Meningitis outbreak response in sub-Saharan Africa

WHO guideline

World Health Organization

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Contents

Definitions and abbreviations

Definitions

Suspected case (of meningitis): Any person with sudden onset of fever (>38.5 ^{o}C rectal or >38.0 ^{o}C axillary) and one of the following signs – neck stiffness, flaccid neck, bulging fontanelle, convulsion or other meningeal signs

Confirmed case (of meningitis): Isolation or identification of the causal pathogen (*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae* type b) from the cerebrospinal fluid of a suspected or probable case by culture, polymerase chain reaction (PCR) or agglutination test

Operational threshold: Criteria that trigger specific actions to prepare for an epidemic (the alert threshold) or respond to an epidemic (the epidemic threshold) in health districts, sub-districts or populations at risk

Alert threshold: A level of incidence that triggers action to prepare for an epidemic, including strengthening surveillance, confirming cases, distributing treatment protocols and informing the authorities

Epidemic threshold: A higher level of incidence that triggers an epidemic response, including mass vaccination, antibiotic distribution and raising public awareness

Abbreviations

AFRO	WHO Regional Office for Africa
AGREE	Appraisal of Guideline, Research and Evaluation in Europe
AMSTAR	Assessment of Multiple Systematic Reviews
CERMES	Centre de Recherche Médicale et Sanitaire, Niger
CSF	cerebrospinal fluid
DECIDE	Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence
GAVI	Global Alliance for Vaccines and Immunization
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hib	*Haemophilus influenzae* type b
ICG	International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control
IQR	interquartile range
MenAfriVac	serogroup A meningococcal conjugate vaccine
MRC	Medical Research Council, UK
Nm	*Neisseria meningitidis* (NmA, serogroup A; NmW, serogroup W, etc.)
NNV	number needed to vaccinate
PCR	polymerase chain reaction

PPV	positive predictive value
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized controlled trial
RDT	rapid diagnostic test
Spn	*Streptococcus pneumoniae*
ST	(multi locus) sequence type
UK	United Kingdom of Great Britain and Northern Ireland
USA	United States of America
WHO	World Health Organization

Executive summary

The meningitis belt of sub-Saharan Africa runs across the continent from Senegal to Ethiopia. This region is prone to major epidemics of meningococcal meningitis, with a high case fatality and serious sequelae that place a heavy strain on national and local health services. Until recently, most epidemics were due to *Neisseria meningitidis* serogroup A (NmA), such that the existing WHO guidelines have been directed mainly at the control of these epidemics. However, since 2010, countries in the meningitis belt have started to introduce a new serogroup A meningococcal conjugate vaccine (MenAfriVac) that is expected to confer both long-lasting individual protection and herd immunity. Following the successful roll-out of this vaccine, epidemics due to NmA are disappearing, but other meningococcal serogroups (e.g. NmW, NmX and NmC) still cause epidemics, albeit at a lower frequency and of a smaller size.

Due to these changes in the epidemiological pattern of meningitis, WHO set up a Guideline Development Group to review the evidence and recommendations for epidemic control in the meningitis belt. Four main topics were selected for review: operational thresholds for investigation and response to outbreaks, rapid diagnostic tests in outbreak management, antibiotic regimens in epidemics, and prophylaxis for household contacts of cases. This guideline does not include recommendations on vaccines that are already covered in existing WHO guidance.

The evidence was collected either through systematic searches for surveillance data (for questions on operational thresholds and antibiotic regimens) or through systematic literature reviews (for questions on rapid diagnostic tests and prophylaxis for households). The quality of the evidence was assessed – using Grading of Recommendations Assessment, Development and Evaluation (GRADE) – as "low" or "very low" for most questions. To move from evidence to recommendations, the framework from the "Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence" (DECIDE) project was followed, to assess the priority of the problem, quality of evidence, benefits and harms, values and preferences, resource use, equity, acceptability and feasibility before reaching a recommendation. Of the 16 recommendations developed (listed below), four were "strong" recommendations that were made in favour of an intervention, where potential benefits clearly outweighed any potential harms; the remaining 12 recommendations were "conditional".

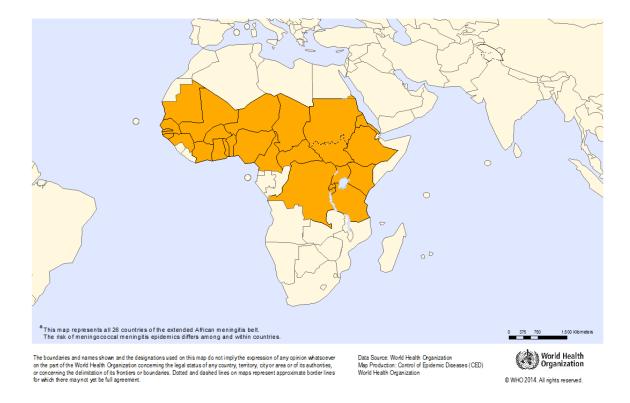| Recommendations |
| --- |
| **Operational thresholds** |
| *(i) Timeliness of response*. It is recommended that vaccination campaigns be implemented as soon as possible, and within 4 weeks of crossing the epidemic threshold
(Strong recommendation; low-quality evidence)
(ii) Population size for use in calculating operational thresholds. The recommended population denominators are <30 000 and 30 000–100 000. Where district populations are >100 000, assessment of incidence is recommended in administrative zones of 30 000–100 000
(No change [a]) (Conditional recommendation; low-quality evidence)
(iii) Alert threshold for populations of 30 000–100 000. The recommended alert threshold is 3 cases/100 000 people in a week (Strong recommendation; low-quality evidence)
(iv) Alert threshold for populations <30 000. The recommended alert threshold is either two cases in 1 week or a higher incidence than in a non-epidemic year
(No change [a]) (Conditional recommendation; expert opinion)
(v) Epidemic threshold for populations of 30 000–100 000. The recommended epidemic threshold is 10 cases/100 000 people in a week (Conditional recommendation; low-quality evidence)
(vi) Epidemic threshold for populations <30 000. The recommended epidemic threshold is five cases in 1 week, or a doubling of incidence in a 3-week period
(No change [a]) (Conditional recommendation; expert opinion)
(vii) Vaccination in populations adjacent to epidemic areas. Vaccination is recommended if the population is considered to be at risk (Conditional recommendation; expert opinion)
(viii) Special situations such as mass gatherings, refugees, displaced persons, or closed institutions such as schools or barracks. An immediate response, including mass vaccination, is recommended when two cases of meningococcal disease are confirmed in 1 week
(No change [a]) (Conditional recommendation; expert opinion) |
| **Rapid diagnostic tests** |
| (i) Rapid diagnostic tests (latex agglutination or immunochromatography dipsticks) are recommended for use in the investigation of meningitis outbreaks
(Conditional recommendation; low-quality evidence)
(ii) If rapid diagnostic tests are positive for a vaccine preventable serogroup, verification of serogroup by polymerase chain reaction (PCR) or culture is recommended before a decision is taken to initiate a vaccine response (Strong recommendation; expert opinion) |
| **Antibiotic regimens in epidemics** |
| (i) For treatment of suspected bacterial meningitis in children aged under 2 months, a 7-day course of ceftriaxone is recommended
(No change [a]) (Conditional recommendation; expert opinion)
(ii) For treatment of suspected bacterial meningitis in adults and in children aged 2 months and over, a 5-day course of ceftriaxone is recommended
(Conditional recommendation; very low quality evidence) |
| **Prophylaxis for household contacts** |
| (i) Antibiotics are recommended as a prophylactic measure for household contacts of all ages in non-epidemic periods, but not during epidemics
(No change [a]) (Conditional recommendation; very low quality evidence)
(ii) Ciprofloxacin is the preferred prophylactic agent, with ceftriaxone as an alternative when ciprofloxacin is contraindicated (Conditional recommendation; very low quality evidence)
(iii) Rifampicin is not recommended for use as a prophylactic agent
(Strong recommendation; low-quality evidence)
(iv) Vaccination is not recommended for household contacts(No change [a]) (Conditional recommendation; low-quality evidence) |

[a] No change from previous WHO guidelines

Background

Epidemiology

For over 100 years, major epidemics of meningococcal disease have occurred every few years within the African meningitis belt, which runs across the continent from Senegal to Ethiopia (Lapeyssonie, 1963). These epidemics are very disruptive, requiring the establishment of emergency treatment centres, and placing a severe strain on routine health services. The reason for the susceptibility of this region of Africa to major epidemics of meningococcal disease is at least in part related to its climatic features, with outbreaks occurring mainly in the hot, dry season (Sultan et al., 2005). Most epidemics have been due to *Neisseria meningitidis* serogroup A (NmA), and some have been due to serogroups W, X and C, but there has been a conspicuous absence of outbreaks due to serogroups B and Y. The hypervirulent clonal complexes ST-5 (mainly serogroup A) and ST-11 (mainly serogroup W) have accounted for most epidemics in this region. NmW, in particular, has been responsible for several epidemics in the past 10 years (e.g. in Burkina Faso, Ghana and Niger), but the dynamic of these NmW outbreaks appears to differ from those due to NmA. Based on district-level data from 2002 to 2012 in Burkina Faso, Chad, Niger and Nigeria, and defining an epidemic as crossing a weekly threshold of 10 cases/100 000 population, there were fewer NmW epidemics (36) than NmA epidemics (177) during this period. On average, NmW epidemics were 78% the size of NmA epidemics, with median cumulative attack rates of 109/100 000 (interquartile range [IQR] 79–134) for NmW and of 139/100 000 (IQR 99–230) for NmA.

