Neonatal infection: antibiotics for prevention and treatment

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8 December 2020 to 5 January 2021

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Anglia Ruskin University	Guideline	007	001 - 003	Very good point as this is rarely articulated in documents and is so necessary in enabling parental understanding and informed consent	Thank you for your comment and support for this guideline.
Anglia Ruskin University	Guideline	009	028	Parents often need to know or have some indication of what is meant by 'change in skin colour' and health professionals need to be reminded that they need to articulate this for parents. Therefore, this statement needs greater clarification, for example, 'changes in usual skin colour where the baby becomes very pale or skin shade becomes blue-grey'	Thank you for your comment. The committee agreed that it would be helpful to provide a description of change in skin colour, and so examples have been added to the recommendation ("where the baby becomes very pale or blue/grey or dark yellow").
Anglia Ruskin University	Guideline	011	General	Clear guidance signposting supplementary guidance	Thank you for your comment and support for this guideline.
Anglia Ruskin University	Guideline	012	005 - 006	Requires some rationale for clarity, i.e. 'why therapeutic drug monitoring may be required'	Thank you for your comment. The committee discussed how therapeutic drug monitoring is only needed when gentamicin or vancomycin is given for a long period. There are often times when only a single dose is given, such as when a woman delivers quickly and has no signs of infection. In situations such as this, a second dose of antibiotics is not required and so therapeutic drug monitoring is not needed. The committee therefore decided that the recommendation did not need additional clarification.
Anglia Ruskin University	Guideline	016	General	If the highlighted text takes the reader to an explanation and evaluation of the calculator – then this is fine. However, if the need for audit is due to on-going evaluation of the calculator, this needs to be clarified within the text	Thank you for your comment. The hyperlink takes the reader to an explanation of the calculator and online tool that allows the calculator to be implemented.
Anglia Ruskin University	Guideline	019	014 - 015	Reason for taking this measurement requires a short rationale within the text and adding in that blood culture still remains the gold standard	Thank you for your comment. An explanation of the need for a baseline CRP measurement has been added to the rationale, as well as statement that blood culture remains the gold standard.
Association for Improvements in the Maternity	Guideline	General	General	AIMS would like to suggest that when there is mention of 'increased risk' throughout the document, it would be beneficial for the reader to know how much the risk is increased and the absolute risk, what the chance is actually of the problem occurring e.g. increased from 1 in 1000 to 2 in 1000.	Thank you for your comment. Many of the recommendations that mention increased risk are from the previous version of this guideline and are outside the scope of this update. The committee could therefore not update these recommendations. The recommendations for

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Services (AIMS)					management of babies at increased risk of infection (1.3.8 and 1.3.9) are based on a clinician's decision using the signs and symptoms, or the outcome of the Kaiser Permanente calculator. There is currently no evidence to confidently state what the change in risk would be for these babies.
Association for Improvements in the Maternity Services (AIMS)	Guideline	General	General	AIMS is disappointed to find that there is consistently no mention of the side-effects of the antibiotics. Parents and carers need to know and understand any consequences of any drugs being offered to themselves or to their baby.	Thank you for your comment. The committee thought it was important to include a link to the patient experience guideline in recommendation 1.1.1. This includes a section on tailoring healthcare services for each patient, which explains the importance of discussing the risks and benefits of treatment. Recommendation 1.1.3 also highlights the need to discuss the risks and benefits of treatment with parents and carers, which would include any potential side-effects. We therefore think that discussions of the side-effects of antibiotics has been covered in the recommendations.
Association for Improvements in the Maternity Services (AIMS)	Guideline	General	General	AIMS is concerned to note that there is no mention of any individualised care plan for mother or baby.	Thank you for your comment. Recommendation 1.1.1 refers to the NICE guideline on patient experience in adult NHS services which provides information on tailoring services to each patient. Recommendation 1.1.13 includes the need for a post-discharge management plan. The committee felt that these covered the important information needed when planning care.
Association for Improvements in the Maternity Services (AIMS)	Guideline	006	001	In the box under Recommendations, it should say "Parents and carers have the right to **make decisions about their baby's health and care,** as set out in the NHS Constitution and summaries in NICE's information on making decisions about your care. They must therefore be involved in planning their baby's health and care, and be given information and support to enable them to **make informed decisions about care options.**"	Thank you for your comment. This section uses standard wording that is common to all NICE guidelines about children and young people. The wording reflects the fact that the right of parents and carers to make decisions about their baby's care is not always absolute, and in some circumstances may be overridden, if judged to be in the baby's best interests. The wording is in line with the NHS constitution: 'You have the right to be involved in planning and making decisions about your health and care with your care

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					provider or providers, including your end of life care, and to be given information and support to enable you to do this. Where appropriate, this right includes your family and carers. This includes being given the chance to manage your own care and treatment, if appropriate.'
Association for Improvements in the Maternity Services (AIMS)	Guideline	006	011	AIMS would like to see the medical professionals doing more than just 'talking' to the parents and carers: - to acknowledge that this is an extremely worrying time for parents and carers - clarification of what neonatal infection is - implications of neonatal infection - step by step guidance of treatment - step by step guidance on the effects of the treatment agree an individualised care plan with the parents and carers	Thank you for your comment. We believe that recommendations 1.1.2-1.1.3 provide more detailed information on what medical professionals should discuss with parents and carers in relation to neonatal infection. This includes explaining what the infection is, the reasons for any treatment, what to expect and the potential benefits and risks. Recommendation 1.1.13 includes the need for a post-discharge management plan. The committee felt that these covered the important information needed when planning care.
Association for Improvements in the Maternity Services (AIMS)	Guideline	007	004	Can you please turn around the sentence to read 'Discuss with the parents' at the beginning.And it should say "the recommendation (or the offer) of antibiotics" rather than "If giving antibiotics" - which assumes they will be given.	Thank you for your comment.. We think that moving 'discuss with parents' to the beginning of the sentence would be less clear because the bullets would not follow on directly from the stem. We have changed 'giving' to 'advising' in the recommendation to make it clear that parents should be involved in the decision making.
Association for Improvements in the Maternity Services (AIMS)	Guideline	007	010	AIMS is asking for any potential side effects to be explained to the parents and carers, and an individualised care plan to be included here.	Thank you for your comment. We believe that explaining potential side effects is included in recommendation 1.1.3 which suggests that the risks and benefits of treatment are discussed with parents and carers. The development of an individualised care plan is expected to be part of standard practice, and is supported by recommendation 1.1.13 which includes the need for a post-discharge management plan.
Association for Improvements in the Maternity Services (AIMS)	Guideline	007	016	AIMS would like to see mention of what has already been discussed with the mother, and what has already been offered.	Thank you for your comment. The recommendations on information and support for parent and carers of babies who are at risk of early-onset neonatal infection were not updated as part of this guideline update and we did not review evidence in this area. We are therefore unable to make the suggested change.

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Association for Improvements in the Maternity Services (AIMS)	Guideline	008	024	Please include what long-term support or care pathway will be provided, if relevant, at this stage.	Thank you for your comment. Long-term support and care pathways were out of scope for this guideline update and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
Association for Improvements in the Maternity Services (AIMS)	Guideline	010	011	AIMS is concerned to see that antibiotics will be offered to all women in preterm labour. AIMS would like to see more reasoning here and evidence base, eg what if mum and baby are both healthy, there are no other risk factors, due dates are not 100% accurate.	Thank you for your comment. The committee considered evidence on intrapartum antibiotics for women in preterm labour that showed a reduction in maternal infections when antibiotics were given, although evidence was not available on the effect on neonatal infections. However, the committee noted that preterm birth is an important risk factor for neonatal infection, and so concluded that intrapartum antibiotics should be offered to reduce this risk. The committee also discussed how the GBS status of most women is unknown and that the outcomes for preterm babies with a GBS infection are worse than they are for term babies. They therefore decided that this group of women should be treated as if they are GBS positive to reduce the risk of a preterm baby developing an infection.
Association for Improvements in the Maternity Services (AIMS)	Guideline	012	004	We would like to see more clarification on how antibiotics are administered. The implication is that antibiotics are given continually but there is not mention of how, how often, etc.	Thank you for your comment. We have given information about the mode of administration (intravenous) within the recommendations. The committee also made a recommendation about the frequency of gentamicin dosing, which they recommended should be given once daily. NICE guidelines are intended to be read alongside the summary of product characteristics for each drug that is recommended as well as the British National Formulary. These documents provide more detailed information on dosing and frequency of administration.
Association for Improvements in the Maternity	Guideline	012	008	AIMS is concerned that immediate delivery is offered without further testing for current evidence of an infection. The implication is unnecessary interventions/caesarean births with all the additional stress to parents and carers, longer healing period for mothers, and additional costs to NHS.	Thank you for your comment. GBS testing is beyond the scope of this guideline and so the committee could not make recommendations on this. An economic model was included as part of this review which showed immediate delivery to be the dominant option, that is, it provided both

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Services (AIMS)					more quality adjusted life years (QALYs) and was cheaper compared to expectant management.
Association for Improvements in the Maternity Services (AIMS)	Guideline	013	005	Could Box 1 be placed here where it is relevant.	Thank you for your comment. Box 1 is referred to in both recommendations 1.3.1 and 1.3.3 so we believe that the best placement for this is following recommendation 1.3.3.
Association for Improvements in the Maternity Services (AIMS)	Guideline	013	011	AIMS is disappointed that there is no mention of discussion with the parents and carers as a priority.	Thank you for your comment. Recommendations 1.1.1 - 1.1.13 are intended to apply throughout this guideline and so this would include when a clinician is assessing the risk of infection after birth. Recommendation 1.1.2 covers discussions that should be had with parents when there are concerns about infection.
Association for Improvements in the Maternity Services (AIMS)	Guideline	013	013	Could Box 2 be placed here where it is relevant.	Thank you for your comment. Box 2 is referenced after Box 1 in recommendation 1.3.3. As such, we decided that it should be placed immediately after Box 1 in the guideline.
Association for Improvements in the Maternity Services (AIMS)	Guideline	015	Box 2	Could you give a brief explanation of what Apnoea is, as not all parents and carers will recognise this term.	Thank you for your comment. The committee decided that it would be helpful to add an explanation of apnoea to the clinical indicators box, and so they have added the definition "stopping breathing".
Association for Improvements in the Maternity Services (AIMS)	Guideline	017	011	Could you expand and clarify what information and advice is given to parents and carers.	Thank you for your comment. This recommendation has been updated to refer to recommendations 1.1.12 and 1.1.13 which provide information on the information and advice to give to parents and carers.
Association for Improvements in the	Guideline	019	013	AIMS would like to suggest that you explain to the parents and carers what a blood culture is and what happens, procedure, implications, results.	Thank you for your comment. The section on information and support is intended to be applied to the recommendations throughout this guideline.

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Maternity Services (AIMS)					Recommendation 1.1.2 highlights that a clinician should discuss the options for management with parents and carers. This will include any investigations such as blood cultures.
Association for Improvements in the Maternity Services (AIMS)	Guideline	019	016	We find this comment 'if it is safe to do so' unhelpful and unmeaningful when it comes to doing a lumbar puncture. Who and how is this decided. Please also explain the procedure to the parents and carers, and the risk involved to the baby.	Thank you for your comment. The committee discussed this terminology but decided that 'if safe to do so' is widely understood and can vary depending on a baby's individual circumstances. They therefore decided against modifying this recommendation. They were also satisfied that explanations about procedures are covered in section 1.1 of the guideline about information and support for parents and carers.
Association for Improvements in the Maternity Services (AIMS)	Guideline	026	006	AIMS would like to see clarification of 'who' is reviewing the baby.	Thank you for your comment. The committee discussed how this will be a senior staff member. However, they did not think this needs to be stated in the recommendation as this is current practice. This will also maintain consistency with the recommendations for treatment duration of early-onset neonatal infection.
Association for Improvements in the Maternity Services (AIMS)	Guideline	037	020	AIMS would like to see how the recommendation might affect practice. There is confusion over the term 'immediate delivery'. Impact could be further interventions. If caesarean, then AIMS would like to see reference to the differences in after birth care required.	Thank you for your comment. Immediate delivery could be either caesarean section or induction of labour, and so the committee did not think this would result in any major changes in practice. To make the recommendation as clear as possible, the committee included a statement to clarify that immediate birth could either be induction of labour or caesarean birth.
Association for Improvements in the Maternity Services (AIMS)	Guideline	039	020 - 021	AIMS would like more explanation given of what is the impact of more antibiotics being given to babies when maternal infection is not strongly suspected.	Thank you for your comment. We have added an explanation about the potential harms to the baby and risks of antibiotic resistance to rationale and impact section for this recommendation.
Association for Improvements in the	Guideline	049	001 - 008	This summary on the importance and significance of Neonatal Infection could be viewed at the beginning of the report to explain what the guidelines are all about. AIMS suggests including some	Thank you for your comment. Data collected from users of the NICE website has shown that users are more likely to access recommendations if they are presented first, which

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Maternity Services (AIMS)				figures or a percentage to illustrate the significance and the concern.	is the reason that the context for the guideline appears later. The final version of the guideline will be displayed as a webpage which will make navigating between sections much easier.
Association of Paediatric Emergency Medicine	Guideline	General	General	We wondered if there may be an acknowledgement that a number of unwell babies will present and be managed in the emergency department, and this may necessitate different strategies to those babies being managed on a neonatal unit. Perhaps a separate paragraph describing this scenario and linking to other guidance such as Fever in under 5s: assessment and initial management (NG 143), Sepsis: recognition, diagnosis and early management (NG 51) and Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG 102)	Thank you for your comment. The committee discussed this point and agreed that it was useful to refer to other NICE guidelines, which contain more detailed information on the assessment of babies admitted from home. A recommendation has been added to the section on risk factors for late onset infection (recommendation 1.8.3) to direct the reader to the NICE guidelines on fever in under 5s and sepsis.
Association of Paediatric Emergency Medicine	Guideline	007	001 - 003	Whilst we support parents having the opportunity to have time to think about the information they have been given as it relates to their baby receiving antibiotics, and we recognise that the guideline states "when possible", we wonder if the guideline should be clearer about the importance of the baby receiving antibiotics without delay where infection is a possibility, to try to reduce the chances of late administration of antibiotics and the potential morbidity that may result.	Thank you for your comment. We have added a statement to this recommendation to explain that antibiotic treatment should not be delayed.
Association of Paediatric Emergency Medicine	Guideline	009	017	Where it says "seek medical help", we wonder if there should be a level of urgency applied here, as the symptoms described in lines 20 – 28 are concerning and may signal a rapid deterioration if not dealt with urgently. We would advise "seek urgent medical help" or seek medical help "as soon as possible" which we feel may better convey the level of urgency required from the symptoms listed.	Thank you for your comment. This recommendation has been updated to "seek urgent medical help" as suggested.
Association of Paediatric Emergency Medicine	Guideline	009	018	Regarding points of contact for parents after a baby is discharged from the hospital or midwifery-led unit, we wonder why there is no recommendation for the midwifery-led unit or hospital from where they have been discharged to offer advice?	Thank you for your comment. The committee discussed whether other points of contact should be added to the recommendation, but they thought that many labour wards or community led units might not be able to provide advice as the baby is no longer under their care. They were concerned that this might delay the time until advice is

