NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive (post-consultation)

Clinical guideline

CG102: Bacterial meningitis and meningococcal septicaemia: Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care

Publication date

June 2010

Surveillance report for GE (post-consultation)

February 2015

Surveillance recommendation

GE is asked to consider the following proposal which was consulted on for two weeks:

- The bacterial meningitis guideline should not be considered for an update at this time.

- GE is also asked to consider withdrawing reference to throat swabs in Section 5.4 of the guideline relating to skin samples and throat swabs as the recommendation is not aligned with recommendations in extant Public Health England/Health Protection Agency guidance: Guidance for public health management of meningococcal disease in the UK. It is proposed that recommendation 1.3.14, which explicitly recommends against taking throat swabs, be amended to remove reference to throat swabs.

Key findings

	Potential impact on guidance	
	Yes	**No**
Evidence identified from Evidence Update		✓
Evidence identified from literature search		✓
Feedback from Guideline Development Group	✓	
Feedback from stakeholders during consultation	✓	
Anti-discrimination and equalities considerations		✓

No update	CGUT update	Standard update	Transfer to static list	Change review cycle
✓				

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Surveillance review of CG102: Bacterial meningitis and meningococcal septicaemia: Management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care

Recommendation for Guidance Executive (post consultation)

Background information

Guideline issue date: June 2010
4 year review: 2014

NCC: National Clinical Guidelines Centre

Four year surveillance review

1. An Evidence Update was produced for the guideline in 2012 and was used as a source of evidence for the review proposal. The Evidence Update considered new evidence from 1st January 2008 to 31 July 2011. The Evidence Update indicated that there is currently insufficient new evidence to invalidate the guideline recommendations.

2. A literature search was conducted for randomised controlled trials and systematic reviews between 31st July 2011 (the end of the search period for the Evidence Update) and 4th November 2014 and relevant abstracts were assessed. Clinical feedback was also obtained from members of the guideline development group (GDG) through a questionnaire survey. Half of the questionnaire respondents were not

aware of any evidence that would change the current guideline recommendations and felt that CG102 Bacterial Meningitis and meningococcal septicaemia did not require an update at this time.

3. A further focused search, covering the same period as the main literature search, was conducted for randomised controlled trials, systematic reviews and observational studies on the review question: What is the diagnostic value of throat swabs in children and young people with suspected meningococcal disease?

4. No new evidence was identified through the literature search which would invalidate the guideline recommendations.

Ongoing research

5. An ongoing randomised controlled trial on corticosteroid therapy in childhood severe sepsis (ClinicalTrials.gov NCT00732277) is relevant to recommendation 1.4.45 on units of dosing for corticosteroids for meningococcal septicaemia. It has potential to impact on the guideline recommendation which is inconsistent with the BNF dosing units (per/kg). The trial will evaluate outcomes in children and young people with sepsis (including meningococcal sepsis) who receive low dose hydrocortisone. The dosage of hydrocortisone administered in the study is expressed as mg/m^2 and may provide further evidence in favour of these units of dosage.

6. An ongoing cohort study, The UK Childhood Meningitis and Encephalitis Study; UK-ChiMES (http://www.encephuk.org/studies/ukchimes.aspx), is a cohort study of the aetiology, clinical features and outcomes of childhood meningitis, and may provide new information on rates of disease. It has potential relevance to CG102 recommendations 1.1.1-1.1.9 on symptoms, signs and initial assessment.

7. An ongoing cohort study is relevant to the clinical area of long term management, particularly relating to recommendation 1.5.5 on post discharge follow up: The burden of bacterial meningitis in newborn babies in the UK and Ireland: establishing standards of care to improve the outcome. Meningitis Research Foundation. (http://www.meningitis.org/current-projects/the-burden-of-bacterial-22643)

Anti-discrimination and equalities considerations

8. None identified.

Implications for other NICE programmes

9. This guideline relates to a published Quality Standard on Bacterial meningitis and meningococcal septicaemia (QS19). A no to update decision for this guideline is unlikely to impact on the Quality Statements of QS19.

Summary of stakeholder feedback

10. Stakeholders were consulted on the following proposal over a two week consultation period:

The Bacterial meningitis and meningococcal septicaemia guideline should not be considered for an update at this time.

11. In total, fourteen stakeholders commented on the surveillance review proposal recommendation during the two week consultation period. The table of stakeholder comments can be viewed in Appendix 1.

12. Eight stakeholders agreed with the surveillance review proposal to not update the guideline at this time and six stakeholders disagreed.

13. The Diagnostic value of throat swabs
    Two of the stakeholders that disagreed with the decision not to update the guideline felt that the recommendation against using throat swabs when investigating for possible meningococcal disease should either be removed or amended to recommend the use of throat swabs in all suspected cases, in line with extant Public Health England guidance. The clinical guideline considered the use of throat swabs in establishing a clinical diagnosis of bacterial meningitis and the GDG decided, after reviewing the evidence, that throat swabs did not add to the clinical diagnosis. However, the clinical guideline did not consider the additional value of throat swabs in outbreak investigation and tracking resistance, which are the basis of the Public Health England recommendation.

14. No evidence was cited, and there was insufficient new evidence on the use of throat swabs identified through a focused literature search to impact on the recommendation. However, the stakeholders made a forceful case that failure to take throat swabs early on hampers outbreak investigation and tracking of subtypes/resistance. It is therefore proposed that recommendation 1.3.14 be amended to remove reference to throat swabs, and related text specific to throat swabs in section 5.4 of the guideline be withdrawn.

13 Other stakeholder comments related to long-term effects of bacterial meningitis, combinations of symptoms and signs in diagnosis, treatment of raised intracranial pressure, treatment with corticosteroids, and first line antibiotic treatment with cefotaxime or ceftriaxone. The following is a summary of the general comments made by the stakeholders that disagreed with the surveillance review proposal:

14 Combinations of symptoms and signs in diagnosis

One stakeholder highlighted the importance of identifying combinations of, as opposed to individual, signs and symptoms. No evidence was cited, and no new evidence was identified in the surveillance review to address the question of which combinations(s) of symptoms and signs have diagnostic value in investigating suspected cases. This area may be addressed through the ongoing research identified on symptoms and signs and will be evaluated again at the next surveillance review of the guideline. In particular, the UK CHIMES study is a cohort study of the aetiology, clinical features and outcomes of childhood meningitis. It has potential relevance to CG102 recommendations 1.1.1-1.1.9 on symptoms, signs and initial assessment.

15 Treatment of raised intracranial pressure

One stakeholder highlighted evidence on cerebral perfusion pressure for raised intracranial pressure. Assessment of the abstract revealed that although the study was a randomised controlled trial, it would not impact on the guideline. CG102 does not make specific recommendations for treatment of raised intracranial pressure, but defers to local or national protocols.

16 Treatment with corticosteroids

One stakeholder raised a query relating to the reference to the CG102 recommendations on corticosteroids in surveillance review impact statement. The wording of the impact assessment has been amended to clarify the neonatal population concerned. No new evidence was identified or highlighted by stakeholder feedback to impact on the recommendations concerned.