Since 2010, countries in the extended meningitis belt (Figure 1) have started to progressively introduce a new serogroup A meningococcal conjugate vaccine (MenAfriVac) through mass campaigns (WHO, 2013). This preventive measure is expected to confer both long-lasting individual protection and herd immunity (Kristiansen et al., 2013; Novak et al., 2012; Sow et al., 2011). With the support of the Global Alliance for Vaccines and Immunization (GAVI), all but one country in the meningitis belt have, since 2000, introduced *Haemophilus influenzae* type b (Hib) vaccines, and many have already introduced *Streptococcus pneumoniae* (Spn) conjugate vaccines; hence, the incidence of bacterial meningitis due to non-meningococcal pathogens is also evolving.

Figure 1: Countries of the extended African meningitis belt [a]

The epidemiological pattern changed after the introduction of MenAfriVac, as demonstrated in Table 1. NmA declined to a low proportion of confirmed cases after 2010, and there was an accompanying rise in the proportion of cases due to NmW and, to a lesser extent, to NmX. Also, the total number of reported cases declined in the last 3 years. The pathogen distribution partly reflects the laboratory sampling and confirmation capacity, which is higher in Burkina Faso and Niger than in other countries in the belt. The proportion of suspected cases with laboratory confirmation across the belt has been rising over the past 10 years, from 2–3% in 2003 to 6–7% in 2013, but is still at a relatively low level.

Table 1. Reported and confirmed meningitis cases and pathogen distribution, countries of the African meningitis belt, 2003–2013

Year	Suspected cases	Confirmed cases	NmA	(%)	NmW	NmC	NmX	Other Nm	Total Nm	(%)	Spn	Hib	Other
2003	34829	1674	892	(53.3)	221			94	1207	(72.1)	319	86	62
2004	19478	1372	664	(48.4)	111	1	3	30	809	(59.0)	439	124	
2005	13132	777	182	(23.4)	33			53	268	(34.5)	323	125	61
2006	42763	2015	922	(45.8)	37		581	32	1572	(78.0)	274	102	67
2007	54180	1101	609	(55.3)	62			9	680	(61.8)	297	74	50
2008	28076	1464	1062	(72.5)	7			65	1134	(77.5)	243	48	39
2009	78980	2683	1996	(74.4)	167	17		30	2210	(82.4)	358	39	76
2010	24067	1667	439	(26.3)	726	4	55	14	1238	(74.3)	356	47	26
2011	16824	1847	197	(10.7)	514	5	154	6	876	(47.4)	879	53	39
2012	18664	1881	88	(4.7)	1009	4	138	33	1272	(67.6)	539	45	25
2013	10346	884	22	(2.5)	233	10	15	45	325	(36.8)	466	38	55
2004–2013	341339	15684	6181	(39.4)	2899	41	946	310	10377	(66.2)	4174	695	438

Hib: *Haemophilus influenzae* type b; Nm: *Neisseria meningitidis*; Spn: *Streptococcus pneumoniae; % of confirmed cases*

Source: WHO African Regional Office Inter-country Support Team for West Africa. The number of reporting countries has increased over time and varies from year to year. Nineteen countries of the meningitis belt provided enhanced surveillance data in 2013 (WHO, 2014a): Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Gambia, Ghana, Guinea, Mali, Mauritania, Niger, Nigeria, Senegal, South Sudan, Sudan and Togo. Prior to 2010, pathogens reported were NmA, NmW and "other Nm". Information on NmX and NmC prior to 2010 was compiled from other sources.

Current strategy

The current WHO epidemic control strategy (WHO, 2000) is based on the dynamics of epidemics before the introduction of MenAfriVac (Lewis et al., 2001). The main elements of the strategy are as follows (WHO, 2010):

- During the dry season, the epidemic risk is assessed at district level by monitoring the number of cases reported in a given population.
- Based on this risk assessment, operational thresholds have been defined that trigger the reinforcement of surveillance (the alert threshold), and the launch of vaccination campaigns and the use of a specific antibiotic treatment protocol (the epidemic threshold).
- Once the alert threshold is crossed, a sufficient number of cerebrospinal fluid (CSF) samples are taken to confirm the occurrence of a meningococcal meningitis outbreak, and to identify the responsible serogroup to inform the choice of vaccine.
- Once a meningococcal meningitis epidemic is confirmed, single-dose antibiotic treatment is recommended for case management, together with mass vaccination campaigns using an appropriate polysaccharide vaccine.

Because polysaccharide vaccines offer short-term protection only, they are used in outbreak response but not in routine immunization programmes.

Need for review of strategy

The current thresholds have been appraised as being both sensitive and specific for detection of NmA epidemics (Kaninda et al., 2000; Leake et al., 2002; Lewis et al., 2001). Following the introduction of MenAfriVac, NmW is now the predominant serogroup; hence, these threshold incidence rates and the population base for interventions may no longer be valid, and the recommendations for management of epidemic meningitis in the meningitis belt need to be reviewed.

Rapid diagnostic tests (RDTs) support urgent decision-making for outbreak management. Latex agglutination tests and dipsticks, such as those developed by the Centre de Recherche Médicale et Sanitaire (CERMES) in Niger (Chanteau et al., 2006), show variable sensitivity and specificity in field conditions. RDTs can discriminate, for example, between the various bacterial species causing meningitis and, for Nm, between serogroups A, C, W and Y, but not X. With the changing epidemiology, identifying the predominant bacterial agent and meningococcal serogroup in outbreaks has become increasingly important.

The recommended presumptive treatment of bacterial meningitis is administration of ceftriaxone for at least 5 days (WHO, 2010). During epidemics of meningococcal meningitis, to ensure rapid and effective treatment at first contact, single-dose regimens of ceftriaxone or chloramphenicol have been recommended (WHO, 2007). This protocol has been shown to provide effective treatment for meningococcal meningitis (Nathan et al., 2005); it is simple and cheap, and the necessary antibiotics can be made available at the most peripheral level. However, single-dose regimens are not effective against other pathogens such as Hib or Spn, which require longer courses of treatment (Brouwer et al., 2010). With fewer NmA outbreaks, a higher proportion of cases of meningitis due to Hib and Spn is expected, especially where vaccines against these pathogens have not yet been introduced.

Chemoprophylaxis is recommended for household contacts of sporadic cases of meningococcal disease in Africa, but not during epidemics (WHO, 1998). In European countries, no distinction is made between

sporadic cases and outbreaks in terms of recommendations for prophylaxis (antibiotics and vaccination, where relevant), although the scale of outbreaks in the WHO European Region is much smaller than in the meningitis belt. Chemoprophylaxis of household contacts may be effective in settings outside the African meningitis belt (Purcell et al., 2004), and vaccination, where relevant, may offer additional protection (Hoek et al., 2008), but evidence from the meningitis belt is scarce. One randomized trial in Nigeria during an epidemic of serogroup A in the 1970s showed benefit from vaccination of household contacts in the absence of chemoprophylaxis (Greenwood et al., 1978). With the expected reduction in frequency and extent of epidemics in the meningitis belt, it is timely to review this policy.

The objectives of this review were to revise WHO guidelines on control of epidemic meningitis in sub-Saharan Africa concerning:

1. operational thresholds and vaccination responses
2. use of RDTs
3. use of single-dose antibiotic regimens
4. prophylaxis for household contacts.

The outcomes of reviews of these four questions are presented in this guideline. Operational procedures on implementation of the guideline will be produced separately. The guideline only applies to countries of the extended meningitis belt (Figure 1), and does not include guidance on vaccines, which is covered by a WHO position paper (WHO, 2011).

The target audience includes ministries of health, nongovernment organizations (NGOs), WHO regional and country offices, and public health professionals working in the extended African meningitis belt; WHO collaborating centres; manufacturers of vaccines, RDTs and antibiotics; and funding agencies.

Methods

Process and scope

The process developed by the WHO Guideline Review Committee was followed (WHO, 2012a). A WHO Steering Group, a Guideline Development Group and an External Review Group were set up (Annex 1). Members of these groups were selected because of their experience and expertise relating to meningococcal meningitis in African meningitis belt countries. The scope of the guideline and draft PICO (population, intervention, comparator, outcome) questions were reviewed by the WHO Steering Group. The questions were then submitted to the Guideline Development Group and External Review Group through an electronic consultation and scheduled teleconferences, and these groups provided input, endorsed the process that was overseen by an expert methodologist (Scholten R), and agreed on the scope (shown in Box 1 below) and PICO questions (Annex 2).