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					given, and so they decided not to change this recommendation.
Association of Paediatric Emergency Medicine	Guideline	011	007	We wonder if the definitions of a penicillin allergy "that is not severe" or "severe" may be better defined as an IgE or non-IgE mediated allergy?	Thank you for your comment. The committee discussed the definitions of allergy, but as these recommendations will be read by non-specialists as well as clinicians, they decided that "severe" and "not severe" are the terms that will be most easily understood by all users of the guideline.
Association of Paediatric Emergency Medicine	Guideline	014	Box 1	Risk factors for early-onset neonatal infection: Where it states "Confirmed prelabour rupture of membranes at term for more than 24 hours before the onset of labour", we felt that there may be some confusion arising from the definition of "onset of labour" for non-obstetric specialists. Could this be more clearly defined, or changed to "delivery" if still relevant?	Thank you for your comment. The committee discussed how there is no universal definition of labour. They felt that the important issue is to give women antibiotics at the point that the clinician thinks they are going into labour so that treatment is likely to be given at least 4 hours before delivery. The committee therefore decided not to include a more detailed description of the onset of labour..
Association of Paediatric Emergency Medicine	Guideline	015	Box 2	Clinical indicators of possible early-onset neonatal infection: we wonder from where the rationale for determining indicators to be 'red flag' or 'other' came, as in our clinical experience, many of the 'other' indicators on their own would signal severe infection in a neonate.	Thank you for your comment. The decision on red flag indicators was based on those that were most strongly associated with infection in the evidence, as well as committee experience of those that are the most high risk or severe indicators and therefore require immediate action. The committee felt that the other indicators could have other causes so wouldn't necessarily signal immediate treatment for infection. The presence of an 'other' rather than a 'red flag' indicator does not mean that a baby does not receive antibiotics, but just means that the decision should be based on a clinician's judgement (recommendation 1.3.5). As such, the committee were happy with the indicators that were selected as red flags and decided against modifying the recommendation. More explanation on these reasons for the choice of red flag indicators has been added to the rationale section.
Association of Paediatric	Guideline	016	010 - 015	We feel that withholding antibiotics on babies with only 1 clinical indicator for some of the indicators (e.g. hypoxia, signs of neonatal	Thank you for your comment. The committee discussed the use of red flags and clinical indicators and decided that the indicators were appropriate. Recommendation 1.3.5

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Emergency Medicine				encephalopathy, fever etc.) may increase clinical risk and we are concerned may result in under-treatment.	states that when there is only 1 clinical indicator present, clinical judgement should be used to decide if it safe to withhold antibiotics. This means that if a baby only has one indicator, but the clinician thinks that it is a sign of infection, they can still receive antibiotics.
Association of Paediatric Emergency Medicine	Guideline	016	020 - 022	We have some concerns regarding the use of the Kaiser Permanente neonatal sepsis calculator in the emergency department setting. We feel that its use may cause confusion and delay to appropriate treatment. We would recommend a suggestion that its use be restricted to neonatal unit settings.	Thank you for your comment. The committee discussed the settings in which the neonatal sepsis calculator is used and decided that it is most suited to the neonatal unit where the risk of a baby developing an infection is assessed. When a baby is brought into the emergency department, they are likely to already be unwell and therefore treatment should be started quickly rather than waiting to consult the sepsis calculator. The committee have clarified this further in the recommendation by stating that it should only be used for babies not admitted to the hospital from home. Further information on their decision is also included in the rationale and evidence review.
Association of Paediatric Emergency Medicine	Guideline	017	012	Recommendations 1.1.10 and 1.1.11 do not seem to relate to a baby who has been observed and not treated for infection. The two recommendations seem to relate to babies who have been treated for neonatal infection.	Thank you for your comment. This recommendation has been updated to refer to recommendations 1.1.12 and 1.1.13.
Association of Paediatric Emergency Medicine	Guideline	020	001 - 002	We are surprised that urine microscopy or culture has been taken off the list of investigations for late infections. This would contradict NICE guidance Fever in under 5s: assessment and initial management (NG 143) for those babies presenting with fever and may create confusion in the emergency department. Should there be recognition that this is the case?	Thank you for your comment. The recommendation against the use of urine culture is specifically for babies in a neonatal unit. Urine culture would not routinely be done in a neonatal unit and this has now been clarified in the recommendation. An additional recommendation has also been added which indicates that urine microscopy and culture should be performed for babies outside of the neonatal unit, in line with the NICE guideline on urinary tract infection.
British Paediatric Allergy, Immunology &	Guideline	General	General	**Comment from AM:** Looks great thanks	Thank you for your comment and support for this guideline.

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Infection Group					
British Paediatric Allergy, Immunology & Infection Group	Guideline	General	General	**Comment from SP:** I thank NICE for including LOS and EOS in this guideline. However, I find the layout confusion and am not sure that jumping between EOS and LOS helps the reader. I suggest amended the layout of the guidance so that the general principles of Ab use in neonates is discussed (1.6), then EOS (1.2 – 1.3-1.8-1.9) then LOS (1.4 – 1.10 – 1.11) followed by meningitis in neonates. Section 1.7 is challenging as it tries to amalgamate investigations for EOS and LOS. Either this section needs to be amended (as some recommendations apply only to EOS yet this is not clear in the current version ie recommendation not to perform a urine culture which is correct for EOS but incorrect for LOS) or split into "Investigations for EOS" and "Investigations for LOS". (comment from SP)	Thank you for your comment. We have reordered the sections of the guideline in response to this comment and those of other stakeholders to improve the flow of the recommendations. We now group all of the recommendations on early-onset infection together followed by those on late-onset infection. The committee discussed the use of urine culture as a test for late-onset infection. Recommendation 1.9.4 is for babies in a neonatal unit where a urine culture would not routinely be done. This has now been clarified in the recommendation, and an additional recommendation has been added which indicates that urine microscopy and culture should be performed for babies outside of the neonatal unit, in line with the NICE guideline on urinary tract infection.
British Paediatric Allergy, Immunology & Infection Group	Guideline	019 020	014 - 019 001 - 002	**Comment from SP:** 1.72 Blood culture is recognised as a gold standard investigation. The volume of blood taken has a huge impact on the sensitivity of blood cultures – should the guideline include a suggested volume of blood ie 0.5ml minimum. 1.73 The guidelines suggest LP if strong clinical suspicion of neonatal infection. There is a large volume of data suggesting that in babies <28 month with a confirmed UTI and no clinical suspicion of meningitis, then the risk of concurrent meningitis is extremely low (Nugent J, Childers M, Singh-Miller N et al. Risk of Meningitis in Infants Aged 29 to 90 Days with Urinary Tract Infection: A Systematic Review and Meta-Analysis. J Pediatr 2019; 212: 102-10 e5). Should this be recognised in the guidelines? 1.74: This suggests that urine culture should not be performed in babies in whom LOS is being suspected. This is clearly incorrect and I suspect was meant to suggest that routine urine microscopy	Thank you for your comment. This section of the guideline is intended to provide recommendations on the investigations that should take place before starting antibiotics. However, it is not designed to provide more detail on clinical techniques and best practice. Recommendation 1.7.3 (now 1.9.3) is referring to all babies with suspicion of infection, rather than those who already have a confirmed UTI. As it takes time to confirm a UTI, it is likely that the lumbar puncture results would be known before the UTI is confirmed. The committee also discussed the use of urine culture as a test for late-onset infection. Recommendation 1.7.4 (now 1.9.4) is for babies in a neonatal unit where a urine culture would not routinely be done. This has now been clarified in the recommendation, and an additional recommendation has been added which indicates that urine microscopy and culture should be performed for babies outside of the

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				and culture is not required in babies in whom EOS is being suspected.	neonatal unit, in line with the NICE guideline on urinary tract infection.
British Paediatric Allergy, Immunology & Infection Group	Guideline	020	001	**Comment from AM:** I realise evidence for or against urine sampling is lacking here. However, I think this statement implies it's never/rarely worth getting a urine sample, and that could be misleading for some babies. If *late-onset* infection is likely (e.g. fever + vomiting in 3 week old), urine sampling should ideally be performed pre-Abx. Clean catch or catheter specimen or SPA. But not delaying antibiotics if baby unstable. There will be some with 'possible infection' e.g. desats, where UTI would be very unlikely, but on the other hand urine should be strongly considered in some neonates (e.g. indwelling catheters, or renal tract abnormalities), and the statement at 1.7.4 doesn't seem to cover that range of possibilities. It also doesn't seem in keeping with NICE guidelines on UTI or in NICE fever in under 5s. Paediatric teams often see neonates in EDs and in neonatal units and it would make sense for these populations to be treated more similarly for late-onset infection. I would suggest re-wording along the lines of: - Do not routinely perform urine microscopy or culture as part of the investigations for early onset neonatal infection. For late-onset infection, if there are clinical features suggestive of UTI, or risk factors for UTI, consider urine sampling via clean catch or catheter or SPA. Thanks	Thank you for your comment. The recommendation against the use of urine culture is for babies in a neonatal unit where this would not routinely be done. This has now been clarified in the recommendation. An additional recommendation has also been added which indicates that urine microscopy and culture should be performed for babies outside of the neonatal unit, in line with the NICE guideline on urinary tract infection.
British Paediatric Allergy, Immunology &	Guideline	023 024	012 - 027 001 - 029	**Comment from SP:** Many thanks for removing the CRP cut-off of 10mg/L. This previous cut-off has resulted in a huge number of neonates unnecessarily receiving prolonged courses of IVAbs.	Thank you for your comment and support for this guideline.

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British Paediatric Allergy, Immunology & Infection Group	Guideline	025	003 - 010	**Comment from SP:** 1.11.2 Suggests performing LP is "there is a strong clinical suspicion of infection". There is a large volume of data suggesting that in babies <28 month with a confirmed UTI and no clinical suspicion of meningitis, then the risk of concurrent meningitis is extremely low (Nugent J, Childers M, Singh-Miller N et al. Risk of Meningitis in Infants Aged 29 to 90 Days with Urinary Tract Infection: A Systematic Review and Meta-Analysis. J Pediatr 2019; 212: 102-10 e5). Should this be recognised in the guidelines?	Thank you for your comment. Recommendation 1.9.3 is referring to all babies with suspicion of infection, rather than those who already have a confirmed UTI. As it takes time to confirm a UTI, it is likely that the lumbar puncture results would be known before the UTI is confirmed.
Evelina London Children's Hospital	Guideline	014	001	I welcome the removal of "parenteral antibiotic administration" as a 'red flag' risk factor. This has been shown to reduce the incidence of EOS in the newborn (Puopolo et al, Pediatrics, 2011). I am concerned that "confirmed or suspected chorioamnionitis" is included as this is technically a histopathological diagnosis. I am concerned that many women who receive antibiotics for intrapartum fever (which has other causes) will be regarded as "suspected chorioamnionitis" and result in antibiotic treatment of the baby.	Thank you for your comment. The committee discussed the definition of chorioamnionitis and has modified this to 'clinical chorioamnionitis' to emphasise that the woman should be showing clear signs of chorioamnionitis in order for this to be considered a risk factor.
Evelina London Children's Hospital	Guideline	015	001	There are several very non-specific clinical indicators that are common amongst newborns that are listed. For example bile stained vomiting or jaundice in the first 24 hours. I would request that this list is reduced to the clinical indicators that there is evidence to support are most predictive of EOS.	Thank you for your comment. The clinical indicators that were most strongly associated with infection in the evidence have been listed as red flag indicators, and antibiotics are recommended for babies with any of these signs. The committee thought it was important that people were aware of other signs, such as vomiting and jaundice, that were identified in the evidence but not as strongly associated with infection. These have therefore been included as clinical indicators of possible infection and recommendation 1.3.5 states that babies should have at least two of these factors before antibiotics are considered. The committee felt that this should reduce the risk of a baby being given antibiotics for infection unnecessarily.

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Evelina London Children's Hospital	Guideline	016	020	I welcome the addition of the KP sepsis risk calculator. It has been taken up widely across several regions in the UK. Good clinical care is a pre-requisite of the use of the KP calculator. I think this needs to be highlighted.	Thank you for your comment. Good clinical care is expected to be part of standard practice and so the committee did not think that this needed to be stated specifically in the recommendations.
Evelina London Children's Hospital	Guideline	016	029	A definition of 'missed' cases is required. I agree that this should only be babies with culture confirmed infection. I suggest any baby who is re-admitted with a culture confirmed infection within the first 7 days as per the Kaiser Permanente study (Kuzniewicz et al, JAMA Pediatrics 2017). This is easy to audit. A hard cut-off avoids clinicians becoming concerned that sepsis was missed in a baby who was initially asymptomatic but correctly identified and treated before discharge.	Thank you for your comment. The committee discussed the definitions used for the audit and decided that the exact definition of missed cases should be determined by the people running the audit. Infection at 7 days could be a result of late-onset infection and so they were not confident that this definition would fully reflect the effectiveness of the neonatal sepsis calculator. They therefore decided not to further define how a missed case should be classified.
Evelina London Children's Hospital	Guideline	023	009	I am concerned about CRP measurements guiding duration of antibiotic treatment. CRP levels can rise following parturition. More emphasis should be placed on trusting blood cultures and, along with this, emphasis on improving blood culture technique. I would recommend removing the measurement of CRP altogether. This would be in line with the American Academy of Pediatrics Guideline "Management of neonates born at ≥35 weeks gestation with suspected or proven early-onset bacterial sepsis".	Thank you for your comment. Duration of antibiotic treatment for early-onset infection is out of scope for this guideline update and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
Evelina London Children's Hospital	Guideline	024	002	As above.	Thank you for your comments.
Evelina London Children's Hospital	Guideline	025	012	I am unsure of the reason that 48 hours has been chosen for late onset infection.	Thank you for your comment. The committee decided that decisions should be made after 48 hours because of the different bacteria that may cause late-onset infection and the slower rate of growth of these bacteria in comparison to those that cause early-onset infection. They highlighted how it can take longer for a blood culture to become positive for late-onset infection and therefore decided that antibiotic decisions should be made later than for early-onset infection. Further information on their decision is

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					available in the rationale & impact section of the guideline, and in Evidence review H: Antibiotics
Evelina London Children's Hospital	Guideline	039	001	I am concerned about this first sentence. As EOS can occur without risk factors, the KP calculator will score low for several cases. The initial observation period is vital to pick up babies who are initially asymptomatic. Good clinical care after birth should be seen as part of the KP calculator "approach".	Thank you for your comment. Good clinical care is expected to be part of standard practice and so the committee did not think that this needed to be stated specifically in the recommendations.
Group B Strep Support	Evidence Review B	013	023 - 027	The evidence paper states "the committee extended the recommendation from the 2012 version of this guideline to state that women who had GBS in a previous pregnancy, and have not had a negative test in the current pregnancy, should also be offered intrapartum antibiotics." This statement implies that these women should be offered a test, yet doesn't state that explicitly. Of course, the only way to get a negative test in pregnancy is to offer one, and it is disappointing to see no recommendation for this. Previous GBS carriage increases the chance of the mother carrying GBS in a subsequent pregnancy, and the RCOG recommends that a woman who previously carried GBS should be offered the option of testing using GBS-specific tests described by PHE. It is both disappointing and surprising that this recommendation has not also been made in this guideline. Differences in national guidelines are not helpful unless there are clearly stated reasons for them, and such reasons are not stated within this guideline. Approximately 50% of the women who carried GBS in a previous pregnancy will carry it in a subsequent pregnancy (Turrentine and Ramirez, 2008; Tam, Bilinski and Lombard, 2012; Page-Ramsey SM *et al.*, 2013; Turrentine *et al.*, 2016), and around 50% won't. Therefore offering those women a GBS-specific test in the last 5 weeks of pregnancy would help determine which women are carrying GBS and should be offered the intravenous antibiotics, while reducing the use of antibiotics unnecessarily in the other 50% of women who aren't carrying the bacteria.	Thank you for your comment. GBS testing was not included in the scope for this guideline and so the committee did not consider evidence on the diagnostic accuracy of GBS tests and or the effectiveness and cost effectiveness of their use in particular scenarios. They were therefore unable to make recommendations on providing testing for GBS.