17 First line antibiotic treatment with cefotaxime or ceftriaxone

A GDG member raised the question of whether cefotaxime or ceftriaxone should be used as first line treatment, and commented that preparing ceftriaxone as an infusion with an IV line can take longer than just giving a slow injection of cefotaxime. No evidence was cited. The evidence review conducted during guideline development found that there was insufficient evidence to reach a conclusion about whether cefotaxime or ceftriaxone is more effective for empiric treatment of bacterial meningitis and recommendations were based on cost effectiveness data. No evidence was found in the surveillance review to impact on the current recommendations.

18 Long term effects of bacterial meningitis

One stakeholder cited observational study evidence on long-term effects of bacterial meningitis and stated that this supports the need for longer term follow up than the 4-6 week follow up that is currently recommended in CG102. The issue of long term follow up was also raised via clinical feedback during the surveillance review and a large ongoing cohort study being undertaken by the Meningitis Research Foundation was cited as potentially providing important information in this area. The results of this study, in addition to the UK CHIMES study identified by clinical feedback, the case control study cited by the stakeholder, and other available evidence will be evaluated at the next surveillance review point in order to assess impact on CG102.

Conclusion

19 Through the 4 year surveillance review of CG102 no new evidence which may potentially change the direction of guideline recommendations was identified. The proposal is not to update the guideline at this time. However, the guideline should remain on the active surveillance list, due to ongoing research that may have a potential impact on recommendations on symptoms, signs and initial assessment, management in secondary care, and long term management.

20 It is proposed that all references to throat swabs in Section 5.4 of the guideline relating to skin samples and throat swabs should be withdrawn because the recommendation against using throat swabs when investigating for possible meningococcal disease is not aligned with recommendations in extant Public Health England guidance: Guidance for public health management of meningococcal disease in the UK.

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Philip Alderson – Consultant Clinical Adviser
Steve Sharp – Technical Analyst

Centre for Clinical Practice
February 2015

Appendix 1 Surveillance review consultation

Surveillance review consultation comments table
12-23 January 2014

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Meningitis Now	I would like to draw attention to evidence on the burden of meningococcal disease – see comments column – so that this can be considered in the next review alongside any evidence from the Meningitis Research Foundation study listed in the surveillance review document.		**What proportion of children and young people with bacterial meningitis develop physical and psychological morbidity?** Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, Kaczmarski E, Rajput K, Ramsay M and Christie D. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study *Lancet Neurol* 2012; **11:** 774 – 783 These children had meningococcal disease between the ages of one month and 13 years, and were followed up three years post disease. The findings show that……more than a third have one or more deficits	Thank you for your comments and for highlighting the reference relating to disease burden and follow up. The issue of long term follow up was also raised via clinical feedback during the surveillance review. A large ongoing cohort study being undertaken by the Meningitis Research Foundation was cited. The results of this study, in addition to the MOSAIC study and other available evidence, will be reviewed at the next surveillance review point in order to assess impact on the CG102 recommendation 1.5.5, which states that children and young people should be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital to discuss morbidities associated with their condition and offered referral to the appropriate

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			in physical, cognitive and psychological functioning, with the additional burden of memory deficits and executive functioning. These findings ……..suggest that all survivors of meningococcal disease should be screened for psychological disorders and cognitive deficits in addition to hearing loss. We feel that this evidence supports the need for longer term follow-up and improved information for healthcare professionals and parents about the longer term impact of the disease. Meningitis Now and Meningitis Research Foundation have jointly produced a resource “My Journal, Your Guide” to try and address this lack of information. http://www.meningitisnow.org/how-we-help/our-support-services/my-journal/	services. NICE also recognises in CG102 the potential long term sequelae in the recommendation 1.5.7: Healthcare professionals with responsibility for monitoring the child's or young person's health should be alert to possible late-onset sensory, neurological, orthopaedic and psychosocial effects of bacterial meningitis and meningococcal septicaemia.
Digital Assessment Service, NHS Choices	Agree			Thank you
University hospital of Leicester	Disagree		Thank you for reviewing the guideline and the recent evidence. We agree that most of the recent evidence has	Thank you for your comments and for highlighting the trial relating to raised intracranial pressure.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			been looked into and agree that the guideline may not need to be revised. Except for one article which should be considered before we decide whether the guideline should be updated or not. The evidence we are taking about is: Randomized Controlled Trial Comparing Cerebral Perfusion Pressure–Targeted Therapy Versus Intracranial Pressure–Targeted Therapy for Raised Intracranial Pressure due to Acute CNS Infections in Children: in Critical Care Medicine www.ccmjournal.org 2014 • Volume XX • Number XXX by Singhi S et al. This is one of rare article which is done in children's, it is a RCT and not sure if it can be repeated. We feel that in acute brain infection e.g. meningitis like traumatic brain injury there might be benefit in targeting CPP. We would also like to know what the committee's view on this evidence; for our own benefit as well. What the committees decides after reviewing the article we will be happy to go with that.	Assessment of the abstract revealed that although the study was a randomised controlled trial, it would not impact on the guideline. CG102 does not make specific recommendations for treatment of raised intracranial pressure, but instead advises that children with signs of raised intracranial pressure should preferably be managed in consultation with a paediatric intensivist. The GDG was of the opinion that local or national protocols should be available and used for the treatment of raised intercranial pressure in children and young people with suspected bacterial meningitis (recommendation 1.4.20).
GDG Member	Disagree	– see below. Clinical diagnosis relies of a	Is there a combination of symptoms and signs which increase the likelihood of:	Thank you for your comments relating to signs and symptoms and first line antibiotic treatment.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
		combination of symptoms and signs to stimulate investigations and then treatment. Single symptoms and single signs are not usually useful in clinical diagnosis Should cefotaxime or ceftriaxone be used first line?	a) Bacterial meningitis b) Meningococcal septicaemia c) Meningococcal disease (i.e. septicaemia and meningitis) and which would assist clinicians in deciding which children to investigate and treat? assist clinicians in deciding which children to investigate and treat? Ceftriaxone has to be given as an infusion and preparing this and an IV line can take longer than just giving a slow injection of cefotaxime.	<u>Signs and Symptoms</u> The new evidence identified in the Evidence Update and surveillance review was considered to be consistent with the guideline recommendation 1.1.1 on signs, symptoms and initial assessment, which states that some children and young people will present with mostly non-specific symptoms or signs, and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way. It further states that fever and seizure are two of several non-specific signs and symptoms to be considered, but that children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia. No new evidence was identified to address the question of which combinations(s) of symptoms and signs have diagnostic value in investigating suspected cases. This area may be addressed through the ongoing research identified on symptoms and signs and will be evaluated again at the next surveillance review of the guideline. In