Scope of guideline

1. Following the introduction of MenAfriVac, what criteria should be used to determine when to start mass vaccination in outbreaks of meningococcal meningitis?
2. What is the place of rapid diagnostic tests (RDTs) in decisions on outbreak management?
3. Should single-dose antibiotic regimens continue to be recommended for suspected cases of meningitis during a meningococcal meningitis outbreak, and if so, in what circumstances?
4. Should prophylaxis (antibiotics and/or vaccination) be recommended for household contacts of cases of meningococcal meningitis in epidemic and non-epidemic settings?

Evidence retrieval and synthesis

The web annex (*link to be added*) includes the study protocols, systematic reviews and reports for each question.

Question 1: Operational thresholds. Review team: Trotter C (lead), Cibrelus L, Stuart J, Fernandez K, Ronveaux O.

A protocol was developed for a systematic search for primary surveillance data in the countries of the meningitis belt. Data were requested from the WHO Regional Office for Africa (AFRO) and other organizations such as the Agence de Médicine Préventive (France), Médecins sans Frontières Epicentre (France), Centers for Disease Control and Prevention (United States of America, USA), Medical Research Council (MRC) Centre for Outbreak Analysis and Modelling (United Kingdom of Great Britain and Northern Ireland, UK)**.** Also, a literature search was undertaken using PubMed-Medline, EMBASE, African Index Medicus, WHO regional databases and grey literature (using Google with country filters; e.g. meningitis site:gov.nb). The period of the search was from 2002 to 2013 inclusive. Papers in English and French were included. The available data on the course of NmW meningococcal meningitis epidemics (weekly case counts) were used to derive the potential number of cases averted, by using a range of lower alert and epidemic thresholds than the current standard, taking into consideration the effect of any mass vaccination in that population (including the estimated time to deliver a vaccination campaign and for the vaccine to take effect).

Question 2: Rapid diagnostic tests. Review team: Waite T (lead), Telisinghe L, Fernandez K, Ronveaux O, Gobin M, Stuart JM, Scholten R (methodologist).

A systematic review protocol was developed and approved by the methodologist. No date limit was imposed unless a relevant prior review was identified, in which case, primary studies published after the search date of that review were considered. Unless explicitly included in any systematic review, the search for primary studies was extended using African Index Medicus, WHO regional databases and grey literature (using Google with country filters; e.g. meningitis site:gov.nb). There was no language restriction. Studies selected were appraised for quality by two researchers independently using Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 (Whiting et al., 2011). The results of the various tests were compared with the reference standards, and performance under laboratory and field conditions was assessed.

Question 3: Antibiotic regimens in epidemics. Review team: Cibrelus L (lead), Gwanyalla G, Stuart JM, Fernandez K, Ronveaux O.

A systematic search for primary surveillance data in the countries of the meningitis belt was sought, as for Question 1. Data on the incidence of meningitis due to Nm, Hib and Spn during outbreaks of meningococcal meningitis were extracted, together with data on age-specific incidence by pathogen.

Question 4: Prophylaxis of household contacts. Review team: Telisinghe L (lead), Waite T, Fernandez K, Ronveaux O, Gobin M, Stuart JM, Scholten R (methodologist).

A systematic review protocol was developed and approved by the methodologist, using the same search methods and criteria as for Question 2. The quality of systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Shea et al., 2007). For randomized trials, the Cochrane Collaboration tool for assessing risk of bias was used (Higgins & Green, 2008). Meta-analyses of

observational studies were done using Cochrane methodology (Higgins & Green, 2008) and Review Manager software.[1] Systematic reviews were included if they:

- addressed the PICO elements;
- included searching of Medline and at least one other electronic database;
- assessed risk of bias of the three main quality items for randomized controlled trials (RCTs) (allocation concealment, blinding of the outcome assessor and completeness of follow-up) and, if applicable, the main quality items for comparative observational studies (selection of the study cohorts, comparability of the study arms, blinding of the outcome assessor and completeness of follow-up); and
- reported the results of bias assessment for the individual studies.

A separate search without time limit was conducted on risk of meningococcal meningitis in household contacts (Kannangara N).

For all questions, evidence was assessed based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, categorizing quality of evidence and strength of recommendation (Atkins et al., 2004), and supported by the WHO "Handbook for guideline development" (Schunemann et al., 2007; WHO, 2012a) and the "Cochrane handbook for systematic reviews of interventions" (Higgins & Green, 2008). For Question 2, on diagnostic tests, an adapted version of the current GRADE "From evidence to recommendations framework for interventions" was used. A modified approach to GRADE profiling was also developed for Questions 1 & 3 (threshold and antibiotic regimen), because the evidence for these questions was provided by a search of surveillance datasets and a literature review, not through a systematic review. After consultation with the WHO Guidelines Review Committee and the methodologist, surveillance data was considered to be of "high quality" as a starting-point, for the purpose of this review.

The quality of evidence is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the quality of evidence as "high", "moderate", "low" and "very low" (Table 3.1 in Guyatt et al., 2011). RCTs are initially rated as high-quality evidence, but may be downgraded for several reasons, such as risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence. High-quality observational studies (i.e. observational studies that have not been downgraded) may be upgraded if the magnitude of the treatment effect is large, multiple studies show the same effect, evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect (Guyatt et al., 2011). The higher the quality of evidence, the more likely it is that a strong recommendation can be made. Where a systematic review was not conducted or was not available to inform a recommendation, the views of the Guideline Development Group were sought. In such situations, when a unanimous decision was reached, the recommendation is presented in this guideline as "expert opinion".

Evidence to recommendations

The steering group drafted evidence-to-recommendation frameworks using templates developed as part of the "Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence" (DECIDE) project (Treweek et al., 2013). The evidence summaries and frameworks were presented to the Guideline Development Group in Geneva on 15 and 16 May 2014, to discuss the priority of various factors – the problem, quality of evidence, benefits and harms, values and preferences, resource

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[1] Software (also known as "RevMan"), Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

use, equity, acceptability and feasibility – before formulating recommendations. In the absence of a public survey, a paper on costs and values of meningitis in Africa from a literature search was made available to the group (Stuart J, Cibrelus L). Resource use was considered from the perspective of families affected by meningitis and that of the health services. No formal cost–benefit analysis was undertaken. Values and preferences were sought in the same literature search. In 2008, ministers of health of African countries of the meningitis belt referred to the devastating meningitis epidemics that take a heavy socioeconomic and human toll, especially among the young and active population (WHO, 2008). In a community study exploring views of meningitis, the general perception was that the disease is highly dangerous (Desmond et al., 2013). Caregivers of children with serious sequelae from meningitis in Senegal commented on the unaffordability of transport for continuing hospital outpatient visits. In most families, there was someone who was unable to work because they had to look after the affected child. None of the families could afford the treatment that they would have liked for their children (Griffiths et al., 2012).

The draft guideline was reviewed by the External Review Group. The reviewers' comments were compiled and circulated to all members of the Guideline Development Group, together with proposed modifications to the guideline. A WHO intern also assessed the guideline using the Appraisal of Guideline, Research and Evaluation in Europe (AGREE) II criteria (Brouwers et al., 2010). The guideline was revised accordingly, and the final version was approved by the Guideline Development Group.

Recommendations were classified as "strong" or "conditional" (i.e. "weak"). A strong recommendation is one for which the Guideline Development Group is confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects. A conditional recommendation is one for which the Guideline Development Group concluded that the desirable effects of adhering to the recommendation *probably* outweigh the undesirable effects, but was not confident about these trade-offs. The reasons for making a conditional recommendation include the absence of high-quality evidence, imprecision in outcome estimates, variability in the values and preferences of individuals regarding the outcomes of interventions, small benefits, lack of universal applicability, and benefits that may not be worth the costs (including the costs of implementing the recommendation). When applying the guideline, a strong recommendation is one for which most individuals or communities should receive the intervention, and most individuals – on being informed of the potential benefits and risks of a recommended intervention – would opt for its introduction; also, that intervention could unequivocally be used in policy-making (Andrews et al., 2013a, 2013b). A conditional recommendation is one where most well informed individuals or communities would want the intervention, but an appreciable proportion would not, and policy-making would require extensive debate and the involvement of many stakeholders.

Decision-making

The evidence-to-recommendation framework for each of the four questions was discussed in turn, before moving to formulation of recommendations. The first question, on thresholds, was debated in plenary; the other three questions were discussed in working groups, then presented to the whole group for further discussion and endorsement. Comments from the External Review Group were made available to participants and were explicitly considered in discussions on each question. Consensus, defined as group agreement without dissent, was reached on all but two points. The two exceptions related to the appropriate denominator population for calculating alert and epidemic thresholds, and the epidemic threshold itself. After lengthy debate, a vote was held, with a 60% majority reached on recommendations for both points. As agreed in the guideline proposal document, the view of the majority (over 50% of group members) was upheld, and the views and concerns of the minority were recorded and included in the recommendations section of the guideline.

