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Centre for Clinical Practice – Surveillance Programme

Surveillance review consultation document

4-year 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

Background information

Guideline issue date: June 2010
4 year review: 2014

Surveillance review recommendation

Surveillance review proposal put to consultees:

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

Main findings of the current 4 year surveillance review

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 indicated that there is currently insufficient new evidence to generate change to the current guidance recommendations.

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 responders 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.

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?

The results are summarised in the table under the clinical area: **Skin samples and throat swabs for meningococcal disease**.

New evidence was identified for the current 4 year surveillance review relating to the following clinical areas within the Bacterial Meningitis guideline.

Clinical area: Symptoms, signs and initial assessment		
Q: 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? Q: 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?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) 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), and 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 disease (n = 345) in a previous study.	None identified through 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

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 considered to be in accordance with those identified in CG102. A systematic review[3] 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. <u>4-year surveillance review (2014)</u> **Febrile Seizure** 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. **Meningeal Irritation Signs** A systematic review[6] addressed the question of whether meningeal irritation signs, specifically Kernig's		disease that differentiate between these conditions and minor self-limiting infections (including those characterised by fever) remains ongoing.

sign, Brudzinski's sign or 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 routine screening tests for meningitis, are low yield in infants without historical risk factors or suggestive physical examination findings.		
Clinical area: Pre-hospital management of suspected bacterial meningitis and meningococcal septicaemia		
Q: Does giving antibiotics to children and young people with suspected meningitis pre-hospital improve outcome? Q: Does giving antibiotics to children and young people with suspected meningococcal septicaemia pre-hospital improve outcome?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No new evidence identified.	None identified through GDG questionnaire.	There is an absence of any new RCT evidence to support or refute the use of pre-hospital antibiotics in children and young people with suspected meningitis.

4-year surveillance review (2014) 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.		As such, the updated systematic review evidence is unlikely to impact the guideline recommendations 1.2.1 and 1.2.2, to transfer children and young people with suspected bacterial meningitis without non-blanching rash directly to secondary care without giving parenteral antibiotics, 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 updated systematic review evidence is unlikely to impact the guideline recommendations recommendation 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 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?
Clinical area: Investigation and management in children and young people with petechial rash		
Q: 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?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) 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	None identified through GDG questionnaire.	The new evidence from the Evidence Update is consistent with the CG102 recommendation 1.3.3 on carrying out non-specific laboratory tests including CRP and full blood count to confirm or refute the diagnosis of meningococcal disease.

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 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. <u>4-year surveillance review (2014)</u> No new evidence identified.		No relevant evidence was identified through the four year surveillance.
Clinical area: Investigation and management in children and young people with suspected bacterial meningitis		
Evidence summary	**GDG/clinical perspective**	**Impact**
Q: In children and young people up to 16 years of age, are the results of non-specific laboratory tests predictive of bacterial meningitis?		
<u>Evidence Update (2012)</u> 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	Clinical feedback highlighted 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	New evidence on the diagnostic value of laboratory tests, including procalcitonin instead of CRP and inflammatory markers, was consistent with CG102 recommendations 1.3.25 and 1.3.3 on diagnostic tests in secondary care.

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 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 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	review which included systematic reviews and randomised controlled trials only. In the area of variation in clinical practice, clinical feedback 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.	New evidence suggested that neutrophil CD64 expression can be a useful additional test for meningococcal infection. Further research is required on the diagnostic value of neutrophil CD64 expression before it can be considered for inclusion in the CG102 recommendations for diagnosis in secondary care. 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 recommendations for diagnosis in secondary care.

the current recommendations of CG102. 4-year surveillance review (2014) 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 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.		
Clinical area: Investigation and management in children and young people with suspected bacterial meningitis		
Q: In children and young people with suspected meningitis, can CSF variables (white cell count, glucose, protein) distinguish between bacterial and viral meningitis?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) 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	None identified through 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