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
				particular, the UK CHIMES study is a cohort study of the aetiology, clinical features and outcomes of childhood meningitis. It has potential relevance to CG102 recommendations 1.1.1-1.1.9 on symptoms, signs and initial assessment. Antibiotics for suspected bacterial meningitis or meningococcal disease Recommendations 1.4.1-1.4.17 cover antibiotic treatment for suspected and confirmed bacterial meningitis or meningococcal disease. The evidence review conducted during guideline development found that there was insufficient evidence to reach a conclusion about whether cefotaxime or ceftriaxone is more effective for empiric treatment of bacterial meningitis and recommendations were based on cost effectiveness data. No evidence was found in the surveillance review to impact on the current recommendations. Any emerging evidence relating to cefotaxime versus ceftriaxone in first line treatment will be reviewed at the next surveillance review point.
Royal College of Obstetricians and Gynaecologists	Agree			Thank you.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Novartis Vaccines	Disagree	Importance of cultured meningococci in ongoing surveillance of disease in the UK	**Suggestion- that routine throat swab in individuals suspected of meningococcal disease is recommended for epidemiological purposes.** The current guideline is clear and evidence based on the subject of throat swabs for diagnostic purposes. However in discussion with Professor Ray Borrow at the Meningococcal Reference Unit I have learned that an unintended consequence of the current guidance is that <50% of meningococcal diagnoses are now made by culture. As PCR is limited as a technique for checking coverage of a protein based vaccine due to variable expression of encoded proteins by strains, this has an important effect on the ability to judge the efficacy and coverage of the licensed Meningitis B vaccine Bexsero for a patient's disease. This has both direct and indirect effects on patient care. Directly it makes managing an outbreak situation more difficult, and this makes it difficult to advise whether vaccination of contacts will be a useful intervention. Indirectly it makes it difficult to check the real world efficacy of the vaccine as it can be impossible without a cultured organism to assess	Thank you for your comments on whether throat swabs should be taken for epidemiological purposes. As a clinical guideline, CG102 makes recommendations for individual patient diagnosis and management. Its scope does not currently cover prevention, including vaccination. These are covered by related Public Health England guidance: Guidance for Public Health Management of Meningococcal Disease in the UK. Whilst there is insufficient evidence to justify changing CG102 recommendation 1.3.14 to advise taking throat swabs in all suspected cases, we recognise that opposing recommendations between the NICE and Public Health England guidelines could be a source of potential confusion. It is therefore proposed that recommendation 1.3.14 be amended to remove reference to throat swabs and that related text specific to throat swabs be withdrawn.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			whether the infection was vaccine type or not is whether this was a vaccine failure or not. This is particularly important in the immunosuppressed individuals that Bexsero is currently recommended in, but will have a wider significance when a national infant vaccination campaign is started as it will limit the ability of Public Health England to assess the efficacy of the vaccine campaign, as understanding disease epidemiology and vaccine coverage (enabled through culture) provides the basis for optimising the national vaccination schedule and allows for maximum prevention of Invasive Meningococcal Disease in children.	
The Royal College of Paediatrics and Child Health	Agree		Disappointingly, not much new evidence to answer the important questions raised by the original guideline, e.g. when to give steroids, duration of treatment. Advent of new Men B vaccine will change epidemiology so important to consider further revisions in future.	Thank you for your comments. The areas you have highlighted will be evaluated again at the next surveillance review of the guideline.
Neonatal and Paediatric Pharmacists Group (NPPG)	Agree			Thank you.
The Royal			The Royal College of Nursing invited	Thank you.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
College of Nursing			members who expressed interest in this topic to review this surveillance review proposal and no comments were received. There are no comments to make on behalf of the RCN at this time.	
Department of Health			I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
NHS England			I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you.
British Infection Association	Disagree		The BIA is broadly in agreement that the guideline should not be updated. However, we would seek clarification on the following, and suggest that an update might be appropriate if our concern is well-founded: 1. In the Surveillance review consultation document it states in relation to Q: Should corticosteroids be used in the treatment of children and young people with suspected/confirmed bacterial meningitis?	Thank you for your comments relating to adjuvant therapy with corticosteroids. The wording of the impact assessment has been amended as follows to clarify the neonatal population concerned: The systematic review evidence from the Evidence Update and the surveillance review has revealed insufficient evidence of benefit of adjuvant therapy with corticosteroids in neonates. This is consistent with CG102, which does not recommend the use of corticosteroids in children younger than 3 months with suspected or confirmed bacterial meningitis (recommendation 1.4.39).

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			"The systematic review evidence from the Evidence Update and the surveillance review has revealed insufficient evidence of benefit of adjuvant therapy with corticosteroids. This is consistent with CG102, which does not recommend adjuvant therapy." Yet in the CG102 Guideline, it states: 1.4.40 Give dexamethasone (0.15 mg/kg to a maximum dose of 10 mg, four times daily for 4 days)[12] for suspected or confirmed bacterial meningitis as soon as possible if lumbar puncture reveals any of the following: • frankly purulent CSF • CSF white blood cell count greater than 1000/microlitre • raised CSF white blood cell count with protein concentration greater than 1 g/litre • bacteria on Gram stain. Is this an error because the guideline does recommend dexamethasone? Or has the guideline been changed? The BIA Guidelines on the treatment of meningitis will recommend a dosage period of 5 days for adults who are	CG102 Research recommendation 4.4 on adjunctive corticosteroid treatment in neonates is only partially addressed by current evidence, and further research is needed specific to the neonatal population before it can be considered for inclusion in CG102 The totality of systematic review evidence from the Evidence Update and the surveillance review is consistent with recommendation 1.4.40 for administering dexamethasone to children over 3 months. New evidence identified in the 4 year surveillance review is unlikely to impact on CG102 recommendation 1.4.45 due to inconclusive results. The recommendation states that in children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 25 mg/m2 four times daily)] should be used only when directed by a paediatric intensivist. In relation to the BIA guideline recommendation on the dosage period for adults and the proposal for consistent recommendations in CG102, the scope of CG102 does not cover people over 16 years old.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			responding well. If you proceed with an update, can this be included so that we have a consistency between the guidelines? BIA will supply the evidence base.	
The Royal College of Pathologists	Agree		The findings of the ongoing research studies will need to be reviewed at the time of completion of those studies in terms of its impact on the current guidelines and for the need for any changes at a later stage.	Thank you for your comments. The results and conclusions of the ongoing research will be evaluated at the next surveillance review, along with additional emerging evidence to assess impact on CG102 recommendations.
Meningitis Research Foundation	Disagree		We understand that NICE has already considered whether throat swabs should be taken to investigate possible meningococcal disease, as recommended in PHE guidelines, and concluded that the evidence is for doing so is not strong enough to change the current NICE recommendation NOT to use throat swabs. We argue that having 2 guidelines for the same illness with opposing recommendations reduces the credibility of guidelines. Even if NICE cannot recommend using throat swabs because the strength of evidence is insufficient, it would surely be better for NICE to make no recommendation on throat swabs at all.	Thank you for your comments on whether throat swabs should be taken to investigate possible meningococcal disease. Whilst there is insufficient evidence to justify changing the relevant recommendation in CG102 (1.3.14) to advise taking throat swabs in all suspected cases, we recognise that opposing recommendations between the NICE and Public Health England guidelines could be a source of potential confusion. It is therefore proposed that recommendation 1.3.14 be amended to remove reference to throat swabs and related text specific to throat swabs be withdrawn.