Declaration of interest

Signed declaration of interest statements were provided by all members of the Guideline Development Group and External Review Group. In addition, members of the Guideline Development Group were asked to declare any conflict of interest verbally at the beginning of the face-to-face meeting. Several members of the Guideline Development Group and of the External Review Group declared potential conflicts of interest (Annex 3). One member (CT) declared past receipt of consulting fees from the pharmaceutical industry, and three members (JM, JMC, BDG) declared pharmaceutical industry financial support through grants for research. These grants, however, had ceased or were not directly related to the topic of the meeting. One member (MLF) declared current employment with a pharmaceutical company, but that company had no interest in a particular product related to the guideline. Three members (RK, BG, BDG) declared receiving grants for research or other financial support from non-commercial entities (foundations, international organization). Five members (TC, MH, MLF, GE, DS) declared having been involved or currently being involved in academic work related to the topic of the meeting, but none of this work involved either primary research or conducting systematic reviews relating directly to the recommendations in question.

None of the participants declared either a significant academic or a financial interest in a company with a commercial interest in the outcome of the guideline. Therefore, full participation of all members of the Guideline Development Group in the decision-making process and of the External Review Group in advising on the guideline was considered appropriate by the Steering Group. Furthermore, the broad range of constituencies represented on the Guideline Development Group and External Review Group was noted, as was the fact that most members had no declared interests.

Operational thresholds

Evidence

Evidence relating to operational thresholds came from a dataset comprising weekly case counts from 136 district years, each with at least two laboratory confirmed cases of NmW, and over 50% of confirmed cases of Nm diagnosed as cases of NmW. District population sizes ranged from 59 330 to 884 859, with a median size of 263 110.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value of different epidemic thresholds were calculated, for detecting an epidemic defined as a district cumulative attack rate of between 20 and 100 per 100 000. For example, to detect an epidemic defined as a cumulative attack rate of 80/100 000, an epidemic threshold of 10/100 000 per week had a sensitivity of 92% and a PPV of 67%, whereas a threshold of 7/100 000 had a sensitivity of 100% and a PPV of 55%.

The number of cases potentially preventable by reactive immunization was estimated, assuming effective vaccine coverage of 75%. Based on a 4-week interval between crossing the epidemic threshold – when a request for release of vaccines should be submitted to the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG) – and the start of a meningococcal polysaccharide vaccination campaign, an estimated 17 cases per event would be prevented at a threshold of 10 cases/100 000 inhabitants, increasing to 46 cases per event at 3/100 000 (Annex 4). If the interval could be shortened by 2 weeks, the estimated number of cases prevented would be 54 per event at a threshold of 10/100 000, increasing to 71 per event at 3/100 000. The estimated number of cases prevented would be higher at a threshold of 10/100 000 with a 2-week interval than with a threshold of 3/100 000 and a 4-week interval.

The quality of evidence supporting these results was assessed as low because of the low proportion of confirmed cases in the dataset, and the indirect evidence provided by estimating the potential impact of vaccination rather than directly observing an effect (Annex 4). In addition, the data were derived mainly from districts with a population over 100 000, thereby reducing their direct relevance for outbreak detection and response in smaller populations (suggested in current guidelines). Although the wide range in number of cases prevented suggests serious uncertainty in the effect estimates, the heterogeneity of the data is considered to reflect the true variation of epidemic meningitis in the African meningitis belt.

From evidence to recommendations

The Guideline Development Group acknowledged the burden of meningitis perceived by communities in the African meningitis belt (Desmond et al., 2013; WHO, 2008). This burden is partly due to a high case fatality and the occurrence of serious sequelae (Edmond et al., 2010; Ramakrishnan et al., 2009), but also to the economic burden on families of caring for a case of meningitis, such that the socioeconomic impact of meningitis is disproportionally felt by poorer families (Akweongo et al., 2013; Colombini et al., 2009; Griffiths et al., 2012). The group considered that this burden outweighs the harms of the intervention, because polysaccharide and conjugate vaccines are well tolerated and serious adverse events are exceedingly rare, as long as the response is timely enough to avert cases and deaths due to the outbreak.

However, the costs of mass vaccination in relation to potential benefit are highly dependent on vaccine price, and the rapidity and effectiveness of the community intervention. Regular health services may be disrupted during an outbreak, whether due to large numbers of patients or to the effort required to mount a vaccination campaign. Thus, the potential benefit of accepting lower thresholds for vaccination response must be balanced against the possibility of more frequent outbreak responses and the ensuing strain on health service capacity to sustain regular health services. The estimated cost of vaccination (including operational costs) for a district of 100 000 people is US$ 105 000 for MenAfriVac, US$ 360 000 for ACW polysaccharide and US$ 613 000 for quadrivalent polysaccharide vaccine (ICG, 2014 price estimates).

With a 4-week interval from crossing an epidemic threshold to the start of vaccination, the vaccine cost per case prevented (including operational costs) ranged from US$ 31 200 to US$ 13 700 with ACW polysaccharide vaccine, depending on the threshold tested. The corresponding number needed to vaccinate (NNV) to prevent a case varied from 11 600 to 4300. In 2004, the estimated NNV to prevent a case of invasive pneumococcal disease in the USA was similar, at 3300 (Kelly et al., 2004). If implementing community-wide vaccination is possible within 2 weeks of crossing a set epidemic threshold, costs per case prevented range from US$ 10 600 to US$ 8600 (NNV 3700 to 2800) depending on the threshold. Thus, achieving the shortest possible response time improves the cost-effectiveness of the intervention, regardless of the threshold selected.

Question

Following the introduction of MenAfriVac, what criteria should be used to determine when to start mass vaccination in outbreaks of meningococcal meningitis?

Recommendations

Topic	Previous	New
Timeliness of response	Early detection of epidemics is essential for an effective operational response	**It is recommended that vaccination campaigns be implemented as soon as possible, and within 4 weeks of crossing the epidemic threshold.** (Strong recommendation; low-quality evidence)
Population size for use in calculating operational thresholds	Population of <30 000 and populations of 30 000–100 000 [a]In populations >100 000, sub-districts (surveillance zones or health facility catchments) of 30 000–100 000 are advised	**The recommended population denominators are <30 000 and 30 000–100 000.** **Where district populations are >100 000, assessment of incidence is recommended in administrative zones of 30 000–100 000.** (No change from previous WHO guideline) (Conditional recommendation; low-quality evidence)
Alert threshold (threshold to intensify epidemic preparedness)		
Populations of 30 000–100 000	Five cases/100 000 in 1 week	[b]**The recommended alert threshold is three cases/100 000 in a week.** (Strong recommendation; low-quality evidence)
Populations of <30 000	Two cases in 1 week or higher incidence than in a non-epidemic year	**The recommended alert threshold is either two cases in 1 week or a higher incidence than in a non-epidemic year.** (No change from previous WHO guideline) (Conditional recommendation; expert opinion)

Epidemic threshold (threshold to initiate epidemic treatment and vaccination response)		
Population of 30 000–100 000	**10 cases/100 000 in 1 week** if: - no epidemic in last 3 years and vaccination coverage <80% ; or - alert threshold crossed early in the dry season **or** **15 cases/100 000 in a week in other situations**	**The recommended epidemic threshold is 10 cases/100 000 in 1 week** (Conditional recommendation; low-quality evidence)
Population of <30 000	Five cases in 1 week or a doubling of incidence in a 3-week period	**The recommended epidemic threshold is five cases in 1 week or a doubling of incidence in a 3-week period** (No change from previous WHO guideline) (Conditional recommendation; expert opinion)
Vaccination in populations adjacent to areas in epidemic	Vaccinate when alert threshold reached	[c]**Vaccination is recommended if the population is considered to be at risk** (Conditional recommendation; expert opinion)
Special situations such as mass gatherings, refugees, displaced persons, or closed institutions such as schools or barracks	Immediate response, including mass vaccination, when two cases of meningococcal disease are confirmed in 1 week	**An immediate response, including mass vaccination is recommended when two cases of meningococcal disease are confirmed in 1 week** (No change from previous WHO guideline) (Conditional recommendation; expert opinion)

[a] Refers to WHO (2009); all other previous recommendations refer to WHO (2000).

[b] Since an attack rate of 3/100 000 in a week can be reached in population of 30 000 with just one case, a minimum of two cases is suggested. However, even one case in a small population calls for investigation and confirmation.

[c] Guidance has been changed to allow more flexibility in response. An area would be considered at risk in the absence of a recent relevant vaccination programme if cases occurred early in the dry season, or in crowded populations.. As a minimum, crossing the alert threshold with at least one confirmed case due to the outbreak organism would be expected before considering vaccination.

Remarks

- The case definition for threshold calculations is a suspect or confirmed case of meningitis. Confirmation of the causative organism in an outbreak is required before a vaccination campaign with an appropriate meningococcal polysaccharide (or conjugate) vaccine is undertaken.

- Previous recommendations were developed primarily in the context of NmA epidemics. The new guidelines apply primarily to NmW epidemics. The decline in all forms of bacterial meningitis due to vaccine introduction should make it easier to detect outbreaks when they do occur. Therefore, the

group considered that, until field experience and research provide new evidence, these new recommendations should also apply for other vaccine preventable serogroups (e.g. NmC and NmY).

- Strong recommendations were made on timeliness of response and on lowering the alert threshold, despite the low quality of the evidence. The rationale is that both of these recommendations imply no additional interventions in relation to individuals, but at the same time have the potential to bring forward vaccination once the epidemic threshold is crossed, and thus to prevent more cases of meningitis.