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				This is not a screening issue – this is about offering targeted testing to women with specific risk factors, to reduce unnecessary antibiotic use while maintaining effective prevention of early-onset GBS infection. GBSS recommends that this guideline clearly aligns with the RCOG GBS guidelines, clearly stating that women who have had a positive GBS test in a previous pregnancy where the baby was well should be offered the option of testing for GBS carriage in the current pregnancy.	
Group B Strep Support	Evidence Review B	013	026 - 027	The tests that is often used within the NHS where GBS is detected include an HVS test, a urine sample and, less frequently, a blood test or a GBS-specific ECM test or, even less frequently a PCR test. A negative result from the first three of these is not a good indicator of a woman not carrying GBS, whereas it would be for the latter two. A negative result from a test before labour, even a week before, does not absolutely guarantee negativity at the time of labour, although the GBS status is likely to stay the same when established using an ECM GBS test in the last 5 weeks of pregnancy. It is important therefore to give that added detail, and GBSS recommends rewording this sentence to say "and have not had a negative ECM or PCR GBS test in the current pregnancy, should also be offered intrapartum antibiotics."	Thank you for your comment. The recommendation refers to the use of a PCR or ECM test for a negative GBS result. The committee discussed the timing of the GBS test and agreed that this may differ for some women. The recommendation was therefore updated to include women with a negative GBS test 3-5 weeks before their anticipated delivery date.
Group B Strep Support	Evidence Review B	014	008 - 011	This recommendation is not consistent with the 2017 RCOG guidelines, which states that women in preterm labour should be **recommended** to have IAP, which is a stronger recommendation than for other risk factors, where it says they should be *offered* to the woman. The NICE recommendations make no distinction between the various risk factors, stating that the antibiotics should be offered.	Thank you for your comment. There are some differences between the terminology used by the NICE and RCOG guidelines, and an offer recommendation for NICE indicates that an intervention should be used, and this is therefore a similar strength to 'recommend' that is used by RCOG. More information about the terminology used in NICE recommendations is available here:

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				Not making this guideline consistent with the RCOG advice will cause confusion. GBSS recommends that this recommendation is revisited by the committee, and amended to say that IAP is **recommended** for the risk factor of preterm labour. However, if there has to be a difference – and there is no clear explanation of why that should be in the Antibiotics for prevention and Treatment evidence document – please include a clear explanation giving the reasons for the difference.	https://www.nice.org.uk/process/pmg6/chapter/developing-and-wording-guideline-recommendations#wording-the-guideline-recommendations
Group B Strep Support	Evidence Review B	016	022	The tests that are often used within the NHS where GBS is detected include an HVS test, a urine sample and, less frequently, a blood test or a GBS-specific ECM test or, even less frequently a PCR test. A negative result from the first three of these is not a good indicator of a woman not carrying GBS, although it would be for the latter two. It is important therefore to provide that added detail so that health professionals and the lay audience appreciate the differences. Additionally, the test for GBS carriage (the ECM test) is most accurate when done within the last 5 weeks of pregnancy which, for some women for example those expecting twins might be at 32-34 weeks' gestation. Not making this guideline consistent with the RCOG advice will cause confusion, and GBSS recommends that this is revisited by the committee, and amended to so that the NICE and RCOG recommendations align. GBSS recommends rewording this to say "The committee specified that these women should be offered antibiotics unless they were confirmed to be GBS negative by a GBS-specific test collected in the last 5 weeks of pregnancy. The criteria for a test in late pregnancy was added because GBS status is more likely to change before this time. An ECM test taken in the last 5 weeks of pregnancy is a much more reliable predictor	Thank you for your comment. The recommendation refers to the use of a PCR or ECM test for a negative GBS result. The committee discussed the timing of the GBS test and agreed that this may differ for some women. The recommendation was therefore updated to include women with a negative GBS test 3-5 weeks before their anticipated delivery date. The reasons for this have also been added to the committee discussion section of the evidence review for intrapartum antibiotics.

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				of GBS colonisation at delivery, though does not guarantee that a woman's GBS status will be the same at the time of birth."	
Group B Strep Support	Evidence Review C	006	005 - 008	This question does not address what care should be offered to women who tested positive for GBS in a previous pregnancy where the baby was well, or who have previously had a baby with GBS infection, and yet these women have a significantly increased chance of carrying GBS. This seems an oversight. GBSS recommends that the care for these women be addressed, either using evidence, or the expertise of the committee.	Thank you for your comment. The question about whether women with prelabour preterm rupture of membranes between 34 and 37 weeks' gestation was specifically limited to women who have tested positive for GBS in their current pregnancy, and the evidence identified was for this population specifically. Recommendations for women who were positive for GBS in a previous pregnancy therefore could not be made on this issue as it was outside of the scope of the guideline. However, there is advice for women who have had GBS in a previous pregnancy, or who have previously had a baby with GBS infection in the section on intrapartum antibiotics. Recommendation 1.2.1 highlights that these women should be offered intrapartum antibiotics during labour. Further information on this recommendation in in Evidence review B: Intrapartum antibiotics.
Group B Strep Support	Evidence Review C	015	025 - 049	Clearly the committee felt it would almost certainly be an effective use of NHS resources to test women with unknown GBS carriage status and with PPROM at 34-37 weeks' gestation for GBS. However, there is no recommendation to this effect. Nor is there any recommendation for women with a previous positive GBS test result whose baby was well or a previous baby with GBS infection with PPROM. Knowing their GBS carriage status would help inform the decision making around expectant management or immediate delivery. This is not routine antenatal screening. This would be offering women with specific risk factors – those with preterm prelabour rupture of membranes - a test to find out if they are carrying GBS and therefore if their baby is at raised risk of GBS infection. If they are carrying GBS, the research suggests that immediate delivery would result in significant savings for the NHS.	Thank you for your comment. GBS testing was not included in the scope for this guideline and so the committee did not consider evidence on the diagnostic accuracy of GBS tests and or the effectiveness and cost effectiveness of their use in particular scenarios. They were therefore unable to make recommendations on providing testing for GBS.

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				There are other situations where the brief has been expanded. GBSS recommends that this issue be addressed, even though it is outside the scope of the specific question because it is within scope for the guideline, either using existing evidence, or the expertise of the committee.	
Group B Strep Support	Evidence Review E	General	General	It is disappointing that the absence of exposure to breastmilk has not been considered as a risk factor for late-onset neonatal infection, especially in very preterm babies. There is a large literature about this and it would be helpful for the promotion of breastfeeding if the NICE CGDG could recognise this in the guideline. Members of the GBSS Medical Advisory Panel recommend that this issue is addressed within the guideline, taking into account both evidence and the expert opinion of the committee. Some of the literature is summarised below: The role of breastfeeding in prevention of neonatal infection Semin Neonatol 2002; 7: 275–281 Late-Onset Septicemia in a Norwegian National Cohort of Extremely Premature Infants Receiving Very Early Full Human Milk Feeding Pediatrics 2005;115:e269–e276. Sankar MJ, Sinha B, Chowdhury R, et al. Optimal breastfeeding practices and infant and child mortality. A systematic review and meta-analysis. Acta Paediatr 2015; published online Aug 7. DOI:10.1111/apa.13147. Horta BL, Victora CG. Short-term effects of breastfeeding: a systematic review of the benefits of breastfeeding on diarhoea and pneumonia mortality. Geneva: World Health Organization, 2013.	Thank you for your comment. These papers did not meet the inclusion criteria for this guideline, as they either used a different study design to those stated in the protocol or did not include the specified outcomes for the review. The committee therefore could not use this information when making the recommendations. The committee thought that the benefits of breastmilk are already well accepted for preterm babies and so they did not think that there would be any negative effects of not including it in the recommendation. The committee are also aware that more information is needed on the risk factors associated with late-onset infection and therefore made a research recommendation for the development and evaluation of clinical prediction models. This will help develop a more detailed understanding of other risk factors that need to be considered for late-onset infection.

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				Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect www.thelancet.com Vol 387 January 30, 2016.	
Group B Strep Support	Evidence Review E	021	Table	"• Suspected or confirmed infection in another baby in the case of a multiple pregnancy" is not currently listed as a risk factor for late-onset infection, as it is for early-onset. GBSS recommends that adding this risk factor should be considered, taking into account both evidence and the expert opinion of the committee.	Thank you for your comment. The committee discussed whether infection in another baby in the case of a multiple birth should be included as a risk factor for late-onset infection. They decided that, although this is a rare occurrence, it is something that should be considered for the siblings when reviewing a baby with infection who is part of a multiple birth. This was therefore added to recommendation 1.8.1 as a risk factor that should be considered.
Group B Strep Support	Evidence Review E	036	011 - 017	Members of the GBSS Medical Advisory Panel recommend the guideline be updated to clarify that the presence of a centrally placed catheter presents an increased risk of infection and parenteral nutrition (PN) is an additional independent risk factor. This may contribute to the variability in the presence of a catheter being a risk factor for infection. Those babies with a prolonged requirement for parenteral nutrition via a central line, and limited enteral nutrition (i.e. with intestinal failure) are at particularly high risk of late onset neonatal infection, hence the CDC revised definitions for CLABSIs (central line-associated blood stream infections), which account for cases where there is co-existing mucosal barrier injury. (Coffin *et al.*, 2014; Center for Disease and Prevention Control, 2020 (Chapters 4 and 17)	Thank you for your comment. The committee discussed the presence of a central catheter and parenteral nutrition as risk factors for late-onset infection. They were confident that, based on the evidence, presence of a central catheter should remain as a risk factor. However, there was not sufficient evidence that parenteral nutrition was an independent risk factor. The committee also discussed how parenteral nutrition is often delivered via a central line, so in many cases, such as those that meet the Coffin 2014 definition, it is already covered as a risk factor.
Group B Strep Support	Evidence Review E	036	018 - 024	The evidence review of risk factors for late-onset neonatal infection has considered the increased risk of infection in babies who undergo surgery, but not specifically addressed those who have had abdominal surgery and/or have prolonged periods of PN and being nil by mouth. The overall incidence of infection (excluding CoNS) was 2.9/1000 livebirths and 23.5/1000 neonatal admissions. The highest incidence was found in the surgical units (3.6 and 30.3, respectively). (Cailes *et al.*, 2017)	Thank you for your comment. The evidence that matched the inclusion criteria for this review investigated the effects of babies who had major surgery, but not specifically those who had abdominal surgery or prolonged periods of parenteral nutrition. The Cailes 2017 epidemiological study was not included as the study design did not meet the inclusion criteria for the review. The committee were therefore unable to make more specific recommendations on this. However, the committee decided to include a research recommendation which will help further

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				Members of the GBSS Medical Advisory Panel recommend that such a review is undertaken, taking into account both evidence and the expert opinion of the committee.	understand the factors most associated with the development of late-onset infection. This will help committees to consider other factors such as this in more detail if recommendations on risk factors for late-onset infection are updated in future updates of this guideline.
Group B Strep Support	Evidence Review G	General	General	This guideline gives an opportunity to reinforce the importance of how a blood culture is drawn, but this seems not to have been considered: Microbial cultures suffer from low sensitivity and specificity: a negative blood culture result is almost inevitable for a large proportion of blood cultures because of the submission of inadequate volumes of blood and only one culture being drawn (Buttery, 2002; Connell *et al.*, 2007). False positive culture of CoNS is common, making diagnosis of neonatal sepsis using the historical gold standard, a challenge (Chiesa *et al.*, 2004). To avoid false positive cultures, blood for culture should be drawn from a freshly punctured blood vessel using strict aseptic technique and a closed system. The skin disinfectant should be left to dry for at least 1 minute to be insure maximal killing of skin organisms. The common practice of using an open system (insertion of cannula from which blood is aspirated with a separate syringe and needle placed in the hub of the cannula), risks the dilemma of how to interpret a false positive culture result. There is also a risk of false positives if blood is drawn from an indwelling vascular device (Chiesa *et al.*, 2004). GBSS recommends that this issue is addressed within the guideline, taking into account both evidence and the expert opinion of the committee.	Thank you for your comment. This guideline is intended to provide recommendations for treatment but is not designed to provide detailed information on good practice. Further information about drawing blood cultures is therefore beyond the scope of this guideline.
Group B Strep Support	Evidence Review G	General	General	The use of PCR appears to have been dismissed as a potential investigation in neonates: a systematic review and meta-analysis (Pammi *et al.*, 2011) assessed whether molecular assays have sufficient sensitivity (>0.98) and specificity (>0.95) to replace microbial cultures in the diagnosis of neonatal sepsis. Although real-time PCR and broad-range conventional PCR amplification	Thank you for your comment. The committee discussed whether PCR should be considered as one of the investigations for late-onset neonatal infection. However, they decided that this should not be recommended as it is not commonly available in clinical practice, partly because of the large volume of blood required for neonates, which