Appendix 2 Decision matrix

The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
102-01: In children and young people up to 16 years of age, what symptoms and signs or combination of symptoms and signs are predictive of bacterial meningitis?			
A systematic review[1] assessed the clinical features of serious infections (not just meningitis) in children aged 1 month to 18 years in ambulatory care in the developed world (30 studies; 14,453 patients), found 'red flag' symptoms that were in agreement with those identified in CG102.The diagnostic accuracy of 'red flag' symptoms of children with meningococcal disease in primary care were studied further by the same group[2] in a two sample comparison study of children aged 1 month to 16 years. Parents of children with an acute self-limiting infection (n = 407) were asked about symptoms experienced by their child, and the findings compared with the symptoms reported by parents of children with meningococcal	<u>Febrile Seizure</u> Two systematic reviews examined the risk of bacterial meningitis, as diagnosed by lumbar puncture, in children presenting with febrile seizure. The first review[4] included 2 studies (n=150) of children with simple febrile seizure and concluded that the sample sizes were too low for definitive conclusions, but that the findings suggested low risk of bacterial meningitis. The second review[5] included fourteen studies examining subgroups of first seizure and fever, simple febrile seizure, and apparent complex febrile seizure. In all subgroups the risk of bacterial meningitis was low. The review also indicated that the utility of lumbar puncture in these subgroups was low (see 102-11). <u>Meningeal Irritation Signs</u> A systematic review[6] addressed the question of whether meningeal irritation signs, specifically Kernig's sign, Brudzinski's sign or	No clinical feedback was provided through the GDG questionnaire.	The new evidence is consistent with the guideline recommendation 1.1.1 on signs, symptoms and initial assessment, which states that some children and young people will present with mostly non-specific symptoms or signs, and the conditions may be difficult to distinguish from other less important (viral) infections presenting in this way. It further states that fever and seizure are two of several non-specific signs and symptoms to be considered, but that children and young people with the more specific symptoms and signs are more likely to have bacterial meningitis or meningococcal septicaemia. The research recommendation on the symptoms and signs of bacterial meningitis and meningococcal

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
disease (n = 345) in a previous study. The authors noted that the reducing incidence of bacterial meningitis and meningococcal disease makes further studies of the diagnostic accuracy of clinical features in non-hospitalised children and young people extremely challenging and unlikely to be conducted. The findings of significant symptoms of meningococcal disease in this study were generally in accordance with those identified in CG102. A systematic review[3] by considered 31 studies involving approximately 6000 patients and gave a narrative report of the number of studies identifying specific prognostic factors for sequelae of bacterial meningitis. No relevant clinical features beyond those identified in CG102 were noted.	neck stiffness, are reliable signs in helping to diagnose bacterial meningitis. One systematic review and 5 trials (4 included in the review) were included, and the authors concluded that signs of meningeal irritation have variable sensitivity and specificity and therefore cannot be used alone in diagnosing meningitis. A systematic review and validation of prediction rules[7] for identifying children with serious infections (not just meningitis) Included 35 studies and found that the most useful clinical features for ruling in serious infection was parental or clinician overall concern. In low- or intermediate-prevalence settings the presence of fever had some diagnostic value. Additional red flag features included meningeal irritation, petechial rash, decreased consciousness and seizures, which are consistent with CG102. The review also identified and validated the Yale Observation Scale and prediction rules for meningitis and other infections, but did not report in the abstract its diagnostic accuracy for meningitis specifically. A systematic review[8] of 37 studies on physical and historical examination features found that		disease that differentiate between these conditions and minor self-limiting infections (including those characterised by fever) remains ongoing.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	routine screening tests for meningitis, are low yield in infants without historical risk factors or suggestive physical examination findings.		
102-02 In children and young people up to 16 years of age, what symptoms and signs or combination of symptoms and signs are predictive of meningococcal septicaemia?			
A systematic review[1] assessed the clinical features of serious infections (not just meningitis) in children aged 1 month to 18 years in ambulatory care in the developed world (30 studies; 14,453 patients), found 'red flag' symptoms that were in agreement with those identified in CG102. The diagnostic accuracy of 'red flag' symptoms of children with meningococcal disease in primary care were studied further by the same group[2] in a two sample comparison study of children aged 1 month to 16 years. Parents of children with an acute self-limiting infection (n = 407) were asked about symptoms experienced by their child, and the findings compared with the	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	The studies identified in the Evidence Update reported symptoms and signs which are consistent with those identified in CG102. No relevant evidence was identified through the four year surveillance.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
symptoms reported by parents of children with meningococcal disease (n = 345) in a previous study. The authors noted that the reducing incidence of bacterial meningitis and meningococcal disease makes further studies of the diagnostic accuracy of clinical features in non-hospitalised children and young people extremely challenging and unlikely to be conducted. The findings of significant symptoms of meningococcal disease in this study were generally in accordance with those identified in CG102.			
102-03 Does giving antibiotics to children and young people with suspected meningitis pre-hospital improve outcome?			
No new key evidence was found in this section	An updated systematic review[9] assessed the effectiveness and safety of pre-admission antibiotics in people of all ages with suspected meningococcal disease. The search included RCTs and quasi-RCTs, but no RCTs were found that compared preadmission antibiotics with placebo or no treatment.	No clinical feedback was provided through the GDG questionnaire.	The absence of any new RCT evidence to support or refute the use of pre-hospital antibiotics is consistent with the guideline recommendations 1.2.1-1.2.3, to transfer children and young people with suspected bacterial meningitis without non-blanching rash directly to secondary care without giving parenteral antibiotics,

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			unless urgent transfer is not possible. If urgent transfer to hospital is not possible (for example, in remote locations or adverse weather conditions), administer antibiotics to children and young people with suspected bacterial meningitis. The following research recommendation remains ongoing: Does the administration of pre-hospital antibiotics improve outcomes in children and young people with suspected meningococcal disease?
102-04 Does giving antibiotics to children and young people with suspected meningococcal septicaemia pre-hospital improve outcome?			
No new key evidence was found in this section	An updated systematic review[9] assessed the effectiveness and safety of pre-admission antibiotics in people of all ages with suspected meningococcal disease. The search included RCTs and quasi-RCTs, but no RCTs were found that compared preadmission antibiotics with placebo or no treatment.	No clinical feedback was provided through the GDG questionnaire.	The absence of any new RCT evidence to support or refute the use of pre-hospital antibiotics is consistent with the guideline recommendations 1.2.1 and 1.2.4, to transfer children and young people with suspected bacterial meningitis or suspected meningococcal septicaemia to secondary care as an emergency. Give parenteral antibiotics (intramuscular or intravenous benzylpenicillin) at the earliest opportunity, either in primary

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			or secondary care, but do not delay urgent transfer to hospital to give the parenteral antibiotics. The following research recommendation remains ongoing: Does the administration of pre-hospital antibiotics improve outcomes in children and young people with suspected meningococcal disease?
102-05 In children and young people up to 16 years of age with a petechial rash, can non-specific laboratory tests (C-reactive protein, white blood cell count, blood gas) help to confirm or refute the diagnosis of meningococcal disease?			
A systematic review[10] of 14 studies (3981 patients) assessed the diagnostic value of laboratory tests in identifying serious infections (not just meningitis) in febrile children. Measuring inflammatory markers was shown to be diagnostically useful in an emergency department setting, in line with the recommendations in CG102. This study did not demonstrate any advantage for the use of procalcitonin over serum C-reactive protein (CRP) in this setting for serious infections in general, in line with	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	The new evidence from the evidence update is consistent with the CG102 recommendation on carrying out non-specific laboratory tests to confirm or refute the diagnosis of meningococcal disease. No relevant evidence was identified through the four year surveillance.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
recommendations in CG102. A predictive model[11] based on a case control study of suspected meningitis and meningococcal septicaemia in 719 patients admitted to hospitals in London, the South West and West Midlands found 385 confirmed cases for analysis, including 191 children and young people aged 19 years and below with bacterial meningitis/meningococcal septicaemia and 39 with viral meningitis. The model confirmed the diagnostic value of peripheral blood polymorphonuclear (PMN) cell count, CRP and presence of haemorrhagic rash, supporting CG102, and also provided a threshold level for PMN (> 16 x 10^9 /L) and CRP (> 100 mg/L). The probability of a diagnosis of meningitis or meningococcal septicaemia was > 95% if any of these factors were present, which increased to > 99% if two or more factors were present.			