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. 4-year surveillance review (2014) No new evidence identified.		recommendation on performing lumbar puncture and interpreting CSF parameters for suspected bacterial meningitis. No additional relevant evidence was identified through the four year surveillance review.
Clinical area: Skin samples and throat swabs for meningococcal disease		
Q: In children and young people with suspected meningococcal disease what is the diagnostic value of throat swabs?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No new evidence identified. 4-year surveillance review (2014) Through a focused search one study was identified that was relevant to the clinical question. 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.	Clinical feedback highlighted updated Public Health England/Health Protection Agency guidance on throat swabs (Guidance for Public Health 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	Public Health England/Health Protection Agency guidance, available at the time of CG102 development and used as one of its 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

	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. 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.	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 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.
Clinical area: Antibiotics for suspected bacterial meningitis or meningococcal disease		
Q: What antibiotic regimen should be used to treat confirmed bacterial meningitis or meningococcal septicaemia?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No new evidence identified. 4-year surveillance review (2014) **Duration of treatment** A systematic review[17] examined the optimal duration of antibiotic therapy for bloodstream infections. Only 1 included study focused on bacteraemia in neonates, and it should be noted that the age range for the other 23 included studies was unclear from the abstract. The findings suggested that there were no significant differences between shorter vs longer durations of antibiotic therapy.	Clinical feedback highlighted 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. Additional clinical feedback highlighted some new evidence to suggest a shorter duration of treatment, but existing evidence showed cases of listeria occurring up to 60 days and that the	**Optimal Duration** There is insufficient new evidence to impact on CG102 recommendations 1.4.9-1.4.17 on duration of antibiotic treatment for suspected or confirmed meningococcal infection. Further research is required on optimal duration of antibiotic treatment, specifically for bacterial meningitis or meningococcal septicaemia, in children under 16 years before changing the recommendations. **Infants <3 months** Clinical feedback highlighted some new evidence to suggest a shorter duration of treatment for infants <3 months. However, additional clinical feedback stated that existing evidence showed cases of listeria occurring up to 60 days and that the risk, although

Cefotaxime and adjunctive paracetamol 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.	risk could remain up to 90 days.	decreasing, could remain up to 90 days. There is therefore insufficient consistent evidence on the age threshold for discontinuing antibiotics for listeria cover, 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.
Clinical area: Intravenous fluid resuscitation in meningococcal septicaemia		
Q: What are the indications for administering intravenous fluids to resuscitate children and young people with suspected meningococcal septicaemia? Q: What type of intravenous fluid should be used to resuscitate children and young people with suspected meningococcal septicaemia?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No new evidence identified. 4-year surveillance review (2014) **Intravenous fluid bolus** 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	Clinical feedback highlighted 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) significantly increased mortality. This was stated as having a 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.	**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. 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. **Syringe Size** The evidence on syringe size was not directly relevant to the review question. Further larger trials are required

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. However, high income settings were not discussed. **Syringe Size** 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.		on optimal syringe size for conducting manual fluid resuscitation before it can be considered for inclusion in the guideline.
Clinical area: Vasoactive therapy for shock in meningococcal septicaemia		
Q: What are the indications for commencing inotropes in children and young people with suspected/confirmed meningococcal septicaemia?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new evidence identified. <u>4-year surveillance review (2014)</u> 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	None identified through 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.

subgroups were not specified in the abstract, except for the statement that one small paediatric study indicated adverse outcomes from vasopressin.		
Clinical area: Fluid management in suspected or confirmed bacterial meningitis		
Q: Should fluid volume be restricted in children and young people with suspected/confirmed bacterial meningitis?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No new evidence identified. 4-year surveillance review (2014) An updated version of a systematic review[23] included in CG102 examined treatment of acute bacterial meningitis with differing volumes of initial fluid administration. No new evidence was found and the conclusion remained 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.	None identified through GDG questionnaire.	Updated systematic review evidence identified no new evidence on fluid volume restriction for suspected/confirmed bacterial meningitis and is therefore unlikely to have any impact on CG102 recommendation 1.4.23, which states that fluids should not be restricted unless there is evidence of: • raised intracranial pressure, or • increased antidiuretic hormone secretion.
Clinical area: Corticosteroids		
Q: Should corticosteroids be used in the treatment of children and young people with suspected/confirmed bacterial meningitis? Q: Should corticosteroids be used in the treatment of children and young people with suspected/confirmed meningococcal septicaemia?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) 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]	None identified through 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. This is consistent with CG102, which does not recommend adjuvant therapy. Further research is needed on routine adjuvant therapy with dexamethasone before it can be considered for

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 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 identified which 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. The Evidence Update concluded that these publications are unlikely to affect the current recommendations for steroid administration in bacterial meningitis in CG102. 4-year surveillance review (2014) 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)		inclusion in CG102. 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. 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.