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				methods had higher sensitivity (0.9; 95%CI 0.78-0.95) and specificity (0.96; 95%CI 0.94-0.97), than other assays, molecular assays still do not have sufficient sensitivity to replace microbial cultures in the diagnosis of neonatal sepsis but may perform well as "add-on" tests, and are demonstrating increasing utility (Jordan, 2010; Oeser *et al.*, 2020). GBSS recommends that this issue is addressed within the guideline, taking into account both evidence and the expert opinion of the committee.	makes it impractical in practice. This has now been made clearer in the included studies section of the evidence review.
Group B Strep Support	Evidence Review G	General	General	Also not sufficiently considered as an investigation is chest-XR. Pneumonia is a common presentation of neonatal sepsis, and may be missed if a chest radiograph is not performed. GBS pneumonia mimics respiratory distress syndrome (RDS), and should be considered if a baby with radiographic appearances of RDS, is disproportionately sick. The NICE guideline does not give a directive on the role of chest radiography as part of a screen for early-onset neonatal infection, however it is notable that even in older children pneumonia may be present with limited clinical signs, and there is significant added value of chest radiography in the diagnosis of pneumonia. See (Ablow *et al.*, 1977; Ayalon *et al.*, 2013). GBSS recommends that this issue is addressed within the guideline, taking into account both evidence and the expert opinion of the committee.	Thank you for your comment. The committee discussed whether chest x-ray should be included as one of the investigations for late-onset infection. However, no evidence was available for this that met the inclusion criteria of the review. The committee also highlighted that, in their experience, positive results from a chest x-ray do not always indicate infection in neonates, and should only be carried out when the baby has respiratory distress rather than as a routine investigation for late-onset neonatal infection. The committee therefore decided that both the evidence, and their experience, supported the use of blood culture and C-reactive protein concentration as the most accurate diagnosis methods for late-onset infection.
Group B Strep Support	Evidence Review I	019	015 - 024	The evidence review for anti-fungal prophylaxis not only concludes correctly that there are no studies addressing the question of prophylaxis for babies treated with antibiotics for late-onset neonatal infection, but also considers non-UK studies, in countries where fungal infection rates are significantly higher than in the UK. In the most recently published surveillance study of neonatal fungal infection:	Thank you for your comment. While it is true that this review includes non-UK studies where relevant UK studies did not exist, the absolute probability of invasive fungal infection without prophylaxis used in the economic model comes from Oeser (2014). Oeser (2014) report the rate of candidiasis observed in 4 units before the implementation of prophylaxis policies – a rate of 3.15% among extremely low-birthweight infants. We use this number as our base-case estimate of absolute probability of invasive fungal

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				The overall incidence of fungal infection was 2.4/1000 neonatal unit admissions and was highest among babies <1000 g (extreme low birthweight, 18.8/1000). Only five infants (6%) were >1500 g. Extreme low birthweight infants remain at highest risk of invasive fungal infection and prophylaxis should be particularly *considered* for this group. Known risk factors (use of central venous catheter, parenteral nutrition, previous antibiotic use) were common among cases. The number needing to receive prophylaxis to prevent one case *varies significantly* among units, hence unit-specific decisions are required. Further research is still needed into the optimal empiric and therapeutic strategies. Oeser C, Vergnano S, et al and the Neonatal Infection Surveillance Network (neonIN). Neonatal invasive fungal infection in England 2004-2010. Clin Microbiol Infect. 2014 Sep;20(9):936-41. doi: 10.1111/1469-0691.12578. Epub 2014 Mar 6. PMID: 24479862. In a previously published study, the estimated annual incidence was 10.0 (95% confidence interval (CI) 8.0 to 12.0) cases per 1000 VLBW live births. Eighty-one (86%) of the infants were of extremely low birth weight (ELBW: <1000 g), incidence 21.1 (95% CI 16.5 to 25.7) per 1000 ELBW live births. The incidence of invasive fungal infection in VLBW and ELBW infants in the United Kingdom is lower than reported in previous studies from tertiary centres in North America and elsewhere (Clerihew *et al.*, 2006). The results of the studies regarding fungal prophylaxis quoted in the evidence review therefore do not apply to the UK, except perhaps ELBW babies <1000g and those with additional risk factors. While agreeing that studies of prophylaxis could be graded as indirectly applicable to the review it is important not to overstate the evidence and recommend "consideration" versus "to	infection without prophylaxis. This number was preferred over 2.4/1000 neonatal unit admissions (overall incidence of fungal infection) and 18.8/1000 (incidence of fungal infection in extremely low-birth weight infants) from Oeser (2014) as both these rates are unhelpful, for our purposes, because our model aims to distinguish outcomes with and without prophylaxis and these overall data include infants both with and without antifungal prophylaxis and therefore conflate the two. This is detailed in Table HE002 on page 136 of Evidence Review I. Benjamin (2010), a US study, provides us with data that allows us to estimate the extent to which lower gestational age make fungal infections more likely. Although these data come from a different setting to our decision problem, where absolute rates of candidiasis are likely to be different, we only use them to estimate the extent to which gestational age is a relative modifier of risk, which is much more likely to generalise across settings. The committee saw no reason why the relative effect of gestational age on rates of candidiasis in the US, indicating neonates at lower gestational ages are at the highest risk for candidiasis, would not also be applicable in the UK. They were therefore comfortable with the combination of this evidence, that relied on the absolute probability for candidiasis from a UK evidence source and the extent to which gestational age modifies risk of candidiasis from the US. This is further detailed on page 132 of Evidence Review I. The impact of decreasing the absolute probability of candidiasis used in our economic model was also tested in sensitivity analysis. When we used an incidence value of

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				give" all babies screened and treated for late-onset neonatal infection. Members of the GBSS Medical Advisory Panel recommend that this issue is reconsidered, taking into account both evidence and the expert opinion of the committee.	candidiasis of 0.00042 (value for all live births in England and Wales from Cailes et al. (2018) - Table HE 002 on page136 of Evidence Review I) as the absolute probability of candidiasis antifungal prophylaxis remains dominant, that is it provides both more quality adjusted life-years (QALYs) and is less expensive than no prophylaxis. Thus, while it is true that there is likely to be variation between neonatal units, sensitivity analysis using a smaller value for the absolute probability of candidiasis continues to show prophylaxis with nystatin is the preferred option at and below a gestational age of 30 weeks, consistent with the recommendation the committee made. We found no evidence to present to the committee showing any individual unit or regional area having an incidence rate of candidiasis in our population of interest that is lower than the value from Cailes et al. (2018) used in sensitivity analysis, where the model continues to show prophylaxis as the preferred option. Therefore, the committee felt a "give" recommendation was warranted. Additionally, the committee was aware that the evidence for the effectiveness of antifungal prophylaxis was not from our population of interest, (i.e., neonates who have been given antibiotics for suspected late onset infection), but rather from an indirect source of evidence, (i.e., neonates born preterm or at a very low birthweight). The committee decided it was acceptable to use this indirect evidence as many of the neonates who develop suspected late onset neonatal infection will be preterm. Furthermore, the committee was presented with evidence that showed neonates that have been given broad-spectrum antibiotics, a common treatment for neonates with suspected late

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					onset neonatal infection, had an increased odds of developing candidiasis compared to neonates who had not been given broad-spectrum antibiotics. Thus, our model is able to account for the indirectness of our evidence in two ways. First, it is run by gestational age. Therefore, while the model relies on indirect evidence focused on preterm and very low birthweight babies, as described above, we use data to show the risk of candidiasis decreases as gestational age increases (detailed on page 132 of Evidence Review I). Therefore, the risk of candidiasis for a 22 week old neonate in our model is not the same as a 42 week old neonate. Secondly, we apply the odds ratio for candidiasis given broad-spectrum antibiotics to more accurately model our population of interest: neonates who have been given broad-spectrum antibiotics for suspected late onset neonatal infection (Detailed on page 134 of Evidence Review I). Incorporating this odds ratio in turn raises the risk of candidiasis (Shown in Figure HE003 on page 135). Together, the committee felt the model, while at times using indirect evidence, did succeed in modelling our population of interest. The committee also had no reason to believe that either nystatin or fluconazole would have an efficacy that is different in our population of interest, (i.e., neonates given antibiotics for suspected late onset infection), as compared with the indirect population from which the evidence is based, (i.e., neonates born preterm or at a very low birthweight). However, given this uncertainty we also explored the impacts of changing the efficacy of both nystatin and fluconazole within range of their confidence intervals in sensitivity analysis (detailed on page 161).

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					Briefly, at a low gestational age, regardless of exposure to antibiotics, there is no single parameter that can be varied within the range of its confidence interval (including the odds ratio of treatment effect for nystatib versus placebo or fluconazole versus placebo) such that nystatin is not the optimal option when compared with no prophylaxis. The results from the sensitivity analysis in addition to the committee's belief that nystatin would not have a different efficacy in neonates given antibiotics for suspected late onset neonatal infection compared with neonates who are preterm or very low birthweight left them comfortable with both using this indirect evidence and a "give" rather than a "consider" recommendation. In response to your comment we added additional explanations on the use of UK data to estimate the absolute probability of infection and that US data was only used to estimate the relative effects of risk modifiers (gestational age and exposure to broad-spectrum antibiotics). We also added additional sentences to the 'committee's discussion of the evidence' portion of the evidence review to better explain how this indirect evidence was used and why the committee agreed to use it. The committee agreed that there was good evidence that giving preventative antifungal prophylaxis to neonates who were born at less than 30 weeks' gestation or with birthweight under 1500g or would be cost effective. However, they acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a

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					research recommendation for research on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection.
Group B Strep Support	Evidence Review I	021	030 - 037	As it stands the recommendation is evidence-light and will undoubtedly increase unnecessary anti-fungal use. The variability in anti-fungal prophylaxis likely relates to variable fungal infection rates in neonatal units (as in Clarissa Oeser's surveillance paper). Members of the GBSS Medical Advisory Panel strongly suggest a review of this recommendation to "consider" versus "to give" anti-fungals. For some babies this is likely to be an appropriate decision, but that decision will rely on individualised clinical judgement.	Thank you for your comment. Although there was a lack of direct clinical evidence for this population, the committee considered that this evidence was acceptable to use in the economic model. The economic model suggested strong evidence that prophylactic antifungals were more effective and less costly than no prophylaxis. The committee narrowed the recommendation to cover a population that was better aligned with the direct evidence base (<30 weeks, birthweight <1500g). Further details of the assumptions about the evidence used in the economic model are given below: While it is true that this review includes non-UK studies where relevant UK studies did not exist, the absolute probability of invasive fungal infection without prophylaxis used in the economic model comes from Oeser (2014). Oeser (2014) report the rate of candidiasis observed in 4 units before the implementation of prophylaxis policies – a rate of 3.15% among extremely low-birthweight infants. We use this number as our base-case estimate of absolute probability of invasive fungal infection without prophylaxis. This number was preferred over 2.4/1000 neonatal unit admissions (overall incidence of fungal infection) and 18.8/1000 (incidence of fungal infection in extremely low-birth weight infants) from Oeser (2014) as both these rates are unhelpful, for our purposes, because our model aims to distinguish outcomes with and without prophylaxis and these overall data include infants both with and without antifungal prophylaxis and therefore conflate the two. This is detailed in Table HE002 on page 136 of Evidence Review I.

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					Benjamin (2010), a US study, provides us with data that allows us to estimate the extent to which lower gestational age make fungal infections more likely. Although these data come from a different setting to our decision problem, where absolute rates of candidiasis are likely to be different, we only use them to estimate the extent to which gestational age is a relative modifier of risk, which is much more likely to generalise across settings. The committee saw no reason why the relative effect of gestational age on rates of candidiasis in the US, indicating neonates at lower gestational ages are at the highest risk for candidiasis, would not also be applicable in the UK. They were therefore comfortable with the combination of this evidence, that relied on the absolute probability for candidiasis from a UK evidence source and the extent to which gestational age modifies risk of candidiasis from the US. This is further detailed on page 132 of Evidence Review I. The impact of decreasing the absolute probability of candidiasis used in our economic model was also tested in sensitivity analysis. When we used an incidence value of candidiasis of 0.00042 (value for all live births in England and Wales from Cailes et al. (2018) - Table HE 002 on page136 of Evidence Review I) as the absolute probability of candidiasis antifungal prophylaxis remains dominant, that is it provides both more quality adjusted life-years (QALYs) and is less expensive than no prophylaxis. Thus, while it is true that there is likely to be variation between neonatal units, sensitivity analysis using a smaller value for the absolute probability of candidiasis continues to show prophylaxis with nystatin is the preferred option at and

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					below a gestational age of 30 weeks, consistent with the recommendation the committee made. We found no evidence to present to the committee showing any individual unit or regional area having an incidence rate of candidiasis in our population of interest that is lower than the value from Cailes et al. (2018) used in sensitivity analysis, where the model continues to show prophylaxis as the preferred option. Therefore, the committee felt a "give" recommendation was warranted. Additionally, the committee was aware that the evidence for the effectiveness of antifungal prophylaxis was not from our population of interest, (i.e., neonates who have been given antibiotics for suspected late onset infection), but rather from an indirect source of evidence, (i.e., neonates born preterm or at a very low birthweight). The committee decided it was acceptable to use this indirect evidence as many of the neonates who develop suspected late onset neonatal infection will be preterm. Furthermore, the committee was presented with evidence that showed neonates that have been given broad-spectrum antibiotics, a common treatment for neonates with suspected late onset neonatal infection, had an increased odds of developing candidiasis compared to neonates who had not been given broad-spectrum antibiotics. Thus, our model is able to account for the indirectness of our evidence in two ways. First, it is run by gestational age. Therefore, while the model relies on indirect evidence focused on preterm and very low birthweight babies, as described above, we use data to show the risk of candidiasis decreases as gestational age increases (detailed on page 132 of Evidence Review I). Therefore, the risk of candidiasis for a

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					22 week old neonate in our model is not the same as a 42 week old neonate. Secondly, we apply the odds ratio for candidiasis given broad-spectrum antibiotics to more accurately model our population of interest: neonates who have been given broad-spectrum antibiotics for suspected late onset neonatal infection (Detailed on page 134 of Evidence Review I). Incorporating this odds ratio in turn raises the risk of candidiasis (Shown in Figure HE003 on page 135). Together, the committee felt the model, while at times using indirect evidence, did succeed in modelling our population of interest. The committee also had no reason to believe that either nystatin or fluconazole would have an efficacy that is different in our population of interest, (i.e., neonates given antibiotics for suspected late onset infection), as compared with the indirect population from which the evidence is based, (i.e., neonates born preterm or at a very low birthweight). However, given this uncertainty we also explored the impacts of changing the efficacy of both nystatin and fluconazole within range of their confidence intervals in sensitivity analysis (detailed on page 161). Briefly, at a low gestational age, regardless of exposure to antibiotics, there is no single parameter that can be varied within the range of its confidence interval (including the odds ratio of treatment effect for nystatib versus placebo or fluconazole versus placebo) such that nystatin is not the optimal option when compared with no prophylaxis. The results from the sensitivity analysis in addition to the committee's belief that nystatin would not have a different efficacy in neonates given antibiotics for suspected late onset neonatal infection compared with neonates who are

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					preterm or very low birthweight left them comfortable with both using this indirect evidence and a "give" rather than a "consider" recommendation. In response to your comment we added additional explanations on the use of UK data to estimate the absolute probability of infection and that US data was only used to estimate the relative effects of risk modifiers (gestational age and exposure to broad-spectrum antibiotics). We also added additional sentences to the 'committee's discussion of the evidence' portion of the evidence review to better explain how this indirect evidence was used and why the committee agreed to use it. The committee agreed that there was good evidence that giving preventative antifungal prophylaxis to neonates who were born at less than 30 weeks' gestation or with birthweight under 1500g or would be cost effective. However, they acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection.
Group B Strep Support	Guideline	008	010 - 011	This recommendation is not consistent with the 2017 RCOG guidelines (Hughes *et al.*, 2017), which recommends that where a woman has previously tested positive for GBS, she should be **offered** the options of having intrapartum antibiotic prophylaxis (IAP), or bacteriological testing in late pregnancy (using RCOG/PHE recommended tests) and the **offer** of IAP if still positive. (See RCOG Greentop Guideline #36 https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.14821).	Thank you for your comment. We have changed the wording of this recommendation to 'her maternity care team will offer her intravenous antibiotics in labour' as suggested for consistency with the language used in recommendation 1.2.1 ('Offer antibiotics during labour...').