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
102-06 In children and young people up to 16 years of age, are the results of non-specific laboratory tests predictive of bacterial meningitis?			
A systematic review[10] of 14 studies (3981 patients) assessed the diagnostic value of laboratory tests in identifying serious infections (not just meningitis) in febrile children. Measuring inflammatory markers was shown to be diagnostically useful in an emergency department setting, in line with the recommendations in CG102. This study did not demonstrate any advantage for the use of procalcitonin over serum C-reactive protein (CRP) in this setting for serious infections in general, in line with recommendations in CG102. A predictive model[11] based on a case control study of suspected meningitis and meningococcal septicaemia in 719 patients admitted to hospitals in London, the South West and West Midlands found 385 confirmed cases for analysis, including 191 children and young people aged	A meta-analysis[13] explored the predictive values of neutrophil CD64 expression in diagnosing neonatal infection (not just meningococcal). Twelve studies including 1915 neonates were analysed. Results indicated that Neutrophil CD64 expression can be used as an additional test in the diagnosis of neonatal infection, but only in combination with other tests. A systematic review[14] identified and evaluated clinical prediction rules (CPR) for children under 18 with suspected bacterial meningitis, with cerebral spinal fluid culture used as the reference diagnostic standard. CPR performance was evaluated using sensitivity, negative likelihood ratio, and the treatment frequency that would result if the rule was used. Eleven studies involving 6675 children with acute meningitis were included, with 6 CPRs identified. Although the bacterial meningitis score had the highest quality and performance, none of the CPRs were validated to warrant routine use. A meta-analysis[15] investigated the performance of the Bacterial Meningitis Score	One GDG member indicated new observational study evidence specifying risk of bacterial meningitis in children having lumbar puncture, to distinguish between meningitis and meningococcal septicaemia. However, this was outside the scope of the current surveillance review which included systematic reviews and randomised controlled trials only. In the area of variation in clinical practice, one respondent stated that reprovision of laboratory and microbiology services have affected the likelihood of achieving the results of lumbar puncture in less than 4 hours, which in many cases is not possible. No evidence was cited.	Further research is required on the diagnostic value of neutrophil CD64 expression, specifically for meningococcal infection, before it can be considered for inclusion in the guideline. The new evidence for the use of clinical prediction rules is mixed and most rules require further validation to warrant inclusion in the guideline recommendations. There is some evidence to support the use of the Bacterial Meningitis Score in distinguishing between bacterial and aseptic meningitis, although the totality of systematic review evidence remains inconclusive and further research is needed before this tool can be incorporated into CG102.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
19 years and below with bacterial meningitis/meningococcal septicaemia and 39 with viral meningitis. The model confirmed the diagnostic value of peripheral blood polymorphonuclear (PMN) cell count, CRP and presence of haemorrhagic rash, supporting CG102, and also provided a threshold level for PMN (> 16 x 10^9 /L) and CRP (> 100 mg/L). The probability of a diagnosis of meningitis or meningococcal septicaemia was > 95% if any of these factors were present, which increased to > 99% if two or more factors were present. A study[12] provided validation of two clinical decision rules for distinguishing between bacterial and aseptic meningitis in children in the paediatric emergency room or intensive care setting, based on data from 198 children under 18 years (mean age 5 years; 96 cases of bacterial meningitis) from six centres in five European	in diagnosing meningitis in children with cerebrospinal fluid (CSF) pleocytosis. From the 8 included studies (n=5312) the Bacterial Meningitis Score was found to be highly accurate.		

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
tertiary care centres. Both the Bacterial Meningitis Score (BMS) and the Meningitest showed 100% sensitivity. Specificity was poor, though significantly higher with the BMS (BMS: 52% specificity; 95% confidence interval [CI] 42% to 62%; Meningitest: 36% specificity; 95% CI 27% to 46%; $p < 10^{-8}$). Procalcitonin levels did not appear to contribute additional specificity. This high level validation study used appropriate methods, and the findings support the current recommendations of CG102.			
102-07 In children and young people with suspected meningitis, can CSF variables (white cell count, glucose, protein) distinguish between bacterial and viral meningitis?			
A predictive model[11] based on a case control study of suspected meningitis and meningococcal septicaemia in 719 patients admitted to hospitals in London, the South West and West Midlands found 385 confirmed cases for analysis, including 191 children and young people aged	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	The study identified in the Evidence Update provided a model for differentiating acute bacterial from viral meningitis within a few hours of admission to hospital. The model is consistent with the guideline recommendation on performing lumbar puncture and interpreting CSF parameters for suspected

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
19 years and below with bacterial meningitis/meningococcal septicaemia and 39 with viral meningitis. The model confirmed the diagnostic value of peripheral blood polymorphonuclear (PMN) cell count, CRP and presence of haemorrhagic rash, supporting CG102, and also provided a threshold level for PMN (> 16 x 10^9 /L) and CRP (> 100 mg/L). The probability of a diagnosis of meningitis or meningococcal septicaemia was > 95% if any of these factors were present, which increased to > 99% if two or more factors were present.			bacterial meningitis. No additional relevant evidence was identified through the four year surveillance review.
102-08 What is the diagnostic value of blood and CSF PCR in children and young people with suspected meningococcal meningitis or meningococcal septicaemia?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-09 What is the diagnostic value of microscopy and culture of skin aspirates in children and young people with meningococcal septicaemia?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-10 In children and young people with suspected meningococcal disease what is the diagnostic value of throat swabs?			
No new key evidence was found in this section	Through a focused search one study was identified that was relevant to the clinical question.	Clinical feedback highlighted updated Public Health England/Health Protection Agency guidance on throat swabs (Guidance for Public Health	Public Health England/Health Protection Agency guidance, available at the time of CG102 development and used as one of its

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	The study[16] (n=104) found that pre-hospital rapid molecular testing of easily obtained respiratory swabs, including throat swabs, could accelerate diagnosis of meningococcal disease. However this study did not report a defined reference standard in the abstract. The guideline explicitly excluded studies for this question without a defined reference standard.	Management of Meningococcal Disease in the UK). Both the 2006 version of this guidance, available at the time of writing CG102, and the updated 2012 version recommend that throat swabs should be taken to investigate possible meningococcal disease. Recommending that routine throat swabs be taken in suspected meningococcal disease could be important when deciding how best to manage the patient affected, and also in making decisions about vaccinating siblings/close family contacts of the index case. It also has significant implications for monitoring the success or failure of the vaccine programme. CG102 currently recommends that throat swabs are not used to investigate for possible meningococcal disease because the GDG felt that, since throat carriage of meningococci is common in healthy people, throat swabbing would not be helpful.	sources, recommends that throat swabs should be taken to investigate possible meningococcal disease. The updated version of this guidance states additionally that throat swabs may help support the clinical diagnosis alongside other signs and symptoms. It also states that results of nasopharyngeal swabs afford the possibility of identifying a strain in the event of a cluster that requires identification. The GDG were aware of the 2006 version of this guidance during development of CG102 but recommended that throat swabs are not used to investigate for possible meningococcal disease because throat carriage of meningococci is common in healthy people. The Public Health England/Health Protection Agency guidance was updated in 2012 but the recommendations on throat swabs were not altered through this update. A focused literature search in this area was conducted in light of GDG feedback on disparity between

