the ward.

Quanta and the airborne dispersal of TB

The number of quanta in a room is not a direct measurement of the number of TB bacilli present in the atmosphere, but is effectively a surrogate measure of both the quantity and pathogenicity of the infectious material, which also reflects the average susceptibility of the individuals in the enclosed space (Beggs et al. 2010). Quanta reference numbers are reported retrospectively in the literature, having been inferred from known environmental characteristics such as the dimensions of the space and air changes per hour, along with the number of infections an individual causes in an outbreak situation. Quanta production rates vary from case to case, and it has been postulated, though not described mathematically, that quanta rates are associated with TB pathology such as cavitation, drug susceptibility and co-infection with HIV . This variability is challenging when deciding upon a suitable base-case number for modelling infections, and to that end we relied on GDG expert opinion to define a plausible range of quanta values based on examples from the literature, which are summarised in the table below.

Table 7: Published estimates of quanta production rates for TB

Description of case	Calculated Qp/h	Reference
Individual infectors		
TB patient on treatment	1.25	Riley et al. (1962)
Untreated TB case	12.7	Nardell et al.(1991)
Laryngeal case of TB	60	Riley et al. (1962)
Bronchoscopy-related outbreak	250	Nardell et al.(1991)
Bronchoscopy-related outbreak	360	Gammaitoni & Nucci (1997)
Outbreak related to jet-irrigation of abcess	2280	Gammaitoni & Nucci (1997)
Autopsy outbreak	5400	Gammaitoni & Nucci (1997)
Intubation-related outbreak	30840	Gammaitoni & Nucci (1997)
Estimated from multiple infectors		
MDR-TB, mixed HIV status, no mask use	138	Dharmadhikari et al. (2012)
MDR-TB, mixed HIV status, masks worn	34	Dharmadhikari et al. (2012)
Drug susceptible and MDR-TB, HIV co-infection	8.2	Escombe et al. (2007)

Given that our model describes patients undergoing treatment, the Qp/h values reported by Riley et al. (1962) as cited by Nardell et al. (1991) seems, at face value, appropriate for the base case. However, the GDG felt these values needed careful interpretation with regard to the treatments available at the time which are no longer used, and the time differential between diagnosis, the commencement of treatment and the commencement of quanta measurement. Taking these factors into account, the GDG agreed that it was reasonable to proceed using the Qp/h values of an untreated case described by Nardell et. al (1991) and then to explore this uncertainty by modelling different Qp/h rates in deterministic sensitivity analyses. The MDR quanta numbers reported by Dharmadhikari et al. (2012) were not considered appropriate for our analysis because they were based on a study using guinea pigs exposed to MDR –TB patients in the tightly controlled environment of a South African specialist research facility.

Characteristics of inpatient ward

The Department of Health has recommended that hospital wards should be ventilated so as to ensure 6 air changes per hour. We used the dimensions of an enclosed 6-bed bay described by Gilkeson et al. (2013) in their study of airborne infection risk in naturally ventilated hospitals. This study applied a pulse-injection gas tracer method to monitor the

number of air-changes per hour, thus meeting the data requirements of our model and also providing a distribution of ventilation rates useful for sensitivity analysis.

We do not account for bed turnover or variation in occupancy on the ward, as this would require very substantial modelling effort (probably in the form of individual patient simulation) with onerous data requirements. Instead, we assume that the other 5 beds in the 6-bed bay are each occupied by 1 individual for the whole period of exposure. In some respects, this will overestimate the probability of disease transmission (in reality, other beds on the ward will spend some time empty, during which time there is no probability of infection); in other respects, it will lead to an underestimate (in reality, different people will be admitted during the course of the index case's stay, and each of these will have a separate probability of becoming infected, whereas a single individual can only become infected once). These 2 factors will cancel each other out to some degree, though it would only be possible to explore this in detail using methods and data that are beyond the plausible scope of this analysis.

F.2.4.3 Natural history of latent TB

In estimating the costs and consequences of latent TB infection, we used the progression rate from latent to active TB derived from the pooled placebo arms from a network meta-analysis of placebo-controlled trials of LTBI treatment, which was included in the analysis for the review question on optimal treatment for LTBI (see full guideline section 7.2). This value was used to remain consistent with the other health economic analyses presented in the guideline

F.2.4.4 Mortality

The model required an estimate of TB-related mortality for secondary cases of immediately active TB and those that arise after a latent period.

The case fatality rate for active TB was taken from Crofts et al. (2008) which was also used in that model and also the original health economic analysis for diagnosis of latent TB (see full guideline section 3.1.3) and the HTA project on rapid molecular diagnostics (see full guideline section 5.3). Our model parameterisation is therefore consistent with these other analyses.

For immediately active fatalities, the average age of people contracting active TB was estimated (using Crofts et al. 2008), and the average life expectancy of people of that age was calculated using standard life-tables (ONS 2012–2013 life tables, ONS, 2014). This was quality-adjusted using general population utility weights (see F.2.4.7, below). In the base case, the average TB case is aged 41.55, which means that individual has discounted, quality-adjusted life expectancy of 17.63 years; therefore, this was the QALY loss that was applied for each fatality expected from immediately active TB.

Within each cycle of the latent TB submodel, patients can die due to their background mortality risk or can die from a complication relating to active TB. Mortality from all other causes is estimated using the same national mortality statistics (ONS 2012–2013 life tables, ONS, 2014).). In the base case, the average latent TB case (again, we assume a mean age of 41.55) experiences discounted, quality-adjusted life expectancy of 17.386 QALYs, compared with 17.423 for a person of the same age without latent TB. Therefore, a QALY loss of 0.036 was applied for each case of latent TB caused.

F.2.4.5 Treatment effects

The model assumes that the index case is untreated until the point of isolation, and that treatment is 100% effective at preventing onward transmission after 14 days of treatment.

According to the base-case assumption of uniform post-diagnosis infectivity, the index case is assumed to have 100% of the infectivity of an untreated, infectious case on day 13, or any other day before that. Isolation is assumed to be 100% effective at preventing onward transmission of TB, and is assumed to be used appropriately. These initial assumptions were discussed with the GDG in the absence of evidence to the contrary.

F.2.4.6 Costs

The cost of each of the resource use elements within the model are obtained from a number of standard sources.

NHS Reference costs are used as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information. The cost of a secondary case of active TB was taken from the work undertaken by Imperial College London (see full guideline section 7.2) which was uprated for inflation from the previous NICE TB Guideline. This is a composite cost, covering the average cost of treatment, contact tracing and diagnostic testing for a drug susceptible TB case.

F.2.4.7 Quality of life

For both the LTBI Markov submodel and our estimate of QALYs lost due to active-TB-related mortality, we used age-specific health-related quality of life estimates for the general population taken from Kind et al. (1999). In order for this analysis to be consistent with other de-novo health economic work carried out in this guideline, the same utility estimates for TB morbidity were used as in those models (based on values used in the previous NICE guidelines, which were, in turn, derived from Schechter et al. [1990]). A literature review was carried out to determine what QALY decrement is appropriate to apply for a stay in isolation, but no evidence was found that was deemed applicable to TB and single room isolation.

F.2.4.8 Summary of parameters

All parameters used in the model are summarised in Table 8, including details of the distributions and parameters used in probabilistic analysis.