- For the epidemic threshold in larger populations, a single threshold level was proposed as it was considered simpler to apply. A majority of the Guideline Development Group was in favour of using the 10/100 000 threshold, and a minority preferred to lower it to 7/100 000. The discussions revolved around the potential advantages of lowering the threshold to accelerate the time to vaccination, versus the costs of vaccination campaigns in relation to their benefit.

- For the population to be considered in assessment of operational thresholds, a majority of the group favoured populations of 30 000–100 000, as recommended in current guidelines. A minority preferred using either administrative districts of any size (because some countries have been following this practice), or populations over 100 000 (because the available data were derived mainly from districts of this size).

- The thresholds for populations <30 000 were left unchanged, because data were not available on which to base a new recommendation. Similarly, although no data were available regarding vaccination of areas neighbouring those already experiencing an epidemic, the Guideline Development Group agreed that – as NmW outbreaks are more localized then NmA outbreaks – it was preferable not to propose a specific threshold, but to leave the decision to local stakeholders.

- The alert and epidemic thresholds may be adapted if this is judged appropriate by the responsible health authorities. Consultation with WHO is advised before proceeding with an ICG request.

Implications

- Countries in the African meningitis belt should consider keeping national stockpiles of vaccine, to allow for a speedy response, but should balance potential needs with shelf-life, storage capacity and global supply.

- In every country in the meningitis belt, confirmatory diagnostic capacity to support enhanced and case-based surveillance should be available.

- Partners should support the quality and timeliness of country requests to ICG.

- The highest risk of epidemic response is disruption of routine health services, especially routine immunization services. Countries should have in place systems to respond to epidemics (at least, to most epidemics) without adversely affecting routine immunization service delivery.

- WHO will make available to countries the expected timelines of the stages of mounting a vaccination response. These timelines will take into consideration the time from availability of vaccines to the time when they reach the district level for the campaign.

Evaluation and research

Countries, WHO and other partners should;

- monitor and evaluate response timelines, to identify areas for improvement;

- monitor and analyse surveillance data on the dynamics of Nm outbreaks and pathogen distribution, especially in populations <100 000;

- monitor and assess the reappearance of NmA where vaccination campaigns with conjugate vaccines have taken place, to understand NmA epidemiology in this context; and

- monitor and assess the dynamics of outbreaks due to meningitis strains other than A and W (e.g. C, X and Y).

Rapid diagnostic tests

Evidence

The evidence for RDTs was provided through a systematic review (see Annex 5, and full review in web annex)(link to be added). A full search for primary papers was conducted because no previous systematic review of RDTs for bacterial meningitis was identified. Of 3004 records found in the literature search, 18 papers describing 16 observational studies, and two laboratory validation studies, were included in the analysis. In-country polymerase chain reaction (PCR) was considered the "ideal" reference standard. Studies were included only when data comparing an RDT and a reference standard for all patients in the study were available. Results reported are limited to those test kits that are still in production, and those that can both detect and distinguish between NmA, NmC and NmW, and Spn. Four RDTs were assessed: two latex agglutination tests (Pastorex meningitis kit and BD Directigen Meningitis Combo Kit), and two immunochromatographic tests (BinaxNOW *S. pneumonia* and CERMES duplex dipstick).

The 16 observational studies were conducted in two different settings:

- *field studies* – in which the performance of the RDT at a district or regional health facility was assessed (e.g. close to the patient) and conducted by health-care staff or local laboratory staff; and
- *laboratory studies* – in which the performance of the RDT was assessed in a central or national reference laboratory.

Table 2. Performance of different rapid diagnostic tests in detection of *N. meningitidis* serogroups W and A and *S. pneumoniae* under laboratory and field conditions

Test, conditions and organism	Test performance, assuming 20% prevalence of pathogen being tested					
	Sensitivity % (95% CI)	Specificity % (95% CI)	True positives/ 1000 CSFs	False negatives/ 1000 CSFs	True negatives/ 1000 CSFs	False positives/ 1000 CSFs
CERMES ICT Field W	92 (88–94)	95 (93–96)	184 (176–188)	16 (12–24)	760 (744–768	40 (32 -56)
CERMES ICT Lab W	97 (95–98)	95 (93–96)	194 (190–196)	6 (4–10)	760 (744–768)	40 (32–36)
Pastorex LAT Lab W/Y	88 (84–92)	98 (97–99)	176 (168–184)	24 (16–32)	784 (776–792)	16 (8–24)
BD Directigen Lab W	100 (93–100)	40 (12–74)	200 (186–200)	0 (0–4)	320 (96–592)	480 (208–704)
Binax NOW Spn	99 (96–100)	96 (95–97)	198 (192–2000	2 (0–8)	768 (760–776)	32 (24–40)
CERMES ICT Field A	87 (84–89)	79 (76–82)	174 (168–178)	26 (22–32)	632 (608–656)	168 (144–192)
Pastorex LAT Field A	65 (53–75)	84 (72–92)	130 (106–150)	70 (50–94)	672 (576–736)	70 (50–94)
CERMES ICT Lab A	86 (84–89)	77 (74–79)	172 (168–178)	26 (22–32)	616 (592–632)	184 (168–208)
Pastorex LAT Lab A	88 (85–90)	97 (96–98)	176 (170–180)	24 (20–30)	776 (768–784)	24 (16–32)

CERMES: Centre de Recherche Médicale et Sanitaire; CI: confidence interval; CSF: cerebrospinal fluid; ICT: immunochromatographic test; Lab: laboratory; LAT: latex agglutination; Spn: *Streptococcus pneumoniae*

Relatively few field evaluations of RDTs were available. Sensitivity and specificity of CERMES RDTs indicate a satisfactory performance in field testing for NmW (Table 2 and Annex 4). The laboratory performance of Pastorex LAT was also satisfactory, but no NmW field evaluation data were available. BD Directigen had a low specificity. Performance of the tests in diagnosis of NmA under field conditions was more variable for both CERMES and Pastorex tests. Binax NOW perfomed to a high standard in diagnosis of Spn under laboratory conditions. Pastorex cannot distinguish between NmW and NmY, and there were no data on evaluation of NmC tests. The quality based on diagnostic test assessments were mainly low, with one very low (BD Directigen Lab W), one moderate/low (Pastorex LAT Field A) and one moderate (Pastorex LAT Lab A).

From evidence to recommendations

As discussed above, meningitis is perceived as a major burden by communities in the African meningitis belt; hence, the Guideline Development Group considered it important not to miss an outbreak in which vaccination should be given. Multiple testing analysis, based on the PPV of the only test for NmW in which studies were available in field conditions, is presented in Table 3. However, there are still risks of false-negative results of a vaccine preventable serogroup, such that vaccination may not occur when indicated if relying only on RDT results.

Table 3. Estimated number of true NmW positives,[a] given different numbers of observed dipstick positive tests using CERMES ICT

If n tests are positive for NmW (line a), how many are likely to be true NmW (line b)?								
a. Observed number of NmW dipstick positives	3	4	5	6	7	8	9	10
b. Minimum number of true NmW positives	2	3	4	5	6	7	7	8

CERMES: Centre de Recherche Médicale et Sanitaire; ICT: immunochromatographic test; Nm: *Neisseria meningitidis*

[a] This calculation assumes 20% prevalence of NmW

The Pastorex meningitis kit (25 tests) and BinaxNow Spn test kit (22 tests) are both available at about US$ 8 per test. The BD Directigen kit (30 tests) is more expensive, at US$ 40–60 per test. The CERMES dipsticks are not yet commercially available. The group considered that the potential gain in time between epidemic signal detection and start of vaccine response outweighed the costs of the tests. Making RDTs more widely available at short notice could reduce inequity, because it would allow peripheral areas to confirm the pathogen and respond to an epidemic quickly.

There are important logistic limitations to the use of latex agglutination tests, because they need to be kept cold and are not as simple to use as the immunochromatographic tests. Pastorex must be kept at 2–8 °C, has a shelf life of 8 months, and expires 1 month after the pack (25 tests) is opened. Of the immunochromatographic tests, the CERMES dipstick (ACW) has a shelf life of 2 years at up to 25 °C (up to 8 months for Y), and BinaxNOW has a shelf life of 1 year at 2–30 °C.

Question

What is the place of rapid diagnostic tests in decisions on outbreak management?

Recommendations

Topic	Previous	New
Use of RDTs to detect epidemics of meningococcal meningitis	RDTs recommended for use as confirmatory tests to aid decision-making on appropriate vaccine in epidemics. (WHO, 2003)	**RDTs (latex agglutination or immunochromatography dipsticks) are recommended for use in the investigation of meningitis outbreaks** (Conditional recommendation; low-quality evidence)
		If RDTs are positive for a vaccine preventable serogroup, verification of serogroup by PCR or culture is recommended before a decision is taken to initiate a vaccine response[a] (Strong recommendation; expert opinion)

RDT: rapid diagnostic test; PCR: polymerase chain reaction

[a] PCR or culture are the accepted gold standard tests (Boisier et al., 2009; Borel et al., 2006) for confirming a diagnosis of meningococcal meningitis, and the performance of the RDTs in all papers reviewed here was assessed against PCR or culture (or both); hence, a strong recommendation was made that the results of positive RDTs should be verified by PCR or culture. At least one (and preferably more than one) serogroup-positive RDT results should be verified before a vaccine response is initiated.