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				GBSS supports the right of women to make an informed choice about her options and therefore recommends this is reworded to say "- her maternity care team will discuss with her the options of having intrapartum antibiotic prophylaxis (IAP), or bacteriological testing in late pregnancy using recommended tests and offering of IAP if still a carrier of GBS."	
Group B Strep Support	Guideline	009	008	This recommendation is not consistent with the 2017 RCOG guidelines, which recommends that where a woman has previously had a baby who developed GBS infection, intrapartum antibiotic prophylaxis (IAP) should be **offered** in future labours. (See RCOG Greentop Guideline #36 https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.14821). GBSS supports the right of women to make an informed choice about her options. If the maternity team in the next pregnancy are following the RCOG guideline, the statement that "her maternity care team will recommend that she has antibiotics in labour" will not be correct, they will instead 'offer' IAP. Not making this guideline consistent with the RCOG advice will cause confusion, and therefore we recommend this statement is reworded to say "- her maternity care team will offer her intravenous antibiotics in labour."	Thank you for your comment. We have changed the wording of this recommendation to 'her maternity care team will offer her intravenous antibiotics in labour' as suggested for consistency with the language used in recommendation 1.2.1 ('Offer antibiotics during labour...').
Group B Strep Support	Guideline	009	012	The risk to future babies is of early-onset GBS infection, and this should be clearly stated here. GBSS recommends this is reworded to say "- group B streptococcal infection in babies in future pregnancies and after their birth."	Thank you for your comment. The recommendations on information and support for parent and carers of babies who are at risk of early-onset neonatal infection were out of scope for this guideline update and we did not review evidence in this area. The committee were therefore unable to make any changes to this specific recommendation.

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Group B Strep Support	Guideline	010	011	NICE is stating that IAP should be *offered* to women in preterm labour, which is different from the RCOG's 2017 Greentop guideline #36 which says they should be *recommended*. Not making this guideline consistent with the RCOG advice will cause confusion, and GBSS recommends that the guidance aligns. GBSS recommends that this recommendation is revisited by the committee, and amended to say that IAP is **recommended** for the risk factor of preterm labour. However, if there has to be a difference – and there is no clear explanation of why that should be in the Antibiotics for prevention and Treatment evidence document – please include a clear explanation giving the reasons for the difference.	Thank you for your comment. There are some differences between the terminology used by the NICE and RCOG guidelines, and an offer recommendation for NICE indicates that an intervention should be used, and this is therefore a similar strength to 'recommend' that is used by RCOG. More information about the terminology used in NICE recommendations is available here: https://www.nice.org.uk/process/pmg6/chapter/developing-and-wording-guideline-recommendations#wording-the-guideline-recommendations
Group B Strep Support	Guideline	010	017 - 018	The key timing of the test is that the samples are taken within the last 5 weeks of pregnancy, rather than specifically at 35-37 weeks' gestation. So, for example, in a woman expecting twins, this might be at 32-34 weeks' gestation. Not making this guideline consistent with the RCOG advice will cause confusion, and GBSS recommends this statement should align with the RCOG recommendations. We therefore recommend this is reworded to say "…samples collected between 35 and 37 weeks' gestation or 3-5 weeks before the anticipated delivery date in the current pregnancy"	Thank you for your comment. The committee discussed the timing of the GBS test and agreed that the timing may differ for some women. They therefore updated the recommendation to match your suggestion. Further information has also been added to the committee discussion section of the evidence review.
Group B Strep Support	Guideline	012	011 - 012	No recommendation has been made here for women who tested positive for GBS in a previous pregnancy, or who have previously had a baby who developed GBS infection. This seems an oversight. GBSS recommends that this gap is addressed, either using evidence, or the expertise of the committee.	Thank you for your comment. The question about whether women with prelabour preterm rupture of membranes between 34 and 37 weeks gestation was specifically limited to women who have tested positive for GBS in their current pregnancy, and the evidence identified was for this population specifically. Recommendations for women who were positive for GBS in a previous pregnancy therefore could not be made on this issue as it was outside of the scope of the guideline.

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Group B Strep Support	Guideline	012	011 - 012	Offering women a test for GBS carriage could be useful for those women with preterm prelabour prolonged rupture of membranes whose GBS carriage status is unknown or who tested positive in a previous pregnancy, or previously had a baby who developed GBS infection. Knowing their GBS carriage status would help inform the decision making around expectant management or immediate delivery. This is not routine antenatal screening – it is offering women with a specific risk factor (those with preterm prelabour rupture of membranes) a test to find out if they are carrying GBS and therefore if their baby is at raised risk of GBS infection. If they are carrying GBS, the research suggests that immediate delivery would result in significant savings for the NHS. GBSS recommends that this should be considered since, even though it is outside the scope of the specific question, it is within the scope of this guideline - either using existing evidence, or the committee's expertise.	Thank you for your comment. GBS testing was not included in the scope for this guideline and so the committee did not consider evidence on the diagnostic accuracy of GBS tests and or the effectiveness and cost effectiveness of their use in particular scenarios. They were therefore unable to make recommendations on providing testing for GBS.
Group B Strep Support	Guideline	015	Box 2	It would be helpful if there were more lay explanations used in this box. There are for some indicators (for example altered muscle tone) and, as this will also be used by lay people, GBSS recommends that some lay terminology is included for other indicators, specifically to include signs of respiratory distress (for example grunting, noisy breathing, moaning).	Thank you for your comment. The committee discussed whether more explanations should be added to box 2. However, they decided that not all of the terms are relevant to non-clinicians, as the box is termed clinical indicators. However, they decided to add a more detailed description of signs of respiratory distress "(including grunting, recession, tacyypnia)", as they thought that not all clinicians would necessarily be familiar with this terminology.
Group B Strep Support	Guideline	016	003 - 008	The layout of this will make this recommendation difficult for people to follow by just quoting the paragraph numbers, without the content or even the page numbers or a hyperlink. GBSS recommends that the quoted recommendations are repeated here with, if possible, an infographic also.	Thank you for your comment. The final version of the guideline will appear on the NICE website with hyperlinks to allow cross reference between recommendations to make navigation easier. We have also produced a visual summary illustrating this section of the guideline to make it easier to follow. The visual summary will be published at the same time as the guideline.
Group B Strep Support	Guideline	016	020 - 022	Obtaining more data on the impact of the Kaiser Permanente neonatal sepsis calculator is important, and GBSS welcomes the	Thank you for your comment. The committee decided to highlight the importance of the audit further by restructuring

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				statement that the Kaiser Permanente neonatal sepsis calculator can be used only if part of a prospective audit. However, this important caveat may be overlooked in the text as it stands. GBSS recommends that the statement "**only if is part of a prospective audit**" is put in bold or highlighted in some way.	the recommendation into two sentences, one of which emphasises the importance of the audit.
Group B Strep Support	Guideline	017	007 - 009	The layout of this will make this recommendation difficult for people to follow by just quoting the paragraph numbers, without the content or even the page numbers or a hyperlink. GBSS recommends that the quoted recommendations are repeated here with, if possible, an infographic also.	Thank you for your comment. The final version of the guideline will appear on the NICE website with hyperlinks to allow cross reference between recommendations to make navigation easier. We have also produced a visual summary illustrating this section of the guideline to make it easier to follow. The visual summary will be published at the same time as the guideline.
Group B Strep Support	Guideline	018	Table 1	GBSS recommends including stand-alone headings and additions for gastrointestinal indicators: **Gastro-intestinal:** Abdominal distension Vomiting Bilious aspirates Blood in stool or vomit Sudden onset of jaundice or deranged liver function tests **Temperature** Temperature 38°C or more unexplained by environmental factors Temperature less than 36°C unexplained by environmental factors **Neurological** Seizures Bulging fontanelle	Thank you for your comment. The committee discussed whether gastro-intestinal indicators should be added and presented under a separate heading. However, Table 1 is based on the clinical indicators table from the NICE sepsis guideline and so the committee decided against changing the format and adding new indicators in order to maintain consistency with the sepsis guideline.
Group B Strep Support	Guideline	019	019	GBSS recommends that investigations should include a chest XR and /or abdominal XR as clinically indicated	Thank you for your comment. The committee discussed whether chest x-ray should be included as one of the investigations for late-onset infection. However, no evidence was available for this that met the inclusion criteria of the review. The committee also highlighted that,

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					in their experience, positive results from a chest x-ray do not always indicate infection in neonates and should only be carried out when the baby has respiratory distress rather than as a routine investigation for late-onset neonatal infection. The committee therefore decided that both the evidence, and their experience, supported the use of blood culture and C-reactive protein concentration as the most accurate diagnosis methods for late-onset infection.
Group B Strep Support	Guideline	023	005 - 008	In other lists, the connecting word has been put in bold – it would help if the '**and**' words at the end of each bullet are also shown in bold here. GBSS recommends this change is made.	Thank you for your comment. Antibiotics for suspected early-onset infection were outside the scope of this guideline update and so the committee could not make or change recommendations on this.
Group B Strep Support	Guideline	025	021 - 028	GBSS recommends that the fact that antibiotics for a baby with a positive blood culture may also require extended treatment if the baby has intra-abdominal co-pathology, especially necrotising enterocolitis and / or intestinal perforation should be included.	Thank you for your comment. The committee agreed that, based on their clinical experience, intra-abdominal co-pathology and necrotising enterocolitis are reasons that antibiotic treatment might be continued beyond 7 days. These have been added to the recommendation.
Group B Strep Support	Guideline	029	021	Members of the GBSS Medical Advisory Panel recommend that this should be "consider" antifungal prophylaxis versus "give" (please also see our comments relating to the evidence review). There is no data to justify the recommendation to "give all babies <1500g" anti-fungal prophylaxis when screened for late-onset neonatal infection and given antibiotics; it is babies at <1000g who are at highest risk of fungal infection, with babies <1500g being at increased risk along with some other groups. Prophylaxis may be prudent and justifiable in these other groups with risk factors for fungal infection: those on prolonged antibiotic courses, prolonged parental nutrition, indwelling central lines and intestinal failure, especially when nil by mouth for prolonged periods. Such prophylaxis should be individualised depending on clinical circumstances as the evidence pertains to prophylaxis from birth in very preterm babies (from different countries), as discussed in the evidence review.	Thank you for your comment. While it is true that this review includes non-UK studies where relevant UK studies did not exist, the absolute probability of invasive fungal infection without prophylaxis used in the economic model comes from Oeser (2014). Oeser (2014) report the rate of candidiasis observed in 4 units before the implementation of prophylaxis policies – a rate of 3.15% among extremely low-birthweight infants. We use this number as our base-case estimate of absolute probability of invasive fungal infection without prophylaxis. This number was preferred over 2.4/1000 neonatal unit admissions (overall incidence of fungal infection) and 18.8/1000 (incidence of fungal infection in extremely low-birth weight infants) from Oeser (2014) as both these rates are unhelpful, for our purposes, because our model aims to distinguish outcomes with and without prophylaxis and these overall data include infants both with and without antifungal prophylaxis and therefore

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				If commencing anti-fungals, members of the GBSS Medical Advisory Panel recommend the guideline should state that they should be stopped when antibiotics are stopped.	conflate the two. This is detailed in Table HE002 on page 136 of Evidence Review I. Benjamin (2010), a US study, provides us with data that allows us to estimate the extent to which lower gestational age make fungal infections more likely. Although these data come from a different setting to our decision problem, where absolute rates of candidiasis are likely to be different, we only use them to estimate the extent to which gestational age is a relative modifier of risk, which is much more likely to generalise across settings. The committee saw no reason why the relative effect of gestational age on rates of candidiasis in the US, indicating neonates at lower gestational ages are at the highest risk for candidiasis, would not also be applicable in the UK. They were therefore comfortable with the combination of this evidence, that relied on the absolute probability for candidiasis from a UK evidence source and the extent to which gestational age modifies risk of candidiasis from the US. This is further detailed on page 132 of Evidence Review I. The impact of decreasing the absolute probability of candidiasis used in our economic model was also tested in sensitivity analysis. When we used an incidence value of candidiasis of 0.00042 (value for all live births in England and Wales from Cailes et al. (2018) - Table HE 002 on page136 of Evidence Review I) as the absolute probability of candidiasis antifungal prophylaxis remains dominant, that is it provides both more quality adjusted life-years (QALYs) and is less expensive than no prophylaxis. Thus, while it is true that there is likely to be variation between