Table 8: All parameters in original cost–utility model

Parameter	Value (95%CI[a])	Probabilistic	Source
Duration of pre-diagnosis symptoms (d)	136	Not varied in PSA	Lohmann et al. 2012
Index cases causing ≥1 case of active TB			
Baseline			
Probability	0.140 (0.081, 0.212)	Beta: α=15; β=92	Lohmann et al. 2012
Odds	0.163		Calculated
Proportion			
Smear grade			
Negative	0.048 (0.006, 0.129)	Beta: α=2; β=40	Lohmann et al. 2012
Grade 1-2	0.130 (0.029, 0.292)	Beta: α=3; β=20	
Grade 3-5	0.238 (0.124, 0.376)	Beta: α=10; β=32	
OR			
Smear grade			
Negative (ref)	1.000		
Grade 1-2	3.000		Calculated
Grade 3-5	6.250		Calculated
Odds			
Smear grade			

Parameter	Value (95%CI[a])	Probabilistic	Source
Negative	0.047		Calculated
Grade 1-2	0.140		Calculated
Grade 3-5	0.292		Calculated
Probability			
Smear grade			
Negative	0.045		Calculated
Grade 1-2	0.123		Calculated
Grade 3-5	0.226		Calculated
Proportion			
No school contact	0.048 (0.016, 0.096)	Beta: α=5; β=99	Lohmann et al. 2012
Attending or employed at school	0.133 (0.076, 0.204)	Beta: α=14; β=91	
OR			
No school contact (ref)	1.000		
Attending or employed at school	3.046		Calculated
Odds			
No school contact	0.080		Calculated
Attending or employed at school	0.245		Calculated
Probability			
No school contact	0.074		Calculated
Attending or employed at school	0.197		Calculated
Odds			
No school contact			
All smear grades	0.080		Calculated
Smear grade			
Negative	0.023		Calculated
Grade 1-2	0.069		Calculated
Grade 3-5	0.144		Calculated
Attending or employed at school			
All smear grades	0.245		Calculated
Smear grade			
Negative	0.070		Calculated
Grade 1-2	0.210		Calculated
Grade 3-5	0.438		Calculated
Probability over history			
No school contact			
All smear grades	0.074		Calculated
Smear grade			
Negative	0.023		Calculated
Grade 1-2	0.065		Calculated
Grade 3-5	0.126		Calculated
Attending or employed at school			
All smear grades	0.197		Calculated
Smear grade			
Negative	0.066		Calculated
Grade 1-2	0.174		Calculated
Grade 3-5	0.305		Calculated
Number of active cases per case (where ≥1 infections)	1.286 (0.882, 1.875)	Lognormal: μ=0.25; σ=0.19	Lohmann et al. 2012
Index cases causing ≥1 case of LTBI			
Baseline			
Probability	0.577 (0.478, 0.673)	Beta: α=56; β=41	Lohmann et al. (2012)

Parameter	Value (95%CI[a])	Probabilistic	Source
Odds	1.366		Calculated
Proportion			
Smear grade			
Negative	0.364 (0.211, 0.532)	Beta: α=12; β=21	Lohmann et al. 2012
Grade 1-2	0.696 (0.498, 0.861)	Beta: α=16; β=7	
Grade 3-5	0.683 (0.535, 0.814)	Beta: α=28; β=13	
OR			
Smear grade			
Negative (ref)	1.000		
Grade 1-2	4.000		Calculated
Grade 3-5	3.769		Calculated
Odds			
Smear grade			
Negative	0.474		Calculated
Grade 1-2	1.896		Calculated
Grade 3-5	1.786		Calculated
Probability			
Smear grade			
Negative	0.322		Calculated
Grade 1-2	0.655		Calculated
Grade 3-5	0.641		Calculated
Proportion			
No school contact	0.321 (0.224, 0.426)	Beta: α=26; β=55	Lohmann et al. (2012)
Attending or employed at school	0.567 (0.464, 0.667)	Beta: α=51; β=39	
OR			
No school contact (ref)	1.000		Calculated
Attending or employed at school	2.766		Calculated
Odds			
No school contact	0.708		Calculated
Attending or employed at school	1.958		Calculated
Probability			
No school contact	0.414		Calculated
Attending or employed at school	0.662		Calculated
Odds			
No school contact			
All smear grades	0.708		Calculated
Smear grade			
Negative	0.246		Calculated
Grade 1-2	0.982		Calculated
Grade 3-5	0.926		Calculated
Attending or employed at school			
All smear grades	1.958		Calculated
Smear grade			
Negative	0.679		Calculated
Grade 1-2	2.718		Calculated
Grade 3-5	2.561		Calculated
Probability over history			
No school contact			
All smear grades	0.414		Calculated
Smear grade			
Negative	0.197		Calculated

Parameter	Value (95%CI[a])	Probabilistic	Source
Grade 1-2	0.496		Calculated
Grade 3-5	0.481		Calculated
Attending or employed at school			
all smear grades	0.662		Calculated
Smear grade			
Negative	0.405		Calculated
Grade 1-2	0.731		Calculated
Grade 3-5	0.719		Calculated
Number of latent cases per case (where ≥1 infections)	3.788 (3.423, 4.191)	Lognormal: μ=1.33; σ=0.05	Lohmann et al. (2012)
Proportion of infections that become active 'early'			
All smear grades	0.083		Calculated
Smear grade			
Negative	0.054		Calculated
Grade 1-2	0.060		Calculated
Grade 3-5	0.108		Calculated
Ward infectivity			
Parameters for transmission			
Room dimensions			
Length of room (m)	8.00	Not varied in PSA	Gilkeson et al. (2013)
Width of room (m)	8.00	Not varied in PSA	Gilkeson et al. (2013)
Height of room (m)	2.75	Not varied in PSA	Gilkeson et al. (2013)
Volume of room (m3)	200.00		Calculated
Room ventilation rate	6.50 (3.60, 7.40)	Uniform: min=3.5; max=7.5	Gilkeson et al. (2013)
Mean number of susceptibles	5	Not varied in PSA	Gilkeson et al. (2013)
Mean number of infectors	1	Not varied in PSA	assumed
Mean pulmonary ventilation rate	0.48 (0.32, 0.71)	Lognormal: μ=-0.73; σ=0.20	Beggs et al. (2010)
Mean exposure time (hrs)	168.00	Not varied in PSA	Fixed at 7 days
Mean quanta production rate	12.70 (7.83, 19.51)	Lognormal: μ=2.51; σ=0.23	Beggs et al. (2010)
Probability of infection over exposure time	0.545		Calculated – see equation (5)~~(5)~~
Odds of infection over exposure time	1.197		Calculated
Odds			
Smear grade			
Negative	0.343		Calculated
Grade 1-2	1.029		Calculated
Grade 3-5	2.143		Calculated
Probability			
Smear grade			
Negative	0.255		Calculated
Grade 1-2	0.507		Calculated
Grade 3-5	0.682		Calculated
Number of infections over exposure time			
all smear grades	2.724		Calculated
Smear grade			
Negative	1.277		Calculated
Grade 1-2	2.535		Calculated
Grade 3-5	3.409		Calculated