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
		The GDG feedback suggested that the recommendation should be considered through the surveillance review in the light of the disparity with the Health Protection Agency guidance. As such, a focused question was developed and an accompanying focused search was undertaken.	CG102 and the Health Protection Agency guidance. New evidence on the use of throat swabs identified through a focused search did not report a defined reference standard in the abstract. It is therefore unlikely to impact on guideline recommendation 1.3.14 not to use throat swabs in diagnosis of meningococcal disease. Larger studies are required to demonstrate the value and cost effectiveness of throat swabs for all suspected cases.
102-11 When is lumbar puncture contraindicated in children and young people with suspected bacterial meningitis?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-12 When is lumbar puncture contraindicated in children and young people with suspected meningococcal septicaemia?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-13 Should lumbar puncture be performed prior to stopping antibiotic treatment in children less than 3 months of age with bacterial meningitis?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-14 In children and young people with suspected or confirmed bacterial meningitis, can a cranial computed tomography (CT) scan reliably demonstrate raised intracranial pressure?			
No new key evidence was found in this section	No new evidence identified.		No relevant evidence identified.
102-15 What antibiotic regimen (type) should be used to treat children and young people with suspected bacterial meningitis or meningococcal septicaemia in the secondary care setting?			

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-16 What antibiotic regimen should be used to treat confirmed bacterial meningitis or meningococcal septicaemia?			
No new key evidence was found in this section	<u>Duration of treatment</u> A systematic review[17] examined the optimal duration of antibiotic therapy for bloodstream infections. Only 1 included study focused on bacteremia in neonates, **and it should be noted that the age group breakdown for the other 23 included studies was unclear.** The findings suggested that there were no significant differences between shorter vs longer durations of antibiotic therapy. <u>Cefotaxime and adjunctive paracetamol</u> A RCT[18] (n=723) found non-significant improvements in mortality, severe neurological sequelae or deafness from slow infusion of cefotaxime plus adjunctive paracetamol in children with pneumococcal meningitis.	There is new observational study data on epidemiology of meningococcal disease, particularly relating to listeria infection. A recent study of enhanced surveillance of meningitis in babies <3 months of age over a 13 month period found no cases of Listeria in babies older than 1 month of age. The guideline recommendation that empirical antibiotics for babies <3months of age should include amoxicillin or ampicillin to cover Listeria was proposed for reconsideration. However the cited study was outside the scope of the current surveillance review which included systematic reviews and randomised controlled trials only.	Further research is required on optimal duration of antibiotic treatment specifically for bacterial meningitis or meningococcal septicaemia in children under 16 years before it can be considered for inclusion in the guideline. There is insufficient evidence on the age threshold for discontinuing antibiotics for listeria cover in infants <3 months to impact CG102 recommendation 1.4.2, which states that children younger than 3 months with suspected bacterial meningitis should be treated without delay using intravenous cefotaxime plus either amoxicillin or ampicillin. Further research is needed on adjunctive paracetamol before it can be considered for inclusion in CG102.
102-17 What are the indications for administering intravenous fluids to resuscitate children and young people with suspected meningococcal septicaemia?			
No new key evidence was found	<u>Intravenous fluid bolus</u>	One GDG member cited the FEAST trial	<u>Intravenous fluid bolus</u>

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
in this section	One systematic review[19] assessed the evidence base for fluid resuscitation in the treatment of children with shock due to sepsis or severe infection. Of the 13 included studies, the largest trial (FEAST) generated the majority of evidence, which found that fluid boluses were harmful compared to no bolus. The authors concluded that simple algorithms are needed to support health-care providers in the triage of patients to determine who could potentially be harmed by the provision of bolus fluids, and who will benefit. A systematic review[20] evaluated the effects of intravenous fluid bolus compared to maintenance intravenous fluids alone as part of immediate emergency care in children with severe febrile illness and signs of impaired circulation in low-income settings. The 6 included studies were from low, middle and high income countries, and included 2 RCTs, including the FEAST trial. The authors concluded that the FEAST trial provides previously lacking robust evidence that in low-income settings fluid boluses increase mortality in children with severe febrile illness and impaired circulation.	on fluid resuscitation (NEJM 2011, Maitland et al ISRCTN69856593) that was stopped early because results, even before the trial finished, showed that fluid resuscitation with 20-40ml/kg 0.9% saline or albumin given rapidly over <1 hour (most received 20ml/kg) actually significantly increased mortality. This has potential impact on recommendation 1.4.30 which states that if there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. It should be noted, however, that the cited trial was conducted in a low income setting and included a high proportion of malaria patients, with only indirect relevance to the UK population.	New evidence is unlikely to impact on guideline recommendations due to its indirect relevance to the guideline scope. There is insufficient additional evidence on safety concerns in the UK population to impact on recommendation 1.4.30 which recommends that if there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. The research recommendation on the effectiveness of albumin 4.5% solution compared with crystalloid saline 0.9% solution for fluid resuscitation in children and young people with septic shock remains unanswered in the UK paediatric setting. <u>Syringe Size</u> The evidence on syringe size was not directly relevant to the review question. Further larger trials are required on optimal syringe size for

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	However, high income settings were not discussed. <u>Syringe Size</u> A small RCT[21] aimed to determine if an optimal syringe size exists for conducting manual fluid resuscitation in paediatric septic shock. Patients (n=48) were allocated to one of 4 study arms of varied syringe size. The findings suggested that greatest efficiency (total time to administer 900 mL) was achieved with 30 or 60 mL syringes.		conducting manual fluid resuscitation before it can be considered for inclusion in the guideline.
102-18 What are the indications for commencing inotropes in children and young people with suspected/confirmed meningococcal septicaemia?			
No new key evidence was found in this section	A systematic review[22] evaluated the effects of vasopressin and terlipressin on mortality and morbidity outcomes in patients with vasodilatory shock. Seven studies using vasopressin, three using terlipressin and one using both were identified. The findings indicated that Vasopressin and terlipressin were comparable to conventional agents in the maintenance of haemodynamic stability and organ function in vasodilatory shock. Evidence on morbidity and mortality was inconclusive. It should be noted that age subgroups were not specified, except for the statement that one small paediatric study indicated adverse	No clinical feedback was provided through the GDG questionnaire.	The new evidence finding vasopressin and terlipressin to be comparable to conventional agents was insufficient to impact on the guideline recommendation 1.4.32 on vasoactive therapy for shock in meningococcal septicaemia. Further research is needed on inotropes, specifically in the paediatric population, before they can be considered for inclusion in the guideline.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	outcomes from vasopressin.		
102-19 What type of intravenous fluid should be used to resuscitate children and young people with suspected meningococcal septicaemia?			
No new key evidence was found in this section		One GDG member cited the FEAST trial on fluid resuscitation (NEJM 2011, Maitland et al ISRCTN69856593) that was stopped early because results, even before the trial finished, showed that fluid resuscitation with 20-40ml/kg 0.9% saline or albumin given rapidly over <1 hour (most received 20ml/kg) actually significantly increased mortality. This has potential impact on recommendation 1.4.30 which states that if there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. It should be noted, however, that the cited trial was conducted in a low income setting with a high proportion of malaria patients, with only indirect relevance to the UK population.	Intravenous fluid bolus New evidence is unlikely to impact on guideline recommendations due to its indirect relevance to the guideline scope. There is insufficient additional evidence on safety concerns in the UK population to impact on recommendation 1.4.30 which recommends that if there are signs of shock, give an immediate fluid bolus of 20 ml/kg sodium chloride 0.9% over 5–10 minutes. Syringe Size The evidence on syringe size was not directly relevant to the review question. Further larger trials are required on optimal syringe size for conducting manual fluid resuscitation before it can be considered for inclusion in the guideline.
102-20 Should fluid volume be restricted in children and young people with suspected/confirmed bacterial meningitis?			
No new key evidence was found in this section	An updated systematic review[23] examining treatment of acute bacterial meningitis with differing volumes of initial fluid administration	No clinical feedback was provided through the GDG questionnaire.	Updated systematic review evidence identified no new primary evidence on fluid volume restriction for