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					neonatal units, sensitivity analysis using a smaller value for the absolute probability of candidiasis continues to show prophylaxis with nystatin is the preferred option at and below a gestational age of 30 weeks, consistent with the recommendation the committee made. We found no evidence to present to the committee showing any individual unit or regional area having an incidence rate of candidiasis in our population of interest that is lower than the value from Cailes et al. (2018) used in sensitivity analysis, where the model continues to show prophylaxis as the preferred option. Therefore, the committee felt a "give" recommendation was warranted. Additionally, the committee was aware that the evidence for the effectiveness of antifungal prophylaxis was not from our population of interest, (i.e., neonates who have been given antibiotics for suspected late onset infection), but rather from an indirect source of evidence, (i.e., neonates born preterm or at a very low birthweight). The committee decided it was acceptable to use this indirect evidence as many of the neonates who develop suspected late onset neonatal infection will be preterm. Furthermore, the committee was presented with evidence that showed neonates that have been given broad-spectrum antibiotics, a common treatment for neonates with suspected late onset neonatal infection, had an increased odds of developing candidiasis compared to neonates who had not been given broad-spectrum antibiotics. Thus, our model is able to account for the indirectness of our evidence in two ways. First, it is run by gestational age. Therefore, while the model relies on indirect evidence focused on preterm and very low birthweight babies, as described above, we

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					use data to show the risk of candidiasis decreases as gestational age increases (detailed on page 132 of Evidence Review I). Therefore, the risk of candidiasis for a 22 week old neonate in our model is not the same as a 42 week old neonate. Secondly, we apply the odds ratio for candidiasis given broad-spectrum antibiotics to more accurately model our population of interest: neonates who have been given broad-spectrum antibiotics for suspected late onset neonatal infection (Detailed on page 134 of Evidence Review I). Incorporating this odds ratio in turn raises the risk of candidiasis (Shown in Figure HE003 on page 135). Together, the committee felt the model, while at times using indirect evidence, did succeed in modelling our population of interest. The committee also had no reason to believe that either nystatin or fluconazole would have an efficacy that is different in our population of interest, (i.e., neonates given antibiotics for suspected late onset infection), as compared with the indirect population from which the evidence is based, (i.e., neonates born preterm or at a very low birthweight). However, given this uncertainty we also explored the impacts of changing the efficacy of both nystatin and fluconazole within range of their confidence intervals in sensitivity analysis (detailed on page 161). Briefly, at a low gestational age, regardless of exposure to antibiotics, there is no single parameter that can be varied within the range of its confidence interval (including the odds ratio of treatment effect for nystatin versus placebo or fluconazole versus placebo) such that nystatin is not the optimal option when compared with no prophylaxis. The results from the sensitivity analysis in addition to the

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					committee's belief that nystatin would not have a different efficacy in neonates given antibiotics for suspected late onset neonatal infection compared with neonates who are preterm or very low birthweight left them comfortable with both using this indirect evidence and a "give" rather than a "consider" recommendation. In response to your comment we added additional explanations on the use of UK data to estimate the absolute probability of infection and that US data was only used to estimate the relative effects of risk modifiers (gestational age and exposure to broad-spectrum antibiotics). We also added additional sentences to the 'committee's discussion of the evidence' portion of the evidence review to better explain how this indirect evidence was used and why the committee agreed to use it. The committee agreed that there was good evidence that giving preventative antifungal prophylaxis to neonates who were born at less than 30 weeks' gestation or with birthweight under 1500g or would be cost effective. However, they acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection.
Group B Strep Support	Guideline	035	024 - 029	Recent data (O'Sullivan *et al.*, 2018) reported higher rates of infection and death from group B Strep infection in preterm babies. GBSS recommends therefore that women in preterm labour should be **recommended** to have antibiotics in labour (rather than just being **offered** them), which is in line with the RCOG guideline	Thank you for your comment. There are some differences between the terminology used by the NICE and RCOG guidelines, and an offer recommendation for NICE indicates that an intervention should be used, and this is therefore a similar strength to 'recommend' that is used by

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				also. Not making this guideline consistent with the RCOG advice will cause confusion, and GBSS recommends that the guidance aligns. However, if there has to be a difference – and there is no clear explanation of why that should be – please include a clear explanation giving the reasons for the difference.	RCOG. More information about the terminology used in NICE recommendations is available here: https://www.nice.org.uk/process/pmg6/chapter/developing-and-wording-guideline-recommendations#wording-the-guideline-recommendations
Healthcare Safety Investigation Branch	Guideline	009	015	The coding for the 'replacement' 2021 in the update is incorrectly coded and should read 1.1.12 instead of 1.1.11	Thank you for your comment. The replacement recommendation number has been corrected to 1.1.12.
Kit Tarka Foundation	Evidence reviews	General	General	We can see that viral infections have been excluded from all the Evidence Reviews and there may be a good reason for this, however we are extremely worried that excluding them from this updated guideline completely will lead to preventable deaths of newborn babies.	Thank you for your comment. Viral infections are beyond the scope of this guideline and so the committee could not make recommendations on this. We have added a sentence in the section describing what the guideline covers to make it clear that the guideline covers bacterial infections only. We are aware that this area is not currently covered by NICE guidance and have raised this issue with the surveillance team at NICE who will review provision of guidance on neonatal care.
Kit Tarka Foundation	Guideline	General	General	We are very concerned that this guideline does not refer to viral infections at all, especially neonatal herpes/HSV which has an incredibly high rate of mortality and is on the rise in the UK. We are concerned that, as is already often the case, HSV will not be suspected in unwell infants and as a result they will be treated with antibiotics instead of antivirals and subsequently become permanently disabled or die. This guideline presents an opportunity to act as a reminder to clinicians that they should consider HSV infection in ALL unwell babies - even if there is no maternal history of herpes - and treat with antivirals accordingly. Kit Tarka Foundation (KTF) was formed after the death of baby Kit from neonatal HSV when he was just 13 days old after contracting HSV postnatally. Kit was treated with antibiotics and, as HSV wasn't suspected until he was dying in an intensive care unit, he	Thank you for your comment. Viral infections were beyond the scope of this guideline and so the committee were unable to make recommendations on this. We have added a sentence in the section describing what the guideline covers to make it clear that the guideline covers bacterial infections only. We are aware that this area is not currently covered by NICE guidance and have raised this issue with the surveillance team at NICE who will review provision of guidance on neonatal care.

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				never received the antivirals needed to save his life. His story is reflected in many others across the country. We know from the KTF-funded BPSU study currently underway that HSV infections in babies are on the rise and mortality rates among infected babies are incredibly high. Details of the project and interim results can be seen at kittarkafoundation.org/current-projects. Surveys carried out alongside this study indicate a lack of awareness amongst clinicians with many not performing PCR tests or even considering HSV in an unwell infant. We believe HSV infection should also be considered in the prevention and risk factor sections. In particular risk factors should include maternal HSV infection and postnatal exposure. This guideline should reflect the RCOG & BASHH guideline 'Management of Genital Herpes in Pregnancy' particularly in the area of prevention.	
Kit Tarka Foundation	Guideline	006	009	When a woman is identified as having a previous or current genital HSV infection: - treat as per RCOC/BASHH guidance 'Management of Genital Herpes in Pregnancy' advise the woman that her baby is at risk of HSV infection, and provide information on warning signs (including specific signs such as blisters, and non-specific signs such as irritability, lethargy / "tiredness" and difficulty waking.)	Thank you for your comment. Viral infections are beyond the scope of this guideline and so the committee could not make recommendations on this. We have added a sentence in the section describing what the guideline covers to make it clear that the guideline covers bacterial infections only.
Kit Tarka Foundation	Guideline	009	015	Parents should also be told to seek medical help for babies who have extreme tiredness/lethargy, difficulty waking up. Neonatal HSV infection commonly presents with non-specific signs which are easily missed, as was the case with baby Kit.	Thank you for your comment. Viral infection is out of scope for this guideline and so the committee could not make recommendations on this. We have added a sentence in the section describing what the guideline covers to make it clear that the guideline covers bacterial infections only. The committee based the signs and symptoms for this recommendation on those that were most commonly reported in the evidence.

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Kit Tarka Foundation	Guideline	009	015	Parents should be advised to seek medical attention if their baby has an unidentifiable rash or sores on the skin, eye or inside the mouth	Thank you for your comment. There was no evidence for these signs of infection. The committee noted that there were a number of potential signs, and so based this recommendation on those that were most commonly reported in the evidence They also decided to base the recommendations on the signs that are most likely to indicate infection, rather than those that could have other causes. More information on how this recommendation was developed is available in Evidence review A: Information and support
Kit Tarka Foundation	Guideline	010	008	Signpost to RCOG and BASHH guideline 'Management of Genital Herpes in Pregnancy' so that preventative measures (e.g. maternal oral acyclovir or elective c-section) can be discussed and offered as appropriate.	Thank you for your comment. The committee reviewed the evidence and based the recommendation on the groups of women identified as most at risk of having a baby who develops neonatal bacterial infection. Genital herpes in pregnancy was not identified as one of the most common risk factors, and viral infections are out of scope for this guideline. The committee therefore could not make recommendations on this.
Kit Tarka Foundation	Guideline	014	001	Other risk factors should include: - Previous or current maternal genital herpes (see RCOG/BASSH guidance for risk stratification) - Post-natal exposure to HSV infection (including cold sores, herpetic whitlow and herpetic lesions around nipple if breastfeeding)	Thank you for your comment. Viral infections are beyond the scope of this guideline and so the committee could not make recommendations on this.
Kit Tarka Foundation	Guideline	015	001	Other clinical indicators should include extreme tiredness/lethargy/difficulty waking up and vesicular lesions / non-specific rashes to skin, eyes, mouth. (clinicians should have a low threshold for HSV testing if any diagnostic uncertainty)	Thank you for your comment. The committee reviewed the evidence and selected the risk factors based on those that were most strongly associated with bacterial neonatal infection, and based on their clinical experience. Difficulty waking up was one of the clinical indicators identified for late--onset infection and so is included in those recommendations. No evidence was found for lesions and rashes as an indicator of neonatal infection. Testing for viral infections was beyond the scope of this guideline and so the committee could not make recommendations on this.

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Kit Tarka Foundation	Guideline	018	004	Should also include vesicular lesions / non-specific rashes to skin, eyes, mouth. (clinicians should have a low threshold for HSV testing if any diagnostic uncertainty)	Thank you for your comment. Indicators of viral infection are beyond the scope of this guideline and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
Kit Tarka Foundation	Guideline	019	009	Consider including blood PCR for HSV	Thank you for your comment. Investigations for viral infection are beyond the scope of this guideline and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
Kit Tarka Foundation	Guideline	019	016	Include suspicion of HSV infection for when to perform lumbar puncture	Thank you for your comment. Viral infections were beyond the scope of this guideline and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
Kit Tarka Foundation	Guideline	021	001	Should also include guidance re antiviral treatment	Thank you for your comment. Antibiotics for suspected early-onset infection were outside the scope of this guideline update and so the committee could not make or change recommendations on this.
Kit Tarka Foundation	Guideline	023	001	Should also include guidance re antiviral treatment	Thank you for your comment. Antibiotics for suspected early-onset infection were outside the scope of this guideline update and so the committee could not make or change recommendations on this.
Kit Tarka Foundation	Guideline	027	014	Include treatment for positive HSV infection	Thank you for your comment. Viral infections were beyond the scope of this guideline and so the committee could not make recommendations on this.
Kit Tarka Foundation	Guideline	031	018	Request that the guideline committee makes recommendations for HSV research: should all non-specifically unwell babies <1 month age be treated empirically with acyclovir?	Thank you for your comment. Viral infections were beyond the scope of this guideline and so the committee could not make recommendations on this.
Neonatal and Paediatric Pharmacists Group	Guideline	General	General	NPPG welcomes and supports this guideline.	Thank you for your comment and support for this guideline.
Neonatal and Paediatric Pharmacists Group	Guideline	029	019 - 024	Could the use of antifungal prophylaxis be made clearer in the guideline in terms of the dose? For example, some centres might use nystatin 1mL QDS as a dose but in practice the neonate will not cope with this volume especially very small babies and a	Thank you for your comment. The committee discussed whether a specific recommendation could be made on the dose of nystatin that could be used. However, no evidence that compared different doses of nystatin was identified.

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				0.25mL QDS dose seems to work better. This will also save on waste as there maybe more than one baby on the unit who might need it.	The committee acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection. The committee noted that dose information was better placed in the British National Formulary (children), as this is the place that clinicians would look for dose information.
Neonatal and Paediatric Pharmacists Group	Guideline	029 030	019 - 024 001 - 004	We would suggest that topical miconazole should also be considered prophylactically to nappy area.	Thank you for your comment. The committee reviewed the evidence and noted that miconazole did not show any clear benefits in comparison to placebo. Nystatin and fluconazole were both shown to be more effective at reducing the cases of neonatal infection and so the committee decided that these should be recommended rather than miconazole.
Neonatal and Paediatric Pharmacists Group	Guideline	030	001 – 004	Again, could this be made clearer by recommending a dose? • BNFC dose (https://doi.org/10.18578/BNFC.870309169) recommends: Mucosal candidiasis (except genital) *By mouth, or by intravenous infusion* Neonate up to 14 days: 3–6 mg/kg, dose to be given on first day, then 3 mg/kg every 72 hours. Neonate 14 days to 28 days: 3–6 mg/kg, dose to be given on first day, then 3 mg/kg every 48 hours. Prevention of fungal infections in immunocompromised patients *By mouth, or by intravenous infusion* Neonate up to 14 days: 3–12 mg/kg every 72 hours, dose given according to extent and duration of neutropenia. Neonate 14 days to 28 days: 3–12 mg/kg every 48 hours, dose given according to extent and duration of neutropenia.	Thank you for your comment. The committee discussed whether a specific recommendation could be made on the dose on fluconazole that could be used. However, evidence comparing different doses of fluconazole did not favour one dose over another. The committee agreed that dose information was better placed in the British National Formulary (children), as this is the place that clinicians would look for dose information. The committee agreed that there was good evidence that giving preventative antifungal prophylaxis to neonates who were born at less than 30 weeks' gestation or with birthweight under 1500g or would be cost effective. However, they acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research on the optimum