Parameter	Value (95%CI[a])	Probabilistic	Source
Number of active infections over exposure time			
all smear grades	0.227		Calculated
Smear grade			
Negative	0.068		Calculated
Grade 1-2	0.152		Calculated
Grade 3-5	0.369		Calculated
Number of LTBIs over exposure time			
all smear grades	2.497		Calculated
Smear grade			
Negative	1.208		Calculated
Grade 1-2	2.384		Calculated
Grade 3-5	3.041		Calculated
Natural history			
Annual rate of activation of TB	0.0022 (0.0019, 0.0026)	Lognormal: μ=-6.129; σ=0.083	Pooled placebo arms from treatment of LTBI NMA
Per-cycle probability of activation of TB	0.0005		Calculated
Case-fatality rate for active TB			
0-4	0.003 (0.000, 0.013)	Beta: α=1; β=290	Crofts et al. (2008)
5-14	0.002 (0.000, 0.007)	Beta: α=1; β=564	
15-44	0.012 (0.010, 0.015)	Beta: α=88; β=7249	
45-64	0.048 (0.040, 0.056)	Beta: α=125; β=2500	
65+	0.176 (0.160, 0.191)	Beta: α=413; β=1940	
All ages	0.05 (0.04, 0.05)	Beta: α=628; β=12543	
Costs			
Cost of treating 1 secondary case of active TB	£5329.00 (£2347.92, £9509.28)	Gamma: α=8.33; β=639.44	NICE CG 117
Cost per day in single room isolation	£387.40 (£315.20, £466.93)	Gamma: α=100.00; β=3.87[b]	NHS Reference Costs 2013–14
Cost per day on ward	£264.00 (£214.80, £318.20)	Gamma: α=100.00; β=2.64[b]	NHS Reference Costs 2013–14
Quality of life			
QALY loss associated with 1 secondary case of active TB			
QALY loss associated with morbidity	0.08 (0.03, 0.17)	Gamma: α=5.43; β=0.02	NICE CG 117
Average age of active TB case	41.55 (26.02, 57.08)	Triangular: min=21.55; mode=41.55; max=61.55	Crofts et al. (2008)
Sex (p male) of average active TB case	0.54 (0.53, 0.55)	Beta: α=7134; β=6042	Crofts et al. (2008)
General population utility			
Men			
0-24	0.94 (0.92, 0.96)	Beta: α=470.31; β=30.02	Kind et al. (1999)
25-34	0.93 (0.91, 0.95)	Beta: α=779.51; β=58.67	
35-44	0.91 (0.89, 0.93)	Beta: α=659.28; β=65.20	
45-54	0.84 (0.80, 0.87)	Beta: α=341.41; β=65.03	
55-64	0.78 (0.74, 0.82)	Beta: α=333.84; β=94.16	
65-74	0.78 (0.74, 0.82)	Beta: α=388.47; β=109.57	
75+	0.75 (0.70, 0.80)	Beta: α=192.97; β=64.32	
Women			
0-24	0.94 (0.92, 0.96)	Beta: α=647.03; β=41.30	Kind et al. (1999)
25-34	0.93 (0.92, 0.94)	Beta: α=1137.28; β=85.60	
35-44	0.91 (0.89, 0.93)	Beta: α=1009.37; β=99.83	

Parameter	Value (95%CI[a])	Probabilistic	Source
45-54	0.85 (0.82, 0.88)	Beta: α=546.15; β=96.38	
55-64	0.81 (0.78, 0.84)	Beta: α=530.28; β=124.39	
65-74	0.78 (0.75, 0.81)	Beta: α=556.03; β=156.83	
75+	0.71 (0.67, 0.75)	Beta: α=412.39; β=168.44	

[a] *Confidence intervals shown represent 95% limits for parameterised distributions; these may not match perfectly intervals reported in original publications, though any discrepancies should be negligible.*
[b] *Standard error assumed to be 10% of mean.*

F.2.5 Sensitivity analyses

Deterministic sensitivity analysis of inputs to the Gammaitoni and Nucci equations was undertaken where data on plausible ranges was available for the input parameters.

The force of infection over the time period of interest can be calculated from the relative infectivity values derived from the case reports in Lohmann et al. (2012). Once this is estimated, the distribution of infectivity over time can be made to fit any plausible distribution by keeping the area under the curve the same as the base-case but mathematically altering its shape. The GDG were consulted on the potential infectivity profiles both pre and post diagnosis, and 9 potential combinations of curves were fitted using a combination of linear, uniform and exponential curves at the pre and post diagnosis stages (as described in section F.2.4.3) . After discussion with the GDG, these were simplified to base-case and worst-case scenarios. The base-case scenario was selected as the uniform distribution both before and after diagnosis, as this was the simplest assumption possible in the absence of any directly informative evidence. The worst-case scenario was the pre-exponential–post-uniform profile, which meant that the maximum infectivity was reached at the point of diagnosis and remained at this peak level for the 7 day post isolation period. Therefore, the probability of transmission was maximised during the period in which, according to usual care, the patient would be isolated and not spreading TB.

F.2.5.1 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters.

Probabilistic sensitivity analyses were run separately for the different components of the analysis. Probability distributions were estimated for input variables where possible. Distribution parameters were sourced from the study in which the value was obtained, or were estimated based on the usual properties of data of that type. The distribution for each of the parameters used within the probabilistic sensitivity analysis is driven by the variable type and the availability of reported information. Beta distributions are used for variables denoting a probability, as bounded between 0 and 1, where data are reported to estimate the standard error. A beta distribution is also estimated for the utility values, which also traditionally confined to values between 0 and 1. The variables which denote a number of events, are estimated to follow a lognormal distribution. Cost parameters were estimated from gamma distributions.

F.2.6 Original cost–utility model – results

F.2.6.1 Base-case cost–utility results: discharge to community

In the deterministic base-case analysis, isolating patients for 2 weeks before discharging them to their usual place of residence results in comparatively little reduction in QALY losses

compared to shorter isolation (7 days), but does increase costs (Table 9~~Table 9~~). ~~The number of cases transmitted is low, even for strongly smear-positive patients, and the costs associated with LTBI infections that become active are low because of this and due to discounting (as activation of latent TB may occur in the distant future).~~

Table 9: Original cost–utility model – base-case results (discharge to community)

	Discharge to congregate settings				Discharge to home			
	Smear grade				Smear grade			
	Negative	Low	High	All grades	Negative	Low	High	All grades
Secondary cases of active TB								
No. of cases	0.0045	0.0126	0.0238	0.0144	0.0015	0.0044	0.0089	0.0051
Costs	£23.87	£67.03	£127.03	£76.82	£8.03	£23.52	£47.26	£27.22
QALY loss								
Morbidity	0.00038	0.00105	0.00200	0.00121	0.00013	0.00037	0.00074	0.00043
No. of deaths	0.00021	0.00060	0.00114	0.00069	0.00007	0.00021	0.00042	0.00024
QALY loss from deaths	0.00377	0.01057	0.02004	0.01212	0.00127	0.00371	0.00745	0.00429
Total	0.00414	0.01163	0.02203	0.01332	0.00139	0.00408	0.00820	0.00472
Secondary cases of LTBI								
No. of cases	0.0997	0.2476	0.2397	0.2057	0.0426	0.1311	0.1256	0.1029
Costs	£23.72	£58.87	£57.00	£48.91	£10.13	£31.18	£29.88	£24.48
QALY loss	0.0036	0.0090	0.0087	0.0075	0.0016	0.0048	0.0046	0.0038
Isolation costs								
14 days' isolation	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424
Reduced isolation	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712
Totals								
Costs saved by reduced isolation	**£2,664**	**£2,586**	**£2,528**	**£2,586**	**£2,694**	**£2,657**	**£2,635**	**£2,660**
QALYs forgone by reduced isolation	**0.0078**	**0.0206**	**0.0308**	**0.0208**	**0.0029**	**0.0089**	**0.0128**	**0.0085**
ICER	**£342,610**	**£125,223**	**£82,148**	**£124,210**	**£914,940**	**£299,949**	**£206,195**	**£313,975**
Mean ICERs from PSA	**£356,642**	**£127,037**	**£84,259**	**£125,697**	**£940,247**	**£302,139**	**£212,173**	**£318,236**

The number of cases transmitted is low, even for strongly smear-positive patients, and the costs associated with LTBI infections that become active are low because of this and due to discounting (as activation of latent TB may occur in the distant future). As a result, the comparison of 14-day isolation with 7-day isolation is associated with very high ICERs of between £80,000 and £1,000,000 per QALY. These numbers have an interpretation that can be expressed in 2 ways: as the amount of money that would be saved per QALY forgone by moving from a 14-day strategy to a 7-day one (in which case, 7-day isolation would be seen as good value for money – saving an amount that justifies associated QALY losses, assuming society values QALYs forgone at a similar level to QALYs gained) or as the cost that would have to be paid for each QALY gained by 14-day isolation in comparison with a 7-day strategy (in which case, 14-day isolation would be seen as poor value for money, as we assume that the costs it incurs can produce greater QALY gains elsewhere in the health system).