Remarks

- These recommendations do not address the use of RDTs for individual clinical management.

Implications

- Delivery of RDTs should include programmatic elements such as training, organized transmission of results and related information, and quality control.

- In-country capacity for confirmation by PCR and culture should be developed or maintained.

- No preferential recommendation is made between RDTs; however, based on test accuracy for confirmation of serogroup W and A outbreaks, access to heat-stable tests (e.g. immunochromatographic tests) should be promoted.

- Dissemination of RDT testing algorithms and multiple testing tables by the WHO will facilitate decision-making.

Evaluation and research

Countries, WHO and other partners should:

- encourage and conduct field evaluations of performance of existing tests for all serogroups, including serogroup C;

- strongly promote the production of heat-stable RDTs; and
- promote the development of a serogroup X RDT.

Antibiotic regimens during epidemics

Evidence

A total of 22 epidemic events met the inclusion criteria for analysis; 11 NmW/NmX epidemics (i.e. involving NmW, NmX, or both), and 11 NmA epidemics. All events occurred in countries of the meningitis belt between 2002 and 2014. The NmA epidemics all occurred in populations where MenAfriVac had not been introduced.

In NmW and NmX epidemics, about 9% of the cases were due to Hib or Spn (pooled proportion), compared with about 13% in NmA epidemics; confidence intervals were wide, and the differences were not statistically significant (Annex 4). The lower proportion of cases due to Spn or Hib in NmW and NmX epidemics is nonetheless surprising, given the higher proportion of Spn seen in the meningitis belt in recent years (Table 1). The proportion of pathogens per age group was also similar between NmW/NmX and NmA epidemics. However, comparison of age group distribution for NmA epidemics was limited to one country, with small numbers in many age categories. In NmW epidemics, the proportion of other pathogens in 2–14 year olds was 5%, rising to 9% in 15–29 year olds, and was higher in over 29 year olds. The quality of evidence was considered very low due to wide variability between studies, changes in vaccination programs affecting pathogen distribution, and a risk of bias towards reporting findings from larger epidemics.

From evidence to recommendations

The current recommendation for management of epidemic meningitis in the African meningitis belt is to use single-dose antibiotic regimens (ceftriaxone 100 mg/kg intramuscular or oily chloramphenicol 100 mg/kg intramuscular) for suspected cases in those over 2 years of age, review after 24 and 48 hours, and continue treatment if not improving (WHO, 2007, 2010). Single-dose regimens have been shown to be effective for treatment of meningococcal meningitis (Nathan et al., 2005), but not for other causes of bacterial meningitis such as Spn or Hib; thus, antibiotic treatment for 10–14 days (and at least 5 days) is normally recommended for presumptive treatment of acute bacterial meningitis (WHO, 2012b, 2013). In addition, meningitis due to Spn or Hib carries a higher risk of sequelae and death than meningococcal meningitis, meaning that longer treatment should reduce morbidity and mortality. According to the evidence reviewed, the proportion of Hib and Spn meningitis may be similar in NmW, NmX and NmA epidemics; hence, during outbreaks, up to 8% of cases (those due to Hib or Spn)may be treated suboptimally.

Whereas a single dose of ceftriaxone is considered to have only minor side-effects, a 5-day treatment may increase the risk or lead to undesirable consequences of hospitalization (e.g. nosocomial infection) Conversely, the risk of antibiotic resistance may be higher if inappropriate short-term treatment is given. Oily chloramphenicol is also a single intramuscular injection, but is more difficult to administer and costs more per dose than single-dose ceftriaxone. Other formulations of chloramphenicol have been linked to a

risk of bone marrow toxicity (Wallerstein et al., 1969). Also there is an increasing trend towards Nm, Spn and Hib showing resistance to chloramphenicol (WHO, 2012b).

The cost of ceftriaxone for a 5-day course is approximately US$ 7 plus hospitalization costs, representing an added economic burden to both the family and health services, whether the disease is treated at a hospital or a health centre. If all cases of meningitis (including 90% of meningococcal meningitis cases) are given a 5-day course of treatment during epidemics, the number of hospital bed days could be three or four times more than for a single-dose treatment policy. However, hospitalization is not mandatory if the patient is stable and able to return each day for antibiotics, and the increased care costs must be balanced against the potential costs of more sequelae and higher mortality if a single-dose policy is used. For families of patients, the option may be acceptable, provided that governments ensure free treatment during epidemics (as per current policy). The burden of longer hospitalization and multiple journeys to hospital may fall unequally on lower income rural communities, given the views of caregivers about the economic burden of caring for a case of meningitis (Akweongo et al., 2013; Colombini et al., 2009; Griffiths et al., 2012).

The Guideline Development Group considered that the benefit of changing to longer course antibiotic treatment regimens as standard treatment – as recently reviewed for children (WHO, 2012b) – and the resulting potential for reduced mortality and morbidity, outweighed the potential adverse effects and higher costs, given the higher case fatality and sequelae of Hib and Spn meningitis. In the large-scale NmA epidemics, where large numbers of meningococcal cases overwhelmed health centres, the group considered that a single-dose treatment policy followed by longer treatment if the patient was not improving was appropriate. With fewer meningococcal meningitis epidemics and outbreaks of lower magnitude following the introduction of MenAfriVac, longer treatment regimens should be easier to implement.

Question

Should single-dose antibiotic regimens continue to be recommended for suspected cases of meningitis during a meningococcal meningitis outbreak, and, if so, in what circumstances?

Recommendations

Topic	Previous	New *
Antibiotic treatment of meningitis during meningococcal meningitis epidemics	(i) Suspected cases of bacterial meningitis in children aged under 2 months or aged 2-23 months should be treated with a 7-day or 5-day course of ceftriaxone respectively. (ii) Suspected cases of bacterial meningitis aged 2 years and over should be treated with single-dose antibiotics (oily chloramphenicol or cefriaxone) and reviewed at 24 and 48 hours.	**(i) For treatment of suspected bacterial meningitis in children aged under 2 months, a 7-day course of ceftriaxone is recommended** (Conditional recommendation; expert opinion) **(ii) For treatment of suspected bacterial meningitis in adults and in children aged 2 months and over, a 5-day course of ceftriaxone is recommended. Single-dose antibiotic treatment is no longer recommended.** (Conditional recommendation; very low quality evidence)

Remarks

- The recommendations for 7-day and 5-day treatment with ceftriaxone (100mg/kg/day IM or IV once daily) follow the current WHO recommendations for treatment of children with bacterial meningitis in meningococcal meningitis epidemics (WHO, 2013). The only difference is the recommendation not to use single-dose treatment as an alternative. For treatment of children outside epidemics, a 7-10 day course is now recommended.

- In large-scale epidemics, in very remote areas or in areas with weak infrastructure, it may not be feasible to maintain 5-day treatment for all cases; therefore, single-dose treatment protocols may be implemented, provided that it has been established that the epidemic is caused by a meningococcus. In such situations, single-dose ceftriaxone should be used, with review at 24 and 48 hours. Because such circumstances are likely to be increasingly rare, oily chloramphenicol is only advised as an alternative where ceftriaxone is inappropriate or unavailable.

Implications

- The constant threat of emerging antibiotic resistance must be closely monitored to ensure that recommended antibiotic regimens are appropriate, and are adapted as necessary (WHO, 2014b).

- It is important to maintain a policy of free treatment during meningococcal meningitis epidemics; this has cost implications for government health services.

Evaluation and research

- Compliance with recommended treatment protocols and outcomes (morbidity and mortality) should be monitored and evaluated.

Prophylaxis for household contacts

Evidence

The evidence was provided through a systematic review (see Annex 5, and full review in web annex)(*link to be added)*. In the search for systematic reviews, 906 records were identified, of which four reviews met the inclusion criteria. One review met the quality criteria for chemoprophylaxis; no review met the criteria for early vaccination of household contacts. In the subsequent search for primary articles, 2936 records were identified, of which two papers met the inclusion criteria: one on chemoprophylaxis and the other on vaccination.

There is limited evidence of the benefit of chemoprophylaxis (four observational studies) and vaccination (one quasi-randomized trial) on the risk of subsequent meningococcal disease among household contacts of a case of meningococcal disease. The data suggest an 84% lower risk of subsequent meningococcal disease among household contacts given chemoprophylaxis within 30 days (P=0.008) than among those who did not receive chemoprophylaxis (Annex 4). Using the pooled estimate, 200 (95% CI: 111–1000) household contacts would need to be treated to prevent one case of meningococcal disease. Overall, the quality of evidence was assessed as very low, because all studies were observational, study sample sizes were small (and statistically imprecise), and no studies were from the African meningitis belt. One African trial of vaccination of household contacts suggests a 91% lower risk of meningococcal disease among

household contacts given vaccine after exposure, but the quality was low because of risk of bias and imprecision (*P*=0.11).