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	found no new evidence. It retained the conclusion that some evidence supports maintaining intravenous fluids rather than restricting them in the first 48 hours in settings with high mortality rates and where children present late. However, where children present early and mortality rates are lower, there is insufficient evidence to guide practice.		suspected/confirmed bacterial meningitis.
102-21 What are the clinical indications for intubation in children and young people with suspected/confirmed meningococcal septicaemia or bacterial meningitis?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-22 Should corticosteroids be used in the treatment of children and young people with suspected/confirmed bacterial meningitis?			
A Cochrane review[24] (24 studies; 4041 patients) examined the effect of adjuvant corticosteroid therapy compared with controls on mortality, hearing loss and neurological sequelae in children and adults with acute bacterial meningitis. Subgroup analysis of the children found no impact of corticosteroid therapy on mortality (risk ratio [RR] = 0.95; 95% confidence interval [CI] 0.78 to 1.14]. However corticosteroids did appear to reduce risk of any hearing loss (RR = 0.74; 95% CI 0.62 to 0.89) and severe hearing	Two systematic reviews[26,27] including 8 and 5 studies respectively, analysed benefits of adjuvant therapy with dexamethasone for bacterial meningitis in children. The first review concluded that there are no benefits of adjuvant therapy with dexamethasone. The second review concluded that there is insufficient evidence to support routine adjuvant therapy with dexamethasone. An updated systematic review[28] on adjuvant therapy with corticosteroids in all age groups with acute bacterial meningitis retained its conclusion (see evidence update column) A RCT[29] (n=80) found that dexamethasone	No clinical feedback was provided through the GDG questionnaire.	The systematic review evidence from the Evidence Update and the surveillance review has revealed insufficient evidence of benefit of adjuvant therapy with corticosteroids in neonates. This is consistent with CG102, which does not recommend the use of corticosteroids in children younger than 3 months with suspected or confirmed bacterial meningitis (recommendation 1.4.39). CG102 Research recommendation 4.4 on adjunctive corticosteroid

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
loss (RR = 0.67; 95% CI 0.49 to 0.91). Analysis by country income also showed that in 8 high-income countries there was a decreased risk of severe hearing loss (RR = 0.54; 95% CI 0.35 to 0.78) and short-term neurological sequelae (RR = 0.67; 95% CI 0.46 to 0.97) with corticosteroid, but no difference was observed in low-income countries. A randomised controlled trial[25] was not included in the Cochrane review. This study conducted in Argentina, Brazil, Dominican Republic, Ecuador, Paraguay and Venezuela examined the effect of adjuvant intravenous dexamethasone, oral glycerol, both or neither in 383 children aged 2 months to 16 years with meningitis caused by a range of bacteria (mostly *Haemophilus influenzae* type b or *Streptococcus pneumoniae*). Neither dexamethasone nor glycerol prevented hearing loss. These publications are unlikely to	therapy significantly reduced mortality, progression of systemic inflammatory response syndrome and CSF inflammatory indices.		treatment in neonates is only partially addressed by current evidence, and further research is needed specific to the neonatal population before it can be considered for inclusion in CG102. The totality of systematic review evidence from the Evidence Update and the surveillance review is consistent with Recommendation 1.4.40 for administering dexamethasone to children over 3 months. New evidence identified in the 4 year surveillance review is unlikely to impact on CG102 recommendation 1.4.45 due to inconclusive results. The recommendation states that in children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 25 mg/m2 four times daily)] should be

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
affect the current recommendations for steroid administration in bacterial meningitis in CG102.			used only when directed by a paediatric intensivist.
102-23 What is the effect of experimental therapies in children and young people with suspected/confirmed meningococcal septicaemia?			
Activated protein C A Cochrane review[30] of five RCTs (5101 patients), one of which included neonates and children, did not provide evidence to support the use of activated protein C in children and young people with meningococcal septicaemia, confirming the current recommendations of CG102. The US Food and Drug Administration has announced that the manufacturer of activated protein C has withdrawn the product, following failure to show a survival benefit; see www.fda.gov/Drugs/DrugSafety/ucm277114.htm for details. Intravenous Immunoglobin NICE CG102 does not currently include recommendations for the	Activated protein C An updated systematic review[34] found one additional trial but its conclusion remained unchanged in not finding evidence to support the use of activated protein C in children and young people with meningococcal septicaemia Another systematic review[35] found no eligible trials and concluded that there is insufficient data to use activated protein C for the management of severe sepsis in newborn infants. Plasma Filtration A RCT[36] (n=48) found that plasma filtration for septic shock was not significantly different to control in mortality, after adjustment for severity of illness at the time of randomisation. However, the trial was stopped early due to inadequate recruitment. Intravenous Immunoglobin	No clinical feedback was provided through the GDG questionnaire.	The new evidence on activated protein C does not support this intervention and is consistent with recommendations in CG102. Further research is needed on plasma filtration before it can be considered for inclusion in the guideline. The guideline does not include recommendations for the use of intravenous immunoglobulin meningococcal septicaemia. New evidence indicates that monoclonal intravenous immunoglobin does not reduce mortality among neonates with sepsis and should therefore not be recommended in CG102. Further research is needed on adjunctive therapy with Ig-M enriched intravenous immunoglobin before it can be considered for inclusion in the