Probabilistic sensitivity analysis

The PSA provided expected results, given the high ICERs estimated in the deterministic base case. The CEAC (Figure 5) shows that 14 days' isolation can only be considered to provide superior value for money to 7 days' isolation at very high QALY thresholds and, even then, only for people with high-grade smear-positivity.

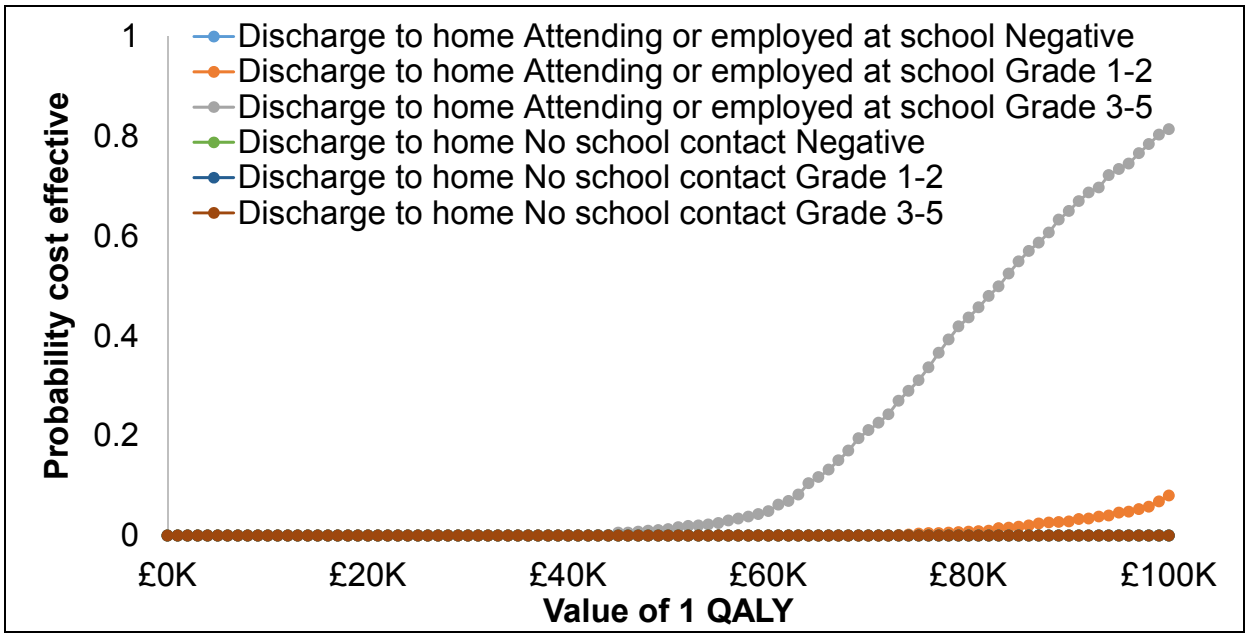

Figure 5: Base-case cost-effectiveness acceptability curve – 14 -v- 7 days' isolation (discharge to community

F.2.6.2 Scenario analysis

Despite the apparent unambiguousness of the base case, further exploration reveals that model results are importantly sensitive to the infectivity profile of the index case before and after diagnosis. A scenario analysis with an exponential followed by a uniform distribution of infectivity (the 'worst-case scenario') would result in enough TB transmission to reduce cost savings and increase QALY losses to the degree that isolation would be considered cost effective for people who are being discharged to congregate settings in 98.6% of simulations in strongly smear-positive patients, and 63.2% for low-smear-grade patients (assuming QALYs are valued at £20,000). Isolating smear-negative patients remains unlikely to be cost-effective.

Table 10: Original cost–utility model – worst-case scenario (discharge to community)

	Discharge to congregate settings				Discharge to home			
	Smear grade				Smear grade			
	Negative	Low	High	All grades	Negative	Low	High	All grades
Secondary cases of active TB								
No. of cases	0.0264	0.0730	0.1356	0.0834	0.0089	0.0260	0.0518	0.0300
Costs	£140.51	£388.92	£722.41	£444.24	£47.49	£138.47	£276.04	£160.02
QALY loss								
Morbidity	0.00221	0.00612	0.01136	0.00699	0.00075	0.00218	0.00434	0.00252
No. of deaths	0.00126	0.00348	0.00646	0.00397	0.00042	0.00124	0.00247	0.00143
QALY loss from deaths	0.02216	0.06134	0.11394	0.07007	0.00749	0.02184	0.04354	0.02524
Total	0.02437	0.06746	0.12530	0.07706	0.00824	0.02402	0.04788	0.02776
Secondary cases of LTBI								
No. of cases	0.5572	1.2642	1.2299	1.0773	0.2462	0.7186	0.6909	0.5739
Costs	£132.50	£300.63	£292.48	£256.19	£58.55	£170.88	£164.30	£136.47
QALY loss	0.0203	0.0461	0.0448	0.0393	0.0090	0.0262	0.0252	0.0209
Isolation costs								
14 days' isolation	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424	£5,424
Reduced isolation	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712	£2,712
Totals								
Costs saved by reduced isolation	**£2,439**	**£2,022**	**£1,697**	**£2,011**	**£2,606**	**£2,402**	**£2,271**	**£2,415**
QALYs forgone by reduced isolation	**0.0447**	**0.1135**	**0.1701**	**0.1163**	**0.0172**	**0.0502**	**0.0731**	**0.0487**
ICER	**£54,582**	**£17,811**	**£9,974**	**£17,291**	**£151,391**	**£47,849**	**£31,089**	**£49,624**
Mean ICERs from PSA	**£356,642**	**£127,038**	**£84,259**	**£125,697**	**£940,247**	**£302,140**	**£212,174**	**£318,237**