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				• Ainsworth, S. Neonatal Formulary (8th edition) p319-21 recommends Prophylactic use in the very low birth weight neonate Age under 2 weeks: Give 6mg/kg of fluconazole on day 1, then a further 6mg/kg every 3rd day Age 2-4 weeks: Give 6mg/kg of fluconazole on day 1, then a further 6mg/kg every 2nd day. Treatment of invasive candidiasis A loading dose of 25mg/kg is recommended and shortens the time to achieving therapeutic levels. Postmenstrual age under 30 weeks: 12mg/kg of fluconazole every day Postmenstrual age 30 weeks or greater: 20mg/kg of fluconazole every day Double the dosage internal after the first two doses if there is renal failure.	regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection.
Neonatal Critical Care Clinical Reference Group – NHSE&I	Guideline	007	022 - 024	GPs are usually informed in writing when a baby is discharged from hospital after being considered to be at increased risk of early-onset infection as they would have been observed and treated with IV antibiotics. It would not be practical (or necessary) to inform the GP verbally as well as in writing.	Thank you for your comment. The recommendations on information and support for parent and carers of babies with early-onset neonatal infection were not updated as part of this guideline update and we did not review evidence in this area. We are therefore unable to make changes to this recommendation.
Neonatal Critical Care Clinical Reference Group – NHSE&I	Guideline	016	019	We welcome the addition of the Kaiser Permanente Neonatal Sepsis Calculator as an alternative framework and agree that prospective audit should be focused on missed cases as defined by positive cultures.	Thank you for your comment and support for this guideline.
Neonatal Critical Care Clinical Reference	Guideline	023 025	001 011	We note the difference in recommended timing of decisions after starting antibiotics in early-onset infection (i.e. 36 hours) and late-onset infection (i.e. 48 hours) and question the rationale for this difference. Most neonatal services would consider stopping antibiotics for suspected late-onset infection, if cultures are	Thank you for your comment. The committee decided that decisions should be made after 48 hours because of the different bacteria that may cause late-onset infection and the slower rate of growth of these bacteria in comparison to those that cause early-onset infection. They highlighted

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Group – NHSE&I				negative, there are no ongoing clinical concerns and the absolute level or trend with CRP is suggestive that late-onset infection is unlikely.	how it can take longer for a blood culture to become positive for late-onset infection and therefore decided that antibiotic decisions should be made later than for early-onset infection. Further information on their decision is available in the rationale & impact section of the guideline, and in Evidence review H: Antibiotics.
NHSE & I	Guideline	General	General	Most of this guideline relates to practice in secondary care. From the primary care perspective, our only comment is that the advice to inform the GP of risk factors is helpful and appropriate. (EN)	Thank you for your comment and support for this guideline
Royal College of Nursing	Guideline	General	General	Dear colleague, Thank you for the opportunity to contribute to this consultation. We do not have any comments on this occasion.	Thank you for your comment and support for this guideline.
Royal College of Paediatrics and Child Health	Guideline	General	General	This is a guideline for neonatal infection, inclusion of non-bacterial infection should at least be acknowledged if not covered. The important infections to consider should include; Herpes, CMV, Enterovirus.	Thank you for your comment. Viral infections were beyond the scope of this guideline and so the committee were unable to make recommendations on this. We have added a sentence in the section describing what the guideline covers to make it clear that the guideline covers bacterial infections only.
Royal College of Paediatrics and Child Health	Guideline	010	013 - 014	Recommending IAP for women who have been colonised in a previous pregnancy is likely to increase the use of IAP in situations of no or marginal benefit and harm progress towards antimicrobial stewardship. Many units do not currently recommend this, therefore there will be a significant effect on practice. In the rationale, the committee admits that there is no evidence of improved outcomes with this approach. It would be a better approach to recommend screening for GBS in the current pregnancy in women who are previously colonised.	Thank you for your comment. Thank you for your comment. GBS testing was not included in the scope for this guideline and so the committee did not consider evidence on the diagnostic accuracy of GBS tests and or the effectiveness and cost effectiveness of their use in particular scenarios. They were therefore unable to make recommendations on providing testing for GBS. However, because GBS colonisation in a previous pregnancy is strongly associated with GBS colonisation in future pregnancies, the committee thought that this was sufficient justification for intrapartum antibiotics to be offered, if no GBS test result is available.
Royal College of Paediatrics and Child Health	Guideline	011	014 - 024	Lines 12 and 23 states: "In March 2021, this was an off-label use of cephalosporins/vancomycin". This statement possibly has an error. It states March 2021 and being something in past. Please consider revising. Could it be that it is meant to be in March 2012?	Thank you for your comment. March 2021 was when they guideline had been expected to publish and so this statement was written to be relevant once the guideline

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					has been published. The expected publishing date is now April 2021, and this has been updated accordingly.
Royal College of Paediatrics and Child Health	Guideline	012	008 - 012	Recommending immediate delivery at 34-37 weeks gestation is likely to lead to more preterm delivery in this group, which may lead to increased NICU admission, respiratory distress etc. There is no mention in the rationale of these possible repercussions, only the effect on antenatal costs and infection rates. Was the impact on NICU admissions, NNU length of stay and respiratory distress modelled?	Thank you for your comment. As part of this research question, a de novo economic model was built which included the impacts of outcomes associated with immediate delivery including respiratory distress syndrome and its long-term consequences, adverse events in future pregnancies occurring as a result of caesarean section, and number of neonatal care days depending on whether or not a neonate was infected or not. Through the economic model the impact of all these outcomes were combined and estimated as quality-adjusted life-years (QALYs).The final results of the model, that captured the impact of all these outcomes, indicated that immediate delivery provided both more QALYs and was less expensive than expectant management. Full details of the model write-up, including its structure, inputs and results are available in Appendix I of Evidence Review C: PPROM. Additionally, the rationale behind the committee's recommendation can be found both in the guideline on page 37 beginning on line 19, and also in section 1.1.10 'The committee's discussion and interpretation of the evidence' in Evidence Review C:PPROM. Hyperlinks for the rationale behind the committee's recommendation and the evidence review appear below this recommendation.
Royal College of Paediatrics and Child Health	Guideline	016	001 - 030	The reviewer is pleased that the committee has recommended that the KP calculator can be used. This should be part of a systematic audit of outcomes. An explicit point should be made in section 1.3.5 that a similar audit should be carried out when using the NICE algorithm. Either that, or the audit of the KP calculator should be considered part of the audit of the NICE guideline generally. It should be highlighted that the evidence base for the KP calculator is more robust than for the NICU algorithm.	Thank you for your comment. The committee discussed whether the NICE algorithm should also be recommended as part of an audit, but they decided that as it is already part of standard practice it is more important to evaluate the Kaiser Permanente calculator. An audit is recommended for the Kaiser Permanente calculator to assess its potential for missing cases of infection. The committee were confident that the research recommendation they made for the evaluation of clinical prediction models for early-onset infection would provide

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					opportunities to compare the effectiveness and safety of the NICE algorithm and the calculator.
Royal College of Paediatrics and Child Health	Guideline	017	017 – 022	Line 19 A full stop is needed stop at the end of sentence the sentence (e.g. …shown in table 1.).	Thank you for your comment. This has been added.
Royal College of Paediatrics and Child Health	Guideline	018	001 - 007	The circulation and hydration section of Table 1 suggests HR limits. It should be emphasised that these should be a 'persistent' abnormality, to stop a one-off HR disturbance from triggering over-investigation.	Thank you for your comment. The committee discussed the circulation and hydration section of the table and agreed that it should be clarified that HR disturbances should be persistent. This has been added to the definition in Table 2.
Royal College of Paediatrics and Child Health	Guideline	018	001 - 007	The table classifies a bradycardia as HR<60. This is too low for a newborn, the reviewer would suggest <100.	Thank you for your comment. The committee discussed the HR definition for bradycardia and agreed that this should be <100 beats per minute. This has been updated in Table 2.
Royal College of Paediatrics and Child Health	Guideline	018	001 - 007	Table 1: Category – 'Other' – this should include spontaneous bleeding.	Thank you for your comment. The committee discussed the factors in the 'Other' section of the table and decided that although spontaneous bleeding can indicate late-onset infection, there are also causes of bleeding other than neonatal sepsis. They therefore decided not to add any additional factors to Table 2.
Royal College of Paediatrics and Child Health	Guideline	018	001 - 007	The review suggested that in the 'Other' section, 'temperature instability' should be added. The definition could be 'persistent variation in temperature above 37.5 and below 36.5 unexplained by environmental factors'	Thank you for your comment. The committee discussed the circulation and hydration section of the table and agreed that it should be clarified that HR disturbances should be persistent. This has been added to the definition in Table 2.
Royal College of Paediatrics and Child Health	Guideline	018	001 - 007	Persistent hyperglycaemia (blood sugar >12) should be included in the table. Consider also including persistent hypoglycaemia.	Thank you for your comment. The committee discussed the factors in the 'Other' section of the table and decided that although hyperglycaemia and hypoglycaemia can indicate late-onset infection, there are also causes of these other than neonatal sepsis. They therefore decided not to add any additional factors to Table 2.
Royal College of Paediatrics	Guideline	019	009 - 019	Although the guideline is about bacterial infection, this is an opportunity to think about herpes infection which often overlaps in its presentation features and the incidence is rising. A single	Thank you for your comment. Viral infections were beyond the scope of this guideline and so we did not review

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and Child Health				centre study from the UK showed a much higher incidence. A one-year BPSU survey result recently presented at the ESPNIC conference also showed higher rates than the previously documented evidence.	evidence on this area. The committee therefore could not make recommendations on this.
Royal College of Paediatrics and Child Health	Guideline	019	009 - 019	An approach where previously well baby presents with symptoms/signs of infection, measuring liver enzymes (ALT) would add value and can be lifesaving. ALT>50 should prompt viral, specifically HSV, investigations and the start of Acyclovir.	Thank you for your comment. Investigations for viral infections are beyond the scope of this guideline and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
Royal College of Paediatrics and Child Health	Guideline	023	018 - 024	Seven days of IV antibiotics are recommended for early onset culture negative sepsis. However, there is no evidence on the duration of antibiotic treatment. Some units give five days of IV antibiotics. A length of course of antibiotics of seven days may have implications for antibiotics stewardship, keeping mothers and babies in hospital for longer than necessary resulting in an impact on families, and will also have an impact on neonatal unit occupancy due to slowing down patient flows.	Thank you for your comment. Treatment duration for early-onset infection without meningitis was outside the scope of this guideline update and so the committee could not make or change recommendations on this.
Royal College of Paediatrics and Child Health	Guideline	024	005 - 014	Presence of a central line should impact the choice of antibiotics for suspected late onset infection. This should be acknowledged in the guideline. Coagulase negative Staph cover may need to be considered.	Thank you for your comment. None of the evidence identified specifically addressed the choice of antibiotics when a central line is in situ. The committee highlighted that the development of infection from coagulase negative staphylococci is rare, and that some babies can still be sensitive to first line antibiotic treatment. With no additional relevant evidence for this review the committee could not make more specific recommendations on the most effective choice and dose of antibiotics.
Royal College of Paediatrics and Child Health	Guideline	025	021 - 028	As above, seven days of IV antibiotics are recommended for early onset culture negative sepsis. A length of course of antibiotics of seven days may have implications for antibiotics stewardship, keeping mothers and babies in hospital for longer than necessary resulting in an impact on families, and will also have an impact on neonatal unit occupancy due to slowing down patient flows.	Thank you for your comment. The committee discussed the importance of stopping antibiotics as soon as possible if they were no longer considered necessary. For this reason, they included recommendation 1.11.6 to guide clinicians on the situations where they could stop giving antibiotics before 7 days.
Royal College of Paediatrics	Guideline	029 030	019 - 022 001 - 004	Antifungal evidence should be topical or systemic. Topical options should be: Miconazole or Nystatin. Systemic should be as is in the guideline for IV Fluconazole.	Thank you for your comment. The committee reviewed the evidence and noted that miconazole did not show any clear benefits in comparison to placebo. Nystatin and

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and Child Health					fluconazole were both shown to be more effective at reducing the cases of neonatal infection and so the committee decided that these should be recommended rather than miconazole.
Royal College of Paediatrics and Child Health	Guideline	029	019 - 024	Prophylactic nystatin, the reviewer would suggest including the dose of 0.25ml oral QDS. The reviewer also questioned whether topical miconazole should also be considered prophylactically to the nappy area.	Thank you for your comment. The committee discussed whether a specific recommendation could be made on the dose of nystatin that could be used. However, no evidence that compared different doses of nystatin was identified. The committee acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection. The committee noted that dose information was better placed in the British National Formulary (children), as this is the place that clinicians would look for dose information. The committee reviewed the evidence and noted that miconazole did not show any clear benefits in comparison to placebo. Nystatin and fluconazole were both shown to be more effective at reducing the cases of neonatal infection and so the committee decided that these should be recommended rather than miconazole.
Royal College of Paediatrics and Child Health	Guideline	029	019 - 024	The guidance for antifungals during antibiotic treatment is based on weak evidence. If this guidance is followed, there will be many babies who get antifungal treatment for antibiotic courses of </= 48 hours. The reviewer would suggest that if antifungals are recommended, it should be for courses of antibiotics >48 hours.	Thank you for your comment. The committee discussed the length of time that antibiotics are given in relation to antifungal treatment. They decided that it is often down to clinical judgement to decide this and without further evidence they were unable to provide more detailed recommendations. The committee acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research

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					on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection.
Royal College of Paediatrics and Child Health	Guideline	030	001 - 002	'Fluconazole use if nystatin cannot be used' – the reviewer suggested that a dose is recommended here.	Thank you for your comment. The committee discussed whether a specific recommendation could be made on the dose on fluconazole that could be used. However, evidence comparing different doses of fluconazole did not favour one dose over another. The committee agreed that dose information was better placed in the British National Formulary (children), as this is the place that clinicians would look for dose information. The committee agreed that there was good evidence that giving preventative antifungal prophylaxis to neonates who were born at less than 30 weeks' gestation or with birthweight under 1500g or would be cost effective. However, they acknowledged that there is considerable uncertainty about the optimum treatment regimen (including dose and duration). They therefore made a research recommendation for research on the optimum regimen for preventative antifungals given to babies treated with antibiotics for late-onset neonatal infection.
The Royal College of Midwives	Guideline	General	General	*There is no mention of women who decline antibiotics in labour. Or women who do not receive antibiotics on time due to precipitate birth. How long will the baby need monitoring postnatally with antibiotics if risk factors are present? *There is variation across the UK when women receive antibiotics with 24 hours PROM. Some units offer after 24 hours, others 48 hours. Could this be addressed?	Thank you for your comments. The committee discussed how babies with risk factors for early-onset neonatal infection should be monitored, even if women do not receive antibiotics in labour for whatever reason. They decided against adding more information to the recommendation, but more explanation about this has been added to the rationale section. Duration of monitoring is covered in recommendation 1.3.5 and in the section on duration of antibiotic treatment for early-onset infection (section 1.6).