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
use of intravenous immunoglobulin (IVIG) in meningococcal septicaemia. This treatment is currently undergoing active research evaluation and the use of polyclonal and/or monoclonal IVIG compared with control has been considered in three recent publications.[31-33] Although the Cochrane review (2010) was suggestive of an effect of polyclonal IVIG on mortality (within the limitations of the included evidence), the subsequent INIS trial now seems to indicate that IVIG may have no effect on death or major disability in neonatal sepsis. CG102 is unlikely to be affected by these results. It should however be noted that none of the evidence considered meningitis specifically as a subset of infection. It should also be noted that this Cochrane review was updated in 2013 but was not retrieved in the surveillance literature search because the strategy focused on	An updated systematic review[37] on intravenous immunoglobulin for sepsis and septic shock concluded from 43 studies that among neonates with sepsis, there is sufficient evidence that standard polyclonal IVIG, as adjunctive therapy, does not reduce mortality based on the inclusion of a large polyclonal IVIG trial on neonates. For Ig-M enriched IVIG, the trials on neonates and adults were small and the totality of the evidence is still insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal IVIGs remains experimental. <u>Osmotic Therapies</u> A systematic review[38] on osmotic therapies added to antibiotics for acute bacterial meningitis in children and adults included 4 trials of low quality. The findings suggested no benefit on mortality, but a possible reduction in deafness. **It should be noted that subgroup analysis by age group was not reported in the abstract.**		guideline. Further research is needed on osmotic therapies in the paediatric population before any of these adjuvant therapies can be considered for inclusion in CG102.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
specificity for CG102 population terms. The 2013 update included the INIS trial and concluded that IVIG should not be recommended. This updated conclusion is unlikely to impact on CG102 recommendations which don't recommend IVIG.			
102-24 Should corticosteroids be used in the treatment of children and young people with suspected/confirmed meningococcal septicaemia?			
No new key evidence was found in this section	A systematic review[39] examined the effects of steroids in children with fluid and/or vasoactive medication-dependent shock. The evidence from the 8 included studies (n=447), all conducted in the developing world, was limited and demonstrated conflicting results.	No clinical feedback was provided through the GDG questionnaire.	New evidence identified in the 4 year surveillance review is unlikely to impact on CG102 recommendation 1.4.45 due to inconclusive results. The recommendation states that in children and young people with shock that is unresponsive to vasoactive agents, steroid replacement therapy using low-dose corticosteroids (hydrocortisone 25 mg/m2 four times daily)] should be used only when directed by a paediatric intensivist.
102-25 What is the effect on outcomes of using scoring systems in children and young people with suspected/confirmed meningococcal septicaemia?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	
102-26 Do specialist transport teams improve outcomes and/or reduce adverse incidents during the transfer of children with meningococcal disease?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
102-27 What proportion of children and young people with bacterial meningitis develop physical and psychological morbidity?			
No new key evidence was found in this section.	A meta-analysis[40] investigated infections (including but not restricted to meningitis) and neurodevelopmental outcome in preterm and very low-birth-weight infants. From the 18 included studies (n=13,755) the findings indicated that mental development was impaired by meningitis, but did not report on its impact on motor development.	One GDG member cited an ongoing cohort study that includes a follow up of babies with Group B Streptococcus meningitis. It may contribute evidence that the current recommendation (p182) for routine follow up of children surviving meningitis to be limited to 4-6 weeks after hospital discharge, unless there are reasons found to continue, may be too short. It is likely that a 6 week follow up appointment would fail to detect significant cognitive and neuromotor sequelae that may not become evident until later in the child's development or when they reach school age. The GDG member stated that the Meningitis Research Foundation is now recommending that the 4-6 week period recommended in CG102 be extended to 2 years for babies <3 months of age.	New evidence is relevant to long term management but does not directly answer the review question and is unlikely to impact on CG102 recommendations. It is also weakened by its restriction to the preterm and very low birth weight infant population. No new evidence was identified to impact on the recommendation 1.5.5 for Children and young people to be reviewed by a paediatrician with the results of their hearing test 4–6 weeks after discharge from hospital. Clinical feedback highlighted ongoing evidence that will be reviewed at the next surveillance point.
102-28 What proportion of children and young people with meningococcal septicaemia develop physical and psychological morbidity?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.
102-29 What is the prevalence of primary immunodeficiency in children and young people with meningococcal disease?			
No new key evidence was found in this section	No new evidence identified.	No clinical feedback was provided through the GDG questionnaire.	No relevant evidence identified.

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
Areas not currently covered in the guideline			
In children and young people with suspected meningococcal disease what is the diagnostic value of magnetic resonance imaging?			
	A systematic review[41] of 5 studies found that MRI had poor sensitivity for diagnosing bacterial meningitis in adult and child populations and, due to a lack of data specific to child age groups, should not be recommended. **It should be noted that no subgroup analysis was reported for child age groups** **It should be noted that the original guideline scope was amended to exclude MRI due to its low use in UK practice.**	The GDG chair confirmed MRI had been excluded from CG102 scope due to low use in UK practice. However, its use is increasing and an additional review question has been added to incorporate new evidence.	The new evidence is consistent with CG102 recommendations, which do not recommend the use of MRI. The new evidence is weakened by a lack of subgroup data on child age groups. Although MRI was omitted from the original scope due to low use in practice, new evidence should be monitored due to the increasing use of MRI, as confirmed by clinical feedback.
Research Recommendations			
RR1 What are the symptoms and signs of bacterial meningitis and meningococcal disease in children and young people aged under 16 years that differentiate between these conditions and minor self-limiting infections (including those characterised by fever)?			
See 102-01 'red flag' symptoms	See 102-01 'red flag' symptoms	No clinical feedback was provided through the GDG questionnaire.	See 102-01
RR2 Does the administration of pre-hospital antibiotics improve outcomes in children and young people with suspected meningococcal disease?			
No new key evidence was found in this section	See 102-04	No clinical feedback was provided through the GDG questionnaire.	See102-04
RR3 What are the normal ranges for blood and CSF parameters in children and young people in the UK?			
No new key evidence was found	None identified.	No clinical feedback was provided	

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
in this section		through the GDG questionnaire.	
RR4 Does repeat lumbar puncture in neonates with bacterial meningitis alter the prognosis?			
No new key evidence was found in this section	None identified.	No clinical feedback was provided through the GDG questionnaire.	
RR5 In children and young people what are the risk factors for meningitis and septicaemia caused by cephalosporin-resistant strains of pneumococcus?			
No new key evidence was found in this section	None identified.	No clinical feedback was provided through the GDG questionnaire.	
RR6 How effective is albumin 4.5% solution compared with crystalloid saline 0.9% solution for fluid resuscitation in children and young people with septic shock?			
No new key evidence was found in this section	See 102-17	See 102-17	See 102-17
RR7 What is the effectiveness of corticosteroids as an adjunct to antibiotic treatment in neonates with suspected or confirmed bacterial meningitis?			
See 102-22	See 102-22	No clinical feedback was provided through the GDG questionnaire.	See 102-22
RR8 How effective is steroid replacement treatment in children and young people with vasopressor-unresponsive shock caused by septicaemia, including meningococcal septicaemia?			
No new key evidence was found in this section	None identified.	No clinical feedback was provided through the GDG questionnaire.	
RR9 Does early intervention with anti-endotoxin treatments such as recombinant bactericidal permeability-increasing protein improve outcomes in children and young people with severe meningococcal septicaemia?			
No new key evidence was found in this section	None identified.	No clinical feedback was provided through the GDG questionnaire.	
RR10 Are severity scoring systems useful for directing clinical management of suspected or confirmed meningococcal disease in children and young people?			
No new key evidence was found in this section	None identified.	No clinical feedback was provided through the GDG questionnaire.	
RR11 Does routine follow-up reduce the incidence of psychosocial stress and long-term morbidity in children and young people who have had bacterial meningitis or meningococcal septicaemia and their families?			
No new key evidence was found	None identified.	No clinical feedback was provided	

Conclusions from Evidence Update (2012)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
in this section		through the GDG questionnaire.	

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