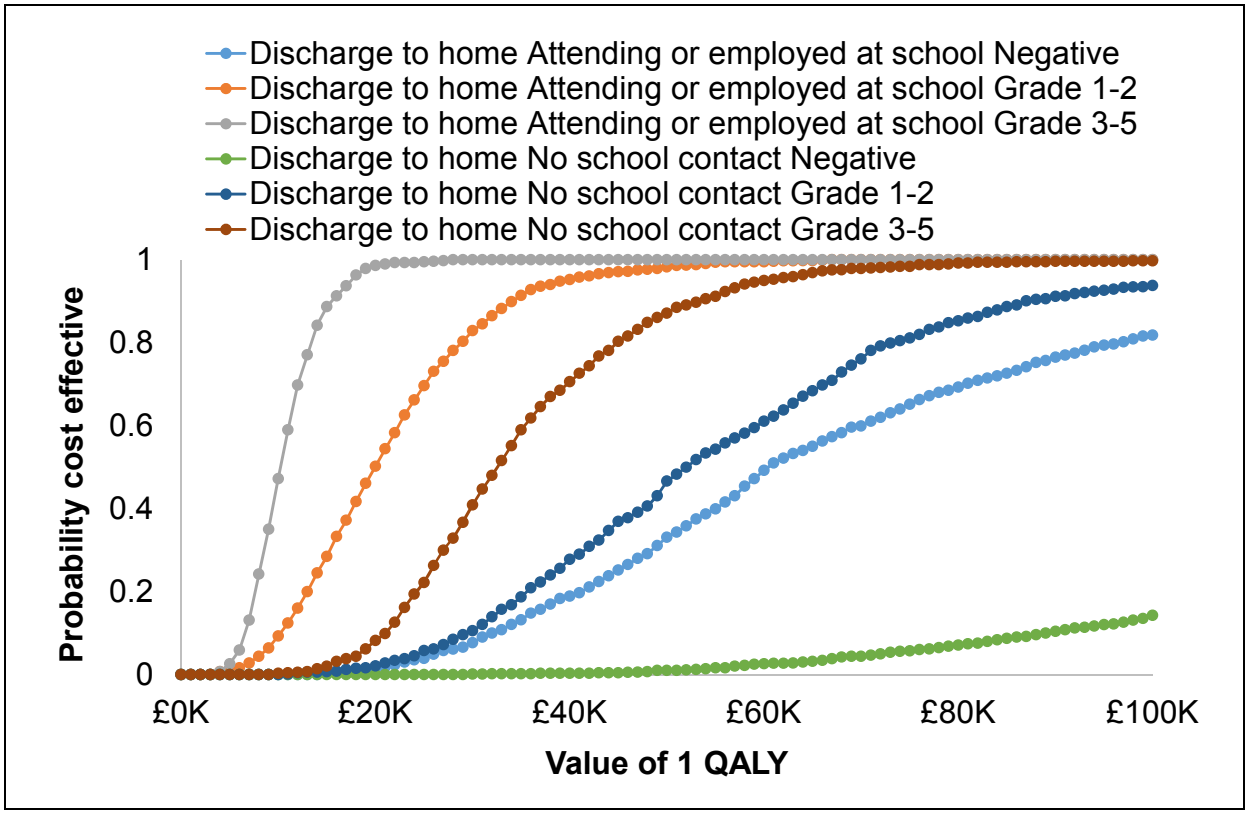

Figure 6: Cost-effectiveness acceptability curve – 14 -v- 7 days' isolation (discharge to community); worst-case infectivity profile

F.2.6.3 Base-case cost–utility results: discharge to an inpatient ward

The base-case for this analysis reflects the case report detailed in Beggs et al. (2003), of an untreated case of TB with cavitatory disease producing an estimated 12.5 quanta per hour. In this scenario, isolating all patients with a positive sputum smear is the dominant strategy (is less costly and minimises health loss). The model estimates that continued isolation of people with a negative smear is also good value for money (less than £2000 saved per QALY forgone). However, it should be noted that, for smear-negative patients, the quanta production rate in the base case may not be a realistic representation of true quanta production, although smear-negative patients have been known to cause around 17% of TB transmission (Lohmann et al. 2012). The PSA supports the finding that discharging patients to an inpatient ward is unlikely to be sensible within the 14 day window of potential infectiousness: if QALYs are valued at £20,000, the probability that 14 days' isolation is cost effective is greater than 89% for all smear grades.

Table 11: Original cost–utility model – base-case results (discharge to inpatient ward)

	Smear grade			
	Negative	**Low**	**High**	**All grades**
Secondary cases of active TB				
No. of cases	0.0684	0.1517	0.3686	0.2270
Costs	£364.28	£808.43	£1,964.26	£1,209.85
QALY loss				
Morbidity	0.00573	0.01271	0.03089	0.01903
No. of deaths	0.00326	0.00723	0.01757	0.01082
QALY loss from deaths	0.05746	0.12751	0.30982	0.19083
Total	0.06319	0.14022	0.34071	0.20985
Secondary cases of LTBI				
No. of cases	1.2084	2.3837	3.0406	2.4971
Costs	£287.35	£566.85	£723.08	£593.82
QALY loss	0.0440	0.0869	0.1108	0.0910
Isolation costs				
14 days' isolation	£5,424	£5,424	£5,424	£5,424
Reduced isolation	£4,560	£4,560	£4,560	£4,560
Totals				
Costs saved by reduced isolation	**£212**	**-£511**	**-£1,824**	**-£940**
QALYs forgone by reduced isolation	**0.10723**	**0.22711**	**0.45154**	**0.30087**
ICER	**£1,979**	**dominant**	**dominant**	**dominant**
Mean ICERs from PSA	**£830**	**dominant**	**dominant**	**dominant**

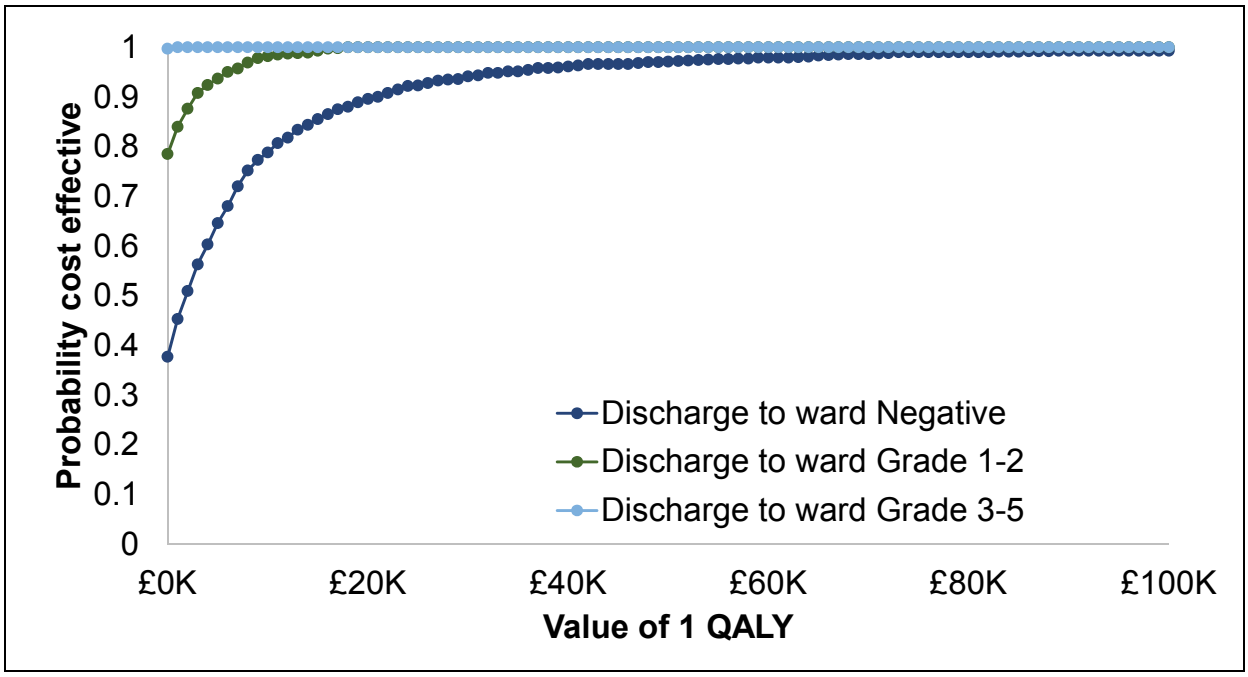

Figure 7: Cost-effectiveness acceptability curve – 14 -v- 7 days' isolation (discharge to inpatient ward)

F.2.6.4 Deterministic sensitivity analysis

A 1-way deterministic sensitivity analysis of quanta production rates (Figure 8) suggests that 14-day isolation remains the cost effective strategy (assuming QALYs are valued at £20,000) for strongly smear-positive patients unless quanta rate is less than 0.5 Q/ph. It is unlikely that such low quanta production rates are compatible with classification as a strongly smear-positive case. For patients with lower smear grades, the threshold is 1.45 Q/ph and, for smear-negative people, it is 4.25 Q/ph. If smear grade is not taken into account, the model estimates that discharging people to an inpatient ward would not be cost effective unless quanta production was lower than 1.05 Q/ph. Notably, this is below the lowest plausible level we have identified (see Table 7): 1.25, calculated by Riley et al. (1967) in their guinea pig studies of infectious TB patients on treatment.