From evidence to recommendations

The literature on meningitis among household contacts of a case in meningitis belt countries showed that, during epidemics, the odds ratio for subsequent cases in the household varied from 0.8 (NmA; Ghana), to 4.8 (NmW; the Gambia) to 36.2 (NmX; Kenya) (Hodgson et al., 2001; Houssain et al., 2013; Mutonga et al., 2009). The relative risk was lowest in Ghana, where background incidence was high and the risk for household members was similar to that of other members of the community. In industrialized countries, the relative risk in household contacts often reaches 1200–1400 in non-outbreak situations.

Meningococcal disease is recognized by ministers of health and communities as a severe disease with high associated costs (Desmond et al., 2013; WHO, 2008). Low-income families may be at higher risk for meningitis and may therefore benefit from effective prophylaxis, but detection and response capacity is variable, and small communities could be at a disadvantage. Side-effects of commonly recommended antibiotics (rifampicin, ciprofloxacin and ceftriaxone) and meningococcal vaccines are generally mild, but the development of antibiotic resistance is a global public health threat. Rifampicin use can lead to resistance among meningococci, and may not be acceptable to meningitis belt countries because of its importance in tuberculosis treatment. Any exposure to antibiotics (prophylaxis or treatment) generates a risk of developing antibiotic resistance in bacteria from the digestive, cutaneous and nasal flora. Ciprofloxacin is not advised in pregnancy (ECDC, 2010). Recommendations for use of ciprofloxacin in children still vary widely (e.g. they are recommended in the UK and eight European countries, but not recommended in the USA and parts of Europe) due to a concern about arthropathy, but recent evidence found no joint damage in young children given ciprofloxacin (ECDC, 2010).

The cost of antibiotic treatment per 100 contacts treated is approximately US$ 48 for rifampicin, US$ 50 for ceftriaxone, US$ 4 for ciprofloxacin and US$ 44 for azithromycin. The cost per 100 people vaccinated would be US$ 60 for MenAfriVac and US$ 250 for ACW Vaccine. Costs of stocking and distributing must be considered, as well as the difficulties in managing vaccine supply for relatively small quantities.

Antibiotic prophylaxis is currently recommended for household contacts of those with sporadic invasive meningococcal disease, but not for widespread use or administration to household contacts during epidemics. Thus, before an epidemic is declared, this policy should be applied for affected families.

The consensus of the Guideline Development Group was that, whereas the benefit of antibiotic prophylaxis in the meningitis belt is uncertain, the cost of giving single-dose ciprofloxacin to household contacts and the risk of adverse effects are both low, such that benefit may outweigh harm even if the absolute benefit is small. However, the group did not find any new information to suggest that, during epidemics, chemoprophylaxis for household contacts of cases would offer any additional benefit to the community in situations where case management and vaccination programmes are being implemented. For vaccination as a household prophylactic measure ahead of mass vaccination, the group considered that any additional benefit would be small in relation to the difficulties of implementation, particularly where mass vaccination is planned for the community.

Question

Should prophylaxis (antibiotics and/or vaccination) be recommended for household contacts of cases of meningococcal meningitis in epidemic and non-epidemic settings?

Recommendations

Topic	Previous	New
Household contacts of cases of meningococcal meningitis	Antibiotics recommended as a prophylactic measure for household contacts of all ages in non-epidemic periods but not during epidemics (WHO, 1998)	**Antibiotics are recommended as a prophylactic measure for household contacts of all ages in non-epidemic periods but not during epidemics** (No change from previous WHO guideline) (Conditional recommendation; very low quality evidence)
	Recommended antibiotics include rifampicin, ciprofloxacin and ceftriaxone	**Ciprofloxacin is the preferred prophylactic agent, with ceftriaxone as an alternative when ciprofloxacin is contraindicated (e.g. in pregnancy)** (Conditional recommendation; very low quality evidence)
		Rifampicin is not recommended for use as a prophylactic agent (Strong recommendation; low-quality evidence)[a]
	Vaccination not recommended for household contacts	**Vaccination is not recommended for household contacts[b]** **(**No change from previous WHO guideline) (Conditional recommendation; low-quality evidence)

[a] Strong recommendation, based on the risk of resistance and the availability of suitable alternative antibiotics

[b] During epidemics, household contacts would be included in any community immunization programme. However, it would be advisable to consider vaccinating household or other close contacts (e.g. in schools or barracks) during an outbreak due to a vaccine preventable serogroup, if mass vaccination is not undertaken or in advance of a vaccination campaign**.**

Implications

- The administration of prophylaxis to household contacts implies a need to confirm a case of meningococcal meningitis promptly.

- Recommendations on dosage, route of administration and contraindications will be made available to countries.

- The constant threat of emerging antibiotic resistance must be closely monitored to ensure that recommended antibiotic regimens are appropriate, and are adapted as necessary (WHO, 2014b).

- Although the previous guideline recommended chemoprophylaxis for household contacts of a person with meningococcal disease, in the experience of the Guideline Development Group, this is not yet a part of routine medical practice in meningitis belt countries. The implication is that local health services need to better disseminate the recommendation, and assess what is needed for implementation.

Evaluation and research

- The effectiveness of this intervention would be best evaluated in a randomized trial. However, the logistic difficulties of mounting a trial across districts and countries, with a sufficient sample size of cases in household contacts outside epidemics, may be prohibitively large.

Publication and dissemination

A summary of the guideline will be published in the Weekly Epidemiological Record (English and French). This guideline will be published in English, and findings from the systematic reviews and retrospective data analysis will be submitted to peer-reviewed scientific journals. The reference guide "Managing meningitis epidemics in Africa" (WHO, 2010) will be revised in English and French, and circulated for wide distribution to those in charge of meningitis outbreak response (WHO country offices, ministries of health and partners). Recommendations relating to this guideline in other WHO guidance documents will be revised (WHO, 2009, 2013) or replaced (WHO, 1998, 2000, 2003, 2007). Web-based documents presenting recommendations will be updated or archived.

The recommendations will be presented at the annual WHO inter-country meeting on surveillance and response to meningitis epidemics in Africa, other meetings when deemed appropriate, workshops and training sessions. Links to the guideline will be placed on the department website and sent to all WHO partners; regional and country offices; WHO collaborating centres; relevant ministries of health; NGOs working in concerned countries; manufacturers of meningitis vaccines, antibiotics and RDTs; and funding agencies.

Quality evaluation, usefulness and impact

The implementation of these updated recommendations will be assessed through consultations with ministries, by requesting feedback at the annual WHO inter-country meeting on surveillance and response to meningitis epidemics in Africa, and by evaluation of the data on meningitis reported to the Inter-country Support Team, Ouagadougou.

The guideline will be reviewed by the WHO within 5 years of publication. The difficulty of reaching clear evidence-based recommendations on a policy of reactive vaccination with polysaccharide vaccines emphasizes the importance of driving forward the development and introduction of polyvalent conjugate vaccines.

Funding

Acknowledgements

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Annex 1: Guideline groups

Guideline Development Group

Name	Affiliation	Gender	Location	WHO Region
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Caroline Trotter	University of Cambridge	F	UK	EURO
Dominique Caugant	NIPH, Oslo	F	Norway	EURO
Judith Mueller	EHESP	F	France	EURO
Jean-Marc Collard	CERMES (former)	M	Belgium	EURO
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Matthew Coldiron	MSF EpiCentre	M	France	EURO
Robert Kezaala	UNICEF	M	USA	AMRO
Tom Clark	CDC	M	USA	AMRO
Ashish Bavdekar	KEM Hospital, Pune	M	India	SEARO

AFRO: WHO Regional Office for Africa; AHRI: Armauer Hansen Research Institute; AMRO: WHO Regional Office for the Americas; CDC: Centers for Disease Control and Prevention: CERMES: Assessment of Multiple Systematic Reviews; CVD: Centre pour les Vaccins en Développement; EHESP: École des hautes études en santé publique (EHESP School of Public Health); EURO: WHO Regional Office for Europe; MSF: Médecins Sans Frontières; MoH: ministry of health; NIPH: National Institute of Public Health; SEARO: WHO Regional Office for South-East Asia; UK: United Kingdom of Great Britain and Northern Ireland; UNICEF: United Nations Children's Fund; USA: United States of America

External review group

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Chantal Kambire	WHO	F	Burkina	AFRO
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Marc LaForce	Serum Institute of India	M	USA	AMRO

AFRO: WHO Regional Office for Africa; AHRI: Armauer Hansen Research Institute; AMP: Agence de Médecine Préventive; AMRO: WHO Regional Office for the Americas; EMRO: WHO Regional Office for the Eastern Mediterranean; EURO: WHO Regional Office for Europe; IST: inter-country support team; LSHTM: London School of Hygiene & Tropical Medicine; MSF: Médecins Sans Frontières; MoH: ministry of health; UK: United Kingdom of Great Britain and Northern Ireland; UNICEF: United Nations Children's Fund; USA: United States of America; WHO: World Health Organization