A RCT[29] (n=80) found that dexamethasone therapy significantly reduced mortality, progression of systemic inflammatory response syndrome and CSF inflammatory indices. A systematic review[30] 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.		
Clinical area: Adjunctive therapies		
Q: What is the effect of experimental therapies in children and young people with suspected/confirmed meningococcal septicaemia?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) **Activated protein C** A Cochrane review[31] 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** CG102 does not currently include recommendations for the use of intravenous immunoglobulin (IVIG) in meningococcal septicaemia. This treatment is currently undergoing active research evaluation and the use of	None identified through 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 for meningococcal septicaemia. As new evidence indicates that monoclonal intravenous immunoglobin does not reduce mortality among neonates with sepsis, further research on the benefits and harms of monoclonal intravenous immunoglobin is needed before considering for inclusion in the guideline. Further research is needed on adjunctive therapy with Ig-M enriched intravenous immunoglobin before it can be considered for inclusion in the guideline. Further research is needed on osmotic therapies,

polyclonal and/or monoclonal IVIG compared with control has been considered in three recent publications.[32-34] 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. The Evidence Update concluded that 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. 4-year surveillance review (2014) **Activated protein C** An updated systematic review[35] 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[36] 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[37] (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** An updated systematic review[38] 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		specifically in the paediatric population, before they can be considered for inclusion in CG102.

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. **Osmotic Therapies** A systematic review[39] 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.		
Clinical area: Long-term effects of bacterial meningitis and meningococcal septicaemia		
Q: What proportion of children and young people with bacterial meningitis develop physical and psychological morbidity?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update (2012)</u> No new evidence identified. <u>4-year surveillance review (2014)</u> 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.	Clinical feedback highlighted 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. Clinical feedback suggested 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. GDG feedback also highlighted 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 of bacterial meningitis 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. Clinical feedback cited ongoing evidence on duration of follow up. As this study is ongoing, this area will be examined again at the next surveillance review. No new published 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 area: Diagnosis in secondary care - Magnetic resonance imaging		
Q: In children and young people with suspected meningococcal disease what is the diagnostic value of magnetic resonance imaging?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update (2012) No new evidence identified. 4-year surveillance review (2014) 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 in the abstract for child age groups.	Clinical feedback confirmed MRI had been excluded from CG102 scope due to low use in UK practice at the time of guideline production, but that use of MRI is now increasing.	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.

For the following areas of the guideline no new evidence was identified:

- What is the diagnostic value of blood and CSF PCR in children and young people with suspected meningococcal meningitis or meningococcal septicaemia?
- What is the diagnostic value of microscopy and culture of skin aspirates in children and young people with meningococcal septicaemia?
- When is lumbar puncture contraindicated in children and young people with suspected bacterial meningitis?
- When is lumbar puncture contraindicated in children and young people with suspected meningococcal septicaemia?
- Should lumbar puncture be performed prior to stopping antibiotic treatment in children less than 3 months of age with bacterial meningitis?
- In children and young people with suspected or confirmed bacterial meningitis, can a cranial computed tomography (CT) scan reliably demonstrate raised intracranial pressure?
- 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?

- What are the clinical indications for intubation in children and young people with suspected/confirmed meningococcal septicaemia or bacterial meningitis?
- What is the effect on outcomes of using scoring systems in children and young people with suspected/confirmed meningococcal septicaemia?
- Do specialist transport teams improve outcomes and/or reduce adverse incidents during the transfer of children with meningococcal disease?
- What proportion of children and young people with meningococcal septicaemia develop physical and psychological morbidity?
- What is the prevalence of primary immunodeficiency in children and young people with meningococcal disease?

Ongoing research

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.

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.

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

None identified.

Conclusion

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.

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