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				*There is no mention of women who test privately using the Enhanced Culture Medium (ECM)- that if she has GBS, then her care should be the same as If this test was performed by the NHS *We are concerned that there is no mention of women who decline antibiotics in labour. Or women who do not receive antibiotics on time due to precipitate birth. How long will the baby need monitoring postnatally with antibiotics if risk factors are present? There is evidence of variation across the UK when women receive antibiotics with 24 hours PROM. Some units offer after 24 hours, others 48 hours. Should this be addressed?	Management of women prelabour rupture of membranes at term is covered in the NICE guideline on intrapartum care and was not included in the scope of this guideline. A link to that guideline has been included in the section on risk factors for early-onset infection in this update. The recommendations in this guideline that refer to women with GBS do not make any distinction between NHS or private GBS testing for a positive test result. Although some tests may have higher false positive rates, all women with positive tests should be treated as if they have GBS so that no mothers who have babies who are at higher risk of infection are missed. Discussions with women who have tested positive for GBS should be the same irrespective of where the test result is from. The committee were more concerned about a woman not receiving treatment as a result of a false negative test result, and so they decided to specify that a negative test should be from enrichment culture or PCR on rectovaginal swab samples.
The Royal College of Midwives	Guideline	007	014	Suggest: The need for antibiotics in labour, whether determined from screening or from risk assessment, should be flagged up by writing GBS on the partogram or on the maternal records where clinicians are easily able to spot the information.	Thank you for your comment. This was out of scope for this guideline update, so the committee were unable to make recommendations on this.
The Royal College of Midwives	Guideline	012	002	Comment: *Please elaborate further. There is a variation with clinicians as to the timing of administering the first dose. Is it from SROM and regular contractions? Or is it SROM without contractions or irregular contractions? Or would giving the first dose be defined as 3-4cm dilated with regular contractions?* Ideally, you would want the antibiotics in the mother's system for at least 4 hours before she gives birth; multiparas progress very quickly if we are waiting on regular contractions.	Thank you for your comment. The committee discussed the timing of the first dose and decided that providing a more detailed description of labour, such as established labour, is likely to lead to many women not receiving antibiotics at least 4 hours before delivery.

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The Royal College of Midwives	Guideline	012	008	We are concerned about the recommendation. Rewording the recommendation in terms of benefits of risks and of IOL and CS should be discussed with woman. And overall clinical picture. What about prophylaxis antibiotics as the first line? What if she is asymptomatic (CRP/Apyrexial?). Risks of PTB and TTN and waiting until she gets to 37/40 This recommendation will be challenging: What if an 'immediate birth cannot be offered' due to acuity and staff shortage, and there is a delay (specifically asymptomatic women/FHR NAD) (**possible litigious implications 'breach of duty' and raised anxiety for the women**) Please share the evidence surrounding asymptomatic women with PRROM receiving abx and neonatal outcomes?	Thank you for your comment. This recommendation is to offer a woman immediate birth. The term 'offer' means that a discussion will be had with the woman, and this should include discussion of the benefits and risks of immediate birth. The committee believed that a woman with ruptured membranes who is in labour should be offered intrapartum antibiotics in line with the recommendations in the section on intrapartum antibiotics. This recommendation is also about a small group of women who are known to be GBS positive. The subheading of this section has been amended to clarify this. For information on antibiotics during labour and the committee's discussion of this evidence, please see the evidence review on intrapartum antibiotics.
The Royal College of Midwives	Guideline	049	001	Statistics would be helpful We were looking for further explanation on why a small portion of women carrying GBS will cause disease, either in the woman or in her baby. For example: In these women, the organism acts as a pathogen causing maternal puerperal sepsis and neonatal septicaemia, whether of which may lead to death. It is not possible to eradicate GBS. Therefore therapy is aimed at those who are known to be carriers at the time of most significant risk (i.e at birth)	Thank you for your comment. This guideline reviewed the risk factors for neonatal infection rather than the mechanisms that explain why GBS colonisation in the mother leads to infection in some babies and not others. As such, an explanation on this is not included in the guideline.
The Royal College of Midwives	Guideline	59	020 - 030	Neonatal Sepsis Calculator https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30232-9/fulltext There needs to be more emphasis on why the sepsis calculator should be used as a prospective audit. A large proportion of EOS cases were 'missed' by the calculator. Further evaluation of the calculator is recommended before rollout into UK clinical practice as some units are using this	Thank you for your comment. The Pettinger 2019 paper did not meet the inclusion criteria for the review, but the results were discussed by the committee. More information on their discussions is available in the 'Other factors the committee took into account' section in the evidence review. We have added extra information to the rationale and impact section of the guideline to explain why an audit is needed. This will provide further evaluation of the effectiveness of the calculator before it can be used more

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					widely in clinical practice without the need to audit it's use. More detailed information is also included in Evidence review D: Risk factors for early-onset infection.
UK Clinical Pharmacy Association Infection Committee	Guideline	General	General	To consider cover for resistant organisms if baby/mother is at higher risk of colonisation e.g MRSA. No mention of this within guidance.	Thank you for your comment. Treatment options for when a baby or mother is at higher risk of colonisation were out of scope for this guideline update. The committee therefore did not review evidence on this and so they were unable to make recommendations. The committee also thought that it would be difficult to identify when a mother or baby is at higher risk of colonisation and so it would be difficult to make a specific recommendation on this.
UK Clinical Pharmacy Association Infection Committee	Guideline	021	006	At GSTFT we recommend a starting dose of 50mg/kg TDS benzylpenicillin for terms babies & 50mg/kg BD for pre-term babies to cover for potential CNS infection – however appreciate that the BNF-C dosing for neonatal sepsis is 25mg/kg BD	Thank you for your comment. This comment is on a section of the guideline that was not updated as part of this update. The committee did not review evidence on antibiotic treatment for early onset neonatal infection and so we cannot make changes to this recommendation.
UK Clinical Pharmacy Association Infection Committee	Guideline	021	1.8	Empirical dosing of benzylpenicillin for early-onset infection is 25mg/kg. Consider adding in statement to use 50mg/kg per dose where CNS cover is required to achieve higher bactericidal concentration in CSF.	Thank you for your comment. Antibiotics for suspected early-onset infection were outside the scope of this guideline update and so the committee could not make or update recommendations on this.
UK Clinical Pharmacy Association Infection Committee	Guideline	027	011 - 021	The rationale for continued gentamicin in neonate with confirmed GBS is unclear. The in vitro sensitivity for this agent is poor and penetration in to CSF is likely sub-optimal. Is a beta-lactam monotherapy not sufficient? The CG102 for bacterial meningitis recommends cefoTAXime IV for this indication which contradicts this recommendation.	Thank you for your comment. This comment is on a section of the guideline that was not updated as part of this update. The committee did not review evidence on antibiotic treatment for meningitis when the bacteria was known and so we cannot make changes to this recommendation.
UK Clinical Pharmacy Association Infection Committee	Guideline	029	019	At GSTFT prophylactic antifungal treatment (PO/IV fluconazole) is recommended for babies that meet the following criteria: <26 weeks gestation <800g birth weight Therapy is continued for 6 weeks until unless ETT & all invasive plastic removed	Thank you for your comment. The committee made recommendations on prophylactic antifungal treatment based on evidence on clinical and cost effectiveness and concluded that preventative antifungals should be given to babies receiving antibiotics for late-onset neonatal infection who were born at <30 weeks gestation age or who have a birthweight of <1500g.

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				Prophylactic antifungal treatment is not routinely started when antibiotics are started for empiric treatment of late onset neonatal infection however fungal sepsis is considered in culture negative sepsis	
University Hospitals Southampton NHS Foundation Trust	Guideline	General	General	We thank NICE for including Late onset sepsis (LOS) and Early onset sepsis (EOS) in this guideline. However, we find the layout confusion and am not sure that jumping between EOS and LOS helps the reader. We suggest amended the layout of the guidance so that the general principles of antibiotic use in neonates is discussed (1.6), then EOS (1.2 – 1.3-1.8-1.9) then LOS (1.4 – 1.10 – 1.11) followed by meningitis in neonates. Section 1.7 is challenging as it tries to amalgamate investigations for EOS and LOS. Either this section needs to be amended (as some recommendations apply only to EOS yet this is not clear in the current version (i.e. recommendation not to perform a urine culture which is correct for EOS but incorrect for LOS) or split into "Investigations for EOS" and "Investigations for LOS".	Thank you for your comment. We have reordered the sections of the guideline in response to this comment and those of other stakeholders to improve the flow of the recommendations. We now group all of the recommendations on early-onset infection together followed by those on late-onset infection. The committee discussed the use of urine culture as a test for late-onset infection. Recommendation 1.9.4 is for babies in a neonatal unit where a urine culture would not routinely be done. This has now been clarified in the recommendation, and an additional recommendation has been added which indicates that urine microscopy and culture should be performed for babies outside of the neonatal unit, in line with the NICE guideline on urinary tract infection.
University Hospitals Southampton NHS Foundation Trust	Guideline	012	007	We are concerned that this recommendation has not fully explored published economic and health impact evidence about being born Late Preterm. The wording concentrates on risk of infection but there is no comment about increased risk of other comorbidities after being born Late Preterm. We do not think they have adequately assessed the harm that immediate delivery does in the longer term and it remains unclear how many babies (and families) are harmed as collateral in preventing a long term sepsis related outcome.	Thank you for your comment. As part of this research question, a systematic review of the economic literature was undertaken. Only one paper met criteria for inclusion. This paper was partially applicable, as the outcomes of the analysis were not quality-adjusted life years (QALYs) as preferred by NICE. The study, however, showed in two separate analyses, using different outcomes, that immediate delivery resulted in a reduction in the odds of sepsis but an increase in the odds of respiratory distress syndrome (RDS). Full details of this search and its results are available in sections 1.1.7 'Economic Evidence' and 1.1.8 'Summary of the included economic evidence' in Evidence Review C: PPROM. In addition to this review of the literature, a de novo economic model was built which included the impacts of several outcomes associated with

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					immediate delivery including the long-term impacts of infection, RDS and its associated long-term consequences, adverse events in future pregnancies occurring as a result of caesarean section, and number of neonatal care days depending on whether or not a neonate was infected or not. Through the economic model the impact of all these outcomes were combined and estimated as QALYs. The final results of the model, that captured the impact of all these outcomes, indicated that immediate delivery provided both more QALYs and was less expensive than expectant management. Full details of the model write-up, including its structure, inputs and results are available in Appendix I of Evidence Review C: PPROM. A hyperlink to the full evidence review appears below this recommendation.
University Hospitals Southampton NHS Foundation Trust	Guideline	019	011	Blood culture is recognised as a gold standard investigation. The volume of blood taken has a huge impact on the sensitivity of blood cultures – should the guideline include a suggested volume of blood ie 0.5ml minimum.	Thank you for your comment. This section of the guideline is intended to provide recommendations on the investigations that should take place before starting antibiotics. However, it is not designed to provide more detail on clinical techniques and best practice.
University Hospitals Southampton NHS Foundation Trust	Guideline	019	016	The guidelines suggest lumbar puncture if strong clinical suspicion of neonatal infection. There is a large volume of data suggesting that in babies <28 month with a confirmed urinary tract infection and no clinical suspicion of meningitis, then the risk of concurrent meningitis is extremely low (Nugent J, Childers M, Singh-Miller N et al. Risk of Meningitis in Infants Aged 29 to 90 Days with Urinary Tract Infection: A Systematic Review and Meta-Analysis. J Pediatr 2019; 212: 102-10 e5). Should this be recognised in the guidelines?	Thank you for your comment. Recommendation 1.7.3 (now 1.9.3) is referring to all babies with suspicion of infection, rather than those who already have a confirmed UTI. As it takes time to confirm a UTI, it is likely that the lumbar puncture results would be known before the UTI is confirmed.
University Hospitals Southampton NHS	Guideline	020	001	This suggests that urine culture should not be performed in babies in whom late onset sepsis is being suspected. This is clearly incorrect and I suspect was meant to suggest that routine urine microscopy and culture is not required in babies in whom early onset sepsis is being suspected.	Thank you for your comment. The recommendation against the use of urine culture is for babies in a neonatal unit where this would not routinely be done. This has now been clarified in the recommendation. An additional recommendation has also been added which indicates that

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Foundation Trust					urine microscopy and culture should be performed for babies outside of the neonatal unit, in line with the NICE guideline on urinary tract infection.
University Hospitals Southampton NHS Foundation Trust	Guideline	022	016 - 019	Many thanks for removing the CRP cut-off of 10mg/L. This previous cut-off has resulted in a huge number of neonates unnecessarily receiving prolonged courses of IVAbs and lumbar punctures. The evidence of inflammatory marker rise in early onset sepsis (EOS) is difficult to interpret but this document now does not give any guidance. I am worried that people will continue to use 10 as no new guidance has been provided, so there won't be a change in the number of well babies receiving prolonged courses of antibiotics for suspected EOS.	Thank you for your comment. Although this guideline update considered investigations for late-onset infection, investigations for early-onset infection were out of scope. During the update of the guideline, concerns were raised about the CRP cut-off of 10 mg/l for early-onset infection and so we were able to remove this from the recommendations. However, as this section of the guideline was out of scope, the committee did not review any evidence on this and were therefore unable to make any further changes to this recommendation.
University Hospitals Southampton NHS Foundation Trust	Guideline	023	009	Many thanks for removing the CRP cut-off of 10mg/L. This previous cut-off has resulted in a huge number of neonates unnecessarily receiving prolonged courses of IVAbs and lumbar punctures. The evidence of inflammatory marker rise in EOS is difficult to interpret but this document now does not give any guidance. I am worried that people will continue to use 10 as no new guidance has been provided, so there won't be a change in the number of well babies receiving prolonged courses of antibiotics for suspected EOS.	Thank you for your comment. CRP levels for early-onset infection were out of scope for this guideline update and so we did not review evidence on this area. The committee therefore could not make recommendations on this.
University Hospitals Southampton NHS Foundation Trust	Guideline	025	003	Suggests performing LP is "there is a strong clinical suspicion of infection". There is a large volume of data suggesting that in babies <28 month with a confirmed UTI and no clinical suspicion of meningitis, then the risk of concurrent meningitis is extremely low (Nugent J, Childers M, Singh-Miller N et al. Risk of Meningitis in Infants Aged 29 to 90 Days with Urinary Tract Infection: A Systematic Review and Meta-Analysis. J Pediatr 2019; 212: 102-10 e5). Should this be recognised in the guidelines?	Thank you for your comment. Recommendation 1.9.3 is referring to all babies with suspicion of infection, rather than those who already have a confirmed UTI. As it takes time to confirm a UTI, it is likely that the lumbar puncture results would be known before the UTI is confirmed.
University Hospitals Southampton NHS	Guideline	026	001	There is no comment here about whether a central line catheter is in situ so therefore no safety net. You can have CONS and this is significant if a central line is in situ and should receive a longer course of antibiotics.	Thank you for your comment. The committee discussed this but believe that it is already addressed by the current wording of recommendation 1.11.5, where there is reference to central venous catheters in the third bullet point.

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