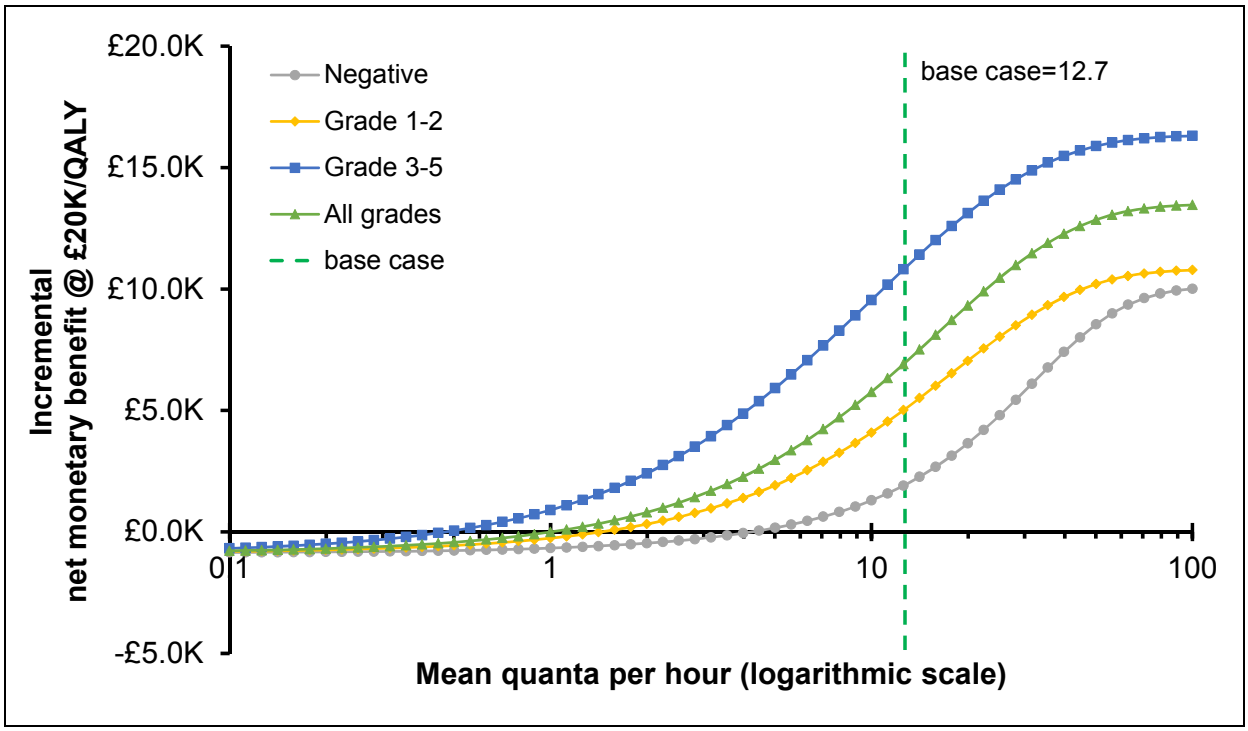

Figure 8: 1-way sensitivity analysis: mean quanta per hour – 14 -v- 7 days' isolation (discharge to inpatient ward)

F.2.7 Discussion

The base-case results suggest that, when compared with usual current practice of isolation for 2 weeks, an isolation period of 1 week followed by discharge to the patient's usual place of residence results in cost savings and QALY losses. Judged according to conventional standards of cost effectiveness (and assuming society would place a similar value on QALYs forgone as on QALYs gained), the cost savings would usually be considered to justify the QALY losses – that is, reducing isolation duration would be seen as good value for money. This is largely due to the relatively small amount of TB spread by the cases in the 7-day period before their infectiousness drops to zero, and reflects the relatively low amount of transmission observed in the Lohmann et al. (2012) study.

However, the results are sensitive to the assumed infectivity profile of the index case before and after diagnosis. In a worst-case scenario, which the GDG felt could plausibly represent the expected profile of infectivity in some patients, a case with an exponential followed by uniform distribution of infectivity would result in enough TB transmission to reduce cost savings and increase QALY losses to the degree that 14 days' isolation would be considered cost-effective, certainly in people with high-grade smear-positivity and/or those who would be discharged to congregate settings.

The base-case analysis for discharge to an inpatient setting supports the current clinical practice of 2 weeks' isolation for all patients with TB. This remains the case as long as the likelihood of transmission – as expressed in quanta production rates – is not at or below the lower end of the range reported in the literature. At low numbers of quanta, such as those observed by Riley et al. (1967) in guinea pig studies of patients on treatment, isolation measures may not be cost effective for smear-negative patients and possibly those with low-grade smear-positivity. The model suggests that, for any quanta production rate within

plausible bounds, it will always be sensible to complete 14 days' isolation for people with high-grade smear-positivity.

F.2.7.1 Strengths of the analysis

This model attempts to provide evidence for the cost effectiveness of isolation measures, which is an area of tuberculosis medicine that has not received much attention in the past. As a result, the existing evidence base for clinical decision makers is scarce. Whilst the model is based on some broad assumptions, it provides a transparent framework under which the full range of uncertainty is accounted for wherever possible.

This analysis enables decision makers to consider the likely impacts of patient characteristics in determining duration of isolation. In particular, it supports the use of sputum smear microscopy grading as part of the diagnostic work-up and risk assessment (which would also consider discharge destination) of a patient's infectiousness before making the decision to discontinue isolation.

The model presents a useful synergy of epidemiology and health economics, which can be easily modified to simulate patients with different natural history of TB.

F.2.7.2 Weaknesses of the analysis

This analysis is based on largely indirect evidence, is heavily reliant on a single contact-tracing study, and required some substantial assumptions that are acknowledged simplifications of a more complicated reality. Whilst we consider the expected number of cases given contact with a TB-positive case in congregate or domestic settings, this part of our analysis does not allow the exploration of the impact of contact time on the probability of infection. Evidence from school studies in South Africa suggests that the spread of TB is correlated with the time that the index patient is in close proximity to contacts, and that there will be concentrations of time spent with family and friends who therefore bear the majority of the exposure risk. A range of plausible infectivity profiles were considered in our analysis and their validity discussed with the GDG. However, the exact profile of infectiousness over time for a typical TB case at the beginning of chemotherapeutic treatment remains undefined in the literature.

The extent to which the index case's quality of life may be impaired by isolation is clearly an area of relevance to this analysis, but one on which we could not identify any informative evidence. We believe it is probably the case that impacts will be relatively minimal over the periods of isolation considered here (7 -v- 14 days), certainly in comparison with some of the very extended periods of isolation that are indicated in cases of MDR-TB – evidence used in the HTA project on molecular diagnosis suggested that people with drug-resistant TB require a minimum of 89 days' isolation (Drobniewski et al. 2015; see full guideline section 5.3.4), and the GDG informed us that many people remain isolated for longer than this. However, if quality of life is measurably impaired in people with drug-sensitive TB undergoing side-room isolation, our analyses will overestimate the desirability of prolonging that isolation.

The LTBI Markov model only considers progression to active disease of those patients infected with LTBI. No consideration is given to the contacts they may infect if they progress to active disease, which means some of the benefits of isolation are underestimated in our analysis.

The inpatient discharge analysis is limited by being unable to account for patient flow dynamics on an inpatient ward. It is reasonable to expect that there will be bed turnover on a ward, and that therefore the exposure time of susceptible patients will vary according to their different lengths of stay. However, modelling average turnover rates that would adequately

represent a typical NHS ward is mathematically complex, especially given the wide variability of ward types, and the clinical status of their patient populations.

Whilst a thorough search of the literature was undertaken, no evidence on the failure rates of isolation could be found. Outbreak studies typically report isolated cases involving incorrect ventilation or aerosolization of TB during procedures. Without knowing more about the throughput of patients over time, failure rates cannot be ascertained and therefore isolation was assumed to be 100% effective at preventing transmission.

A particular limitation of the analysis is that only drug-sensitive patients are considered due to a lack of evidence on the relative infectiousness of MDR-patients. It is evident that current isolation measures are in no small part designed to minimise the risk of a false-negative MDR diagnosis, resulting in incorrect discharge and onward transmission of drug-resistant TB. Whilst MDR-TB represents only 1–2% of the TB burden in England and Wales, the cost of treating a case of MDR-TB is 10 times greater than for a drug-susceptible case, possibly more. In addition, if the utility decrements for MDR-TB treatment adverse events are as severe as assumed in the HTA project on molecular diagnosis (over 1 QALY lost per treated case; Drobniewski et al. 2015; see full guideline section 5.3.4), then the QALY losses associated with any secondary cases will be substantial. Therefore, the precautionary use of isolation measures involves an implicit acceptance that the costs and harms of isolating patients who are assumed to be drug susceptible are at least partly justified by minimising the risk of spreading undetected MDR infection. Amongst those at low risk for drug-resistant disease, the number of patients isolated needed to prevent 1 case of MDR-TB is likely to be high, and the costs associated will also be high. Unfortunately this analysis was not able to conduct a full exploration of the use of isolation measures for MDR-TB, taking into account the role that rapid diagnostic methods might play in the future in reducing that number needed to isolate.

F.2.7.3 Comparison with other CUAs

Without previously published CUAs addressing this question there is a lack of a clear reference point for this analysis.

F.2.8 Conclusions

Isolation of potentially infectious TB patients is expensive, and may have quality of life implications for the patient being isolated that are thus far poorly understood. This analysis supports the use of smear grading as a potentially useful prognostic marker for determining a patient's potential infectivity, albeit using relativities sourced from a single study. This analysis shows the cost effectiveness of isolation for drug-susceptible patients is likely to be related to the probability that they will transmit TB to others, which is defined by the natural history of their TB and the setting to which they would be discharged. Undoubtedly, the suspicion of drug resistance overrides all other considerations because the potential costs and harms of transmitting drug-resistant TB are orders of magnitude greater than in drug-susceptible disease, but this analysis was not able to address this directly. Further work is needed in this area, particularly in light of newer diagnostic technologies such as rapid molecular and genome techniques which may increase diagnostic confidence and guide isolation practice.

F.3 Economic evidence profiles for included studies

F.3.1 Diagnosing active TB (full guideline section 3.3.5)

Table 12 Economic evidence profile for cost effectiveness of NAAT for diagnosing active TB

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental costs/benefits/harms Summary	Conclusions	Uncertainty
Hughes et.al (2010). Addition of NAAT techniques in combination and in place of current diagnostic practice. **Directly applicable** **Potentially serious limitations**[a,b,c,]	Effects: RCT evidence and systematic review Costs: NHS reference costs Utilities: Taken from published economic analyses and expert opinion	Decision tree analysis of 9 potential strategies for the diagnosis of active tuberculosis in adults. NHS care setting.	Base case: Strategies using NAATs are not cost effective. In the base case the optimal strategy is SSM followed by Culture, ICER = £9,748 per QALY.	" …strategies including NAATs are not cost effective for the diagnosis of TB in general circumstances. Current usual care is appropriate…. When there is a high risk of TB, a full diagnostic work-up with SSM, NAAT and Culture is preferable. This suggests that due to NAAT's higher sensitivity, they are best used when the pre-test prevalence of TB is high."	Deterministic sensitivity analysis shows that when time to diagnosis of false negative is decreased 10.4 weeks 'SSM followed by Culture when SSM positive' becomes the optimal choice. When the costs of NAAT are reduced to £42.66, 'SSM and NAAT when SSM negative, otherwise Culture' becomes cost effective. In local settings of high TB prevalence NAAT strategies could well be cost effective for routine use alongside SSM

a Assumption of 100% diagnostic accuracy for NAAT and Culture strategies
b Assumption of 100% adherence and effectiveness of TB therapy (biases the result away from the intervention)
c Pre-test prevalence based on expert opinion, results highly sensitive to this parameter
Key: **NAAT** = Nucleic acid amplification test, **SSM** = Sputum smear microscopy, **QALY** = Quality-adjusted life-year, **ICER** = Incremental cost-effectiveness ratio

Table 1316 Economic evidence profile for cost effectiveness of GeneXpert, MTD, and smear & culture methods for diagnosing active TB

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental costs/benefits/harms Summary	Conclusions	Uncertainty
Choi et.al (2010). Addition of rapid molecular test to standard diagnostics for TB in a U.S. Hospital	Effects: RCT evidence and systematic review Costs: Local costs sourced from Baltimore hospital testing laboratory, cost of rapid diagnosis using GeneXpert based on FDA price estimates Utilities: Taken from published economic analyses and expert opinion	Markov model of MTD-TB and GeneXpert tests vs SSM and culture testing.	The base case strategy of no molecular testing was dominated by all strategies that included a molecular test. Comparing MTD with GeneXpert when patients are smear positive ICER = $23,111 per QALY-gained for GeneXpert ICER = $16,289 per QALY gained for GeneXpert when used on all patients regardless of smear status.	"TB diagnostic algorithms incorporating Xpert in the United States are highly cost-effective."	PSA found that using GeneXpert regardless of smear status was cost-effective in more than 99% of simulations compared to diagnostic algorithms without molecular testing (@ WTP $50,000). Compared to existing molecular assays (MTB) Xpert is cost effective with a mean ICER of $39,992 per QALY gained.
Partially applicable[a]					
Very serious limitations[b,c,d,e,]					

a non- UK/NHS setting
b Utility values for TB morbidity based on expert opinion
c No consideration of transmission and secondary infections
d Costs and laboratory throughput/capacity are unlikely to translate to the NHS
e At the time of the study, the cost of GeneXpert and associated consumables was uncertain (pending FDA approval) although the PSA considered a 'plausible' range.
Key: **FDA** = Food and Drug Administration, **SSM** = Sputum smear microscopy, **WTP** = Willingness to pay, **QALY** = Quality-adjusted life-year, **ICER** = Incremental cost-effectiveness ratio

F.3.2 Diagnosing drug-resistant TB (full guideline section 5.3.4)

Table 1417 Economic evidence profile for the cost effectiveness of rapid diagnostic methods for the diagnosis of drug resistant TB

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental costs/benefits/harms Summary	Conclusions	Uncertainty
Drobniewski et al. (2015) Dynamic transmission model and cost-effectiveness analysis of the impact of the addition of a rapid molecular test to smear and culture diagnosis of patients from subgroups at high risk of drug resistance **Partially applicable**[a] **Potentially serious limitations**[a,b,c,d]	Effects: Systematic review Costs: Standard NHS reference costs, BNF, and expert opinion Utilities: Published estimates of TB QALY losses from Crofts, 2008	The baseline for comparison was smear microscopy, culture for identification of MTB and drug susceptibility testing (DST) for culture positive cases The intervention evaluated was the addition of a rapid molecular assay (MTBDR-Plus, INNO-LIPA, and GeneXpert) for the detection of TB disease and drug resistance The analysis doesn't distinguish between different patterns of drug resistance in costs/benefits/harms	The costs, benefits and harms of the intervention were assessed for three populations: Black Africans, Eastern-Europeans, and South-Asians; and simulated under local or regional laboratory testing scenarios. This produced 18 permutations of the analyses compared to current practice. In all of these, the addition of a rapid molecular test was cost saving and, with the exception of INNO-Lipa (regional) in the Eastern European population, gained QALYs. The magnitude of savings and benefits was different across these populations because of their different sizes and epidemiology of TB	"Overall, all molecular-testing scenarios considered were more cost-effective compared with current practice at conventional threshold values per QALY for the UK"	The PSA supports the base-case findings. The QALY losses associated with MDR treatment are large. (1.03 QALYs). This was not varied in the SA. This may bias the analysis in favour of techniques which reduce the number of patients falsely treated for MDR-TB on the basis of clinical suspicion and diagnostic delay.

a Results may not be generalisable to the whole population beyond the subgroups considered

b No QALY loss associated with negative-pressure/inpatient isolation, despite potentially lengthy inpatient stays.

c Many pathways of treatment explored for patients with different prognostic risk factors, but no scenario analysis of targeted testing for the most at-risk of drug resistance patients.

d Many inputs for costs based on local expert opinion and may not reflect the national picture.

Key: **BNF** = British national formulary, **QALY** = Quality-adjusted life-year, **MDR** = Multi-drug resistant, **PSA** = Probabilistic sensitivity analysis, **ICER** = Incremental cost-effectiveness ratio

F.3.3 Treatment of latent TB (full guideline section 7.2.4)

Table 1512 Economic evidence profile for cost effectiveness of treatment of LTBI using 9H, 4R, or 3HP

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Holland et.al (2009). Simulated cohort of LTBI patients in USA (baseline activation rate 6% lifetime risk) • SA isoniazid daily for 9 months • DOT isoniazid twice-weekly for 9 months • DOT isoniazid plus rifapentine once weekly for 3 months, • SA rifampin daily for 4 months. **Partially applicable**[a]	Effects: RCT evidence, although some effectiveness /adherence/SAE data modelled or interpolated from studies of other regimens. Costs: Health service costs (labs, drugs, physician vists, DOT, hospitalisation for SAE and monitoring of LFT's and patient costs inc. driving to DOT, time off work). Most sourced from two studies on CE of Isoniazid treatment. Utilities: Taken from published economic analyses, also interpolated	Markov model In the base-case analysis, subjects were assumed to have newly positive tuberculin skin tests after recent exposure to infectious TB.	4R: Reference 9H $181.31 3HP: $281.06 No Treatment: $751.06 9H-DOT: $1226.15	4R: Reference 9H: -0.02005 QALYs 3HP: 0.005736 No Treatment: -0.07469 9H-DOT: -0.01439	Referenced to the lowest cost regimen (4R) 4R (REF) 9H: Dominated 3HP: $48,997.34 No treatment: Dominated 9H-DOT Dominated	"…4R was the least expensive regimen for the treatment of LTBI. Over the patient's lifetime, the 4R regimen was less expensive and more effective than the current standard of care (i.e., 9H) over a wide range of estimates for adherence and efficacy. Although more expensive than 4R or 9H, 3HP was more effective, at a cost of $48,997 per QALY compared with 4R and $25,207 compared with 9H, and would therefore be considered cost-effective @ a threshold $50,000 per QALY"	At double the relative risk of activation, 4R and 3HP dominated all other regimens, and 3HP was more effective than 4R, at a cost of $20,099 per QALY. At a relative risk of activation above 5.2 times baseline (consistent with the risk associated with old, healed TB on chest radiograph [4]), 3HP dominated all other options. 9H-DOT was cost-effective compared with 9H above a relative risk of 5.2 times baseline and was cost-saving compared with 9H at a relative risk of 10 times baseline but was never cost-effective compared with 4R or 3HP.

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Potentially serious limitations[b,c,d]							

a non- UK/NHS setting

b based on limited, low quality trial evidence

c Utility values in part based on expert opinion and interpolation (though the mechanism of interpolation and input values are not detailed).

d No PSA

Key: **DOT** = Directly observed therapy, **SA** = Self-administered therapy, **SAE** = Serious adverse event, **LFT** = Liver function test, **CE** = Cost effectiveness, **4R** = 4 months of rifampin, **3HP** = 3 months isoniazid plus rifapentine weekly, **9H** = 9 months of isoniazid, **9H-DOT** = directly observed isoniazid twice-weekly for 9 months, **REF** = Reference case for comparison, **ICER** = Incremental cost-effectiveness ratio

Table 1613 Economic evidence profile for cost effectiveness of LTBI treatment in 20yr old and 40yr old close contacts

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Diel et.al (2005). Simulated cohort of LTBI patients in Germany aged 20yrs and 40yrs (6.2% baseline lifetime risk). INH vs no treatment	Effects: Trial evidence. INH effectiveness assumed to be 80% (+/- 95%CI)protective for mean 19yrs. 80% reflects a reduction due to adherence and resistance Costs: national cost-of-illness study from the German social perspective, Inpatient and outpatient costs (mean combined cost per case €18,850) and the indirect costs arising from loss of productivity (mean indirect costs per case €2,461). Utilities: Taken from published economic analyses	Markov model. Base case scenario assumes 95% specificity and 95% sensitivity for the Mantoux test, the PPV is 89% if there is a prevalence of TB infection of ~30% in the population of close contacts. People who spent an estimated total of >40 hrs with the index cases in the 3 months before diagnosis or during the infection period were assigned (besides household contacts) to the category of ''close contacts''.	Per course of INH: €201.5 (100.75-403) Per case of TB: €18850 (9425-37700) Discount rate 3% per annum	For the 20yr age group: 0.0222 QALY For the 40yr age group: 0.0201 QALYs	For the 20yr age group: 26,088 €/QALY For the 40yr age group: 22,692 €/QALY	"…the model clearly predicts that the implementation of INH chemoprevention in Germany will be more cost-effective and less expensive than the current standard approach, i.e. treating of passively diagnosed TB cases together with screening of their contacts, or may be at least be described as cost-effective by convention."	No PSA "The conclusions of the base-case analysis were not altered by using the lower or upper CI or range limits for probabilities or costs".
Partially applicable[a]							
Potentially serious limitations[b,c,d,e,f]							

a non- UK/NHS setting
b costs very specific to the study locale
c No PSA
d multiple reported outcomes, ICER, QALE, deaths, cases avoided but not clear which outcome has the most weight with regard to the decision rule.
e No PSA

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
f No disutility attributed to Isoniazid treatment related adverse events, assumed to be too rare to consider in the analysis.							

Key: **INH** = Isoniazid, **LTBI** = Latent tuberculosis infection, **QALY** = Quality-adjusted life-year, **PSA** = Probabilistic sensitivity analysis, **ICER** = Incremental cost-effectiveness ratio

Table 1714 Economic evidence profile for cost effectiveness of treatment of LTBI with 3HP or 9H

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Shepardson et.al (2013). Simulated cohorts of 100,000 High Risk (as per CDC guidelines) patients with LTBI in the USA 2 interventions: 3HP vs 9H with a simulation horizon of 20yrs All 3HP patients assumed to have DOT.	Sterling et.al (2011) RCT Relationship between adherence and efficacy (in terms of annual risk of progression) taken from CDC Databases. Costs: Health system costs and societal costs reported including productivity losses and out-of-pocket expenses Utilities: Taken from published economic analyses	Individual patient model Risk of progression a function of treatment completion.	Health System perspective (mean cost per patient) 9H: $511 (497,522) 3HP: $623 (616,632) Societal perspective (mean cost per patient) 9H: $705(691,718) 3HP: $728 (719,737)	Mean QALY Loss per 1000 patients: 9H:44,(40,47) 3HP: 19,(17,22)	Health system perspective: ICER: 3HP vs 9H is $4565 (95%CI 3584–5965). Societal perspective: ICER: 3HP vs 9H is $911 (95%CI 268–1826)	"At higher risk of progression. 3HP is found to be increasingly cost-effective relative to 9H. Similarly, higher rates of secondary transmission and higher costs of treating TB disease lead to 3HP being more cost-effective relative to 9H"	No PSA Trial evidence has 50% fewer cases in the 3HP arm. ICER <20,000USD when equalised.
Partially applicable[a]							
Potentially serious limitations[b,c,d,e]							

a non- UK/NHS setting
b base-case uses a rifapentine price which at the time of the study was half the wholesale price in the U.S
c Trial evidence was unbalanced, equalisation methods not explicitly described.
d considers productivity losses in the calculation of costs – not typically considered in the NICE reference case.
e No PSA
Key: **DOT** = Directly observed therapy, **CDC**= Centre for Disease Control, **LTBI** = Latent TB infection, **3HP** = 3 months isoniazid plus rifapentine, **9H** = 9 months of isoniazid, **QALY** = Quality-adjusted

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
life-year, **PSA** = Probabilistic sensitivity analysis, **ICER** = Incremental cost-effectiveness ratio							

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