WHO Steering Group

Name	Affiliation	Location	WHO Region
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Mamun Malik	WHO/EMRO	Egypt	EMRO

AFRO: WHO Regional Office for Africa; EMRO: WHO Regional Office for the Eastern Mediterranean; HQ: headquarters: HSE: Health Security and Environment; IST: inter-country support team; MVP: Meningitis Vaccine Project; PED: Pandemic and Epidemic Diseases; UK: United Kingdom of Great Britain and Northern Ireland; USA: United States of America; WHO: World Health Organization

Annex 2: PICO questions

PICO 1: In outbreaks of meningococcal meningitis due to vaccine preventable serogroups, how many cases and deaths are potentially averted when mass vaccination is implemented at different thresholds?
Population: total population in a defined district or subdistrict affected by a C, W or Y meningitis outbreak (or A after introduction of MenAfriVac)
Intervention: reactive vaccination campaigns with an appropriate vaccine launched when a given attack rate (or other agreed criteria) is reached
Comparator: reactive vaccination campaigns with an appropriate vaccine launched when the current epidemic threshold is reached
Outcome: cases, deaths

PICO 2: Among suspected cases of bacterial meningitis, what is the diagnostic accuracy (including sensitivity and specificity) of different rapid diagnostic tests compared to the gold standard of culture or PCR?
Population: Suspected cases of bacterial meningitis due to *Neisseria meningitidis* serogroups A, C, W, X, Y, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b
Intervention: Rapid diagnostic tests
Comparator: Culture or Polymerase Chain Reaction (bacterial species and meningococcal serogroup)
Outcome: Sensitivity and specificity of rapid diagnostic test in relation to correct choice of vaccine

PICO 3: Among cases in meningococcal meningitis outbreaks due to NmA before MenAfriVac compared with outbreaks due to other Nm serogroups, what is the proportion of cases receiving "inappropriate" treatment?
Population: Suspected cases in a meningitis outbreak
Intervention: Single-dose antibiotics in NmA meningitis outbreaks (before introduction of MenAfriVac)
Comparator: Single-dose antibiotics in NmC, W, X meningitis outbreaks (or NmA after introduction of MenAfriVac)
Outcome: Number of cases receiving inappropriate antibiotic treatment

PICO 4: Among household contacts of a case, what is the risk of meningococcal meningitis during the month after disease onset among close contacts given and not given prophylaxis?
Population: Household contacts of cases of meningococcal meningitis
Intervention: Prophylaxis to household contacts
Comparator: No prophylaxis to household contacts
Outcome: Attack rate among household contacts within one month after disease onset in index case

Annex 3: Declarations of interest

Members of the Guideline Development Group and the External Review Group each completed the standard WHO form on declaration of interests (DoI). The following declarations were made:

Guideline Development Group

- JM, EHESP French School of Public Health, declared having received research support from Pfizer for an investigator-initiated study grant whose topic was multi-year surveillance of pneumococcal invasive disease in Togo (question 2a of the DoI form).
- GE, PATH, declared working on the Meningitis Vaccine Project (question 5b of the DoI form).
- RK, UNICEF Programme Division, declared that UNICEF paid his travel costs (question 6c of the DoI form).
- JMC, Institute of Public Health, Brussels, declared that while working for CERMES, the Centre received funding from Sanofi-Pasteur from 2006–2009 and 2009–2012, without, however, any patents, products in development or marketed products to declare (question 2a of the DoI form).
- CT, University of Cambridge, declared consultancy payments from GSK for critically evaluating a health economic model on ACWY vaccine and providing advice on the sources of carriage data for dynamic models of ACWY vaccine (question 1b of the DoI form).
- TC, CDC, declared that he had received a grant from the Gates Foundation to the CDC Foundation to support surveillance capacity-building for meningitis in sub-Saharan Africa.

External Review Group

- MLF, Serum Institute of India Ltd, declared employment with Serum Institute from April 2012 to present, and as Director of the Meningitis Vaccine Project from 2001 to 2012 (questions 1a and 5b of the DoI form).
- DS, Emory University, declared servicing as an unpaid adviser for MenAfriCar, London School of Hygiene and Tropical Medicine, and as an unpaid scientific adviser for Meningitis and Vaccine Prevention Disease Branch, CDC (question 1b of the DoI form).
- BMG, London School of Hygiene and Tropical Medicine, declared having received research grants from Welcome Trust (US$ 3 000 000) and Gates Foundation (US$ 7 000 000) to London School of Hygiene and Tropical Medicine (question 2a of the DoI form).
- MH, Médecins Sans Frontières, declared having presented MSF's opinions on the subject matter in several meetings, mainly organized by WHO (question 5b of the DoI form).
- BDG, Agence de Médecine Préventive, declared receiving support from Pfizer, Sanofi-Pasteur, Merck (ceased), Crucell, GSK and Novartis. He added that AMP's main sources of funding are the Gates Foundation and GAVI. AMP receives additional funding from WHO, UNICEF, Save the Children, the French Ministry of Foreign Affairs and other groups. However, AMP also receives grant-specific support from some vaccine manufacturers for work on the epidemiology, anthropology, economics and pharmacovigilance of pneumococcus, human papillomavirus, influenza, malaria and rotavirus-related diseases and vaccines. The support value is variable by year over the past 4 years; however, in all years, the total amount varies from US$ 500 000 to US$ 1 000 000 (question 2a of the DoI form).

Annex 4: GRADE profiles

GRADE Evidence Profile 1: Cases of meningitis prevented at varying thresholds of mass vaccination
Author(s): Trotter C
Date: 2014–04–23
Question: In outbreaks of meningococcal meningitis due to vaccine preventable serogroups, how many cases and deaths are potentially averted when mass vaccination is implemented at different thresholds?
Settings: Meningitis belt of sub-Saharan Africa
Bibliography: PICO 1 Report

Quality assessment								Summary of findings: Mean NmW cases prevented by vaccination per event (range)*					
Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias			Threshold **10** (N events= 49)	Threshold **7** (N events= 66)	Threshold **5** (N events= 77)	Threshold **3** (N events= 98)	Quality	Importance
Modelling study	Serious limitations (low proportion of cases laboratory confirmed)	No serious inconsistency	Serious indirectness (modelling of observational data)	*No serious imprecision (but wide range)	Not relevant	6-week lag		17 (0–325)	19 (0–325)	27 (0–587)	46 (0–1327)	⊕⊕○○ LOW	CRITICAL
As above						4-week lag		54 (0–960)	53 (0–960)	60 (0–1171)	71 (0–1512)	⊕⊕○○ LOW	CRITICAL

Nm: *Neisseria meningitidis*

* The mean and the full range are given here. Although the wide range suggests serious uncertainty in the estimates of effect, this rather reflects the heterogeneity in the epidemiology of epidemic meningitis in the African meningitis belt.

GRADE Evidence Profiles 2a–2i: Performance of rapid diagnostic tests for meningitis
Author(s): Waite T
Date: 2014–05–13
Question: What is the place of rapid diagnostic tests (RDTs) in outbreak management?
Settings: Meningitis belt of sub-Saharan Africa
Bibliography: PICO 2 Report

2a CERMES ICT under field conditions for *N. meningitidis* serogroup W (assuming proportion of NmW among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmW)	2 studies (1717 patients)	Observational studies	Serious [1]	Serious [2]	Not serious	Not serious [3]	Not serious [4]	184 (176 to 188) [5]	LOW
False negatives (patients incorrectly classified as not having NmW)								16 (12 to 24) [5]	
True negatives (patients without NmW)								760 (744 to 768) [6]	
False positives (patients incorrectly classified as having NmW)								40 (32 to 56) [6]	

CERMES: Centre de Recherche Médicale et Sanitaire; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; ICT: immunochromatographic test; Nm: *Neisseria meningitidis*; No.: number; QoE: quality of evidence

1. High risk of bias regarding patient flow in one study.
2. High concern regarding patient selection.
3. Sensitivity and specificity of two studies were pooled separately. Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on pooled sensitivity of 92% (95% CI: 88–94%).
6. Based on pooled specificity of 95% (95% CI: 93–96%).

2b CERMES ICT under laboratory conditions for *N. meningitidis* serogroup W (assuming proportion of NmW among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmW)	3 studies (1751 patients)	Observational studies	Serious [1]	Serious [2]	Not serious	Not serious [3]	Not serious [4]	194 (190 to 196) [5]	LOW
False negatives (patients incorrectly classified as not having NmW)								6 (4 to 10) [5]	
True negatives (patients without NmW)								760 (744 to 768) [6]	
False positives (patients incorrectly classified as having NmW)								40 (32 to 56) [6]	

CERMES: Centre de Recherche Médicale et Sanitaire; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; ICT: immunochromatographic test; Nm: *Neisseria meningitidis;* No.: number; QoE: quality of evidence

1. High risk of bias regarding patient flow in one study.
2. High concern regarding patient selection.
3. Sensitivity and specificity of three studies were pooled separately. Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on pooled sensitivity of 97% (95% CI: 95–98%).
6. Based on pooled specificity of 95% (95% CI: 93–96%).

2c Pastorex LAT under laboratory conditions for *N. meningitidis* serogroup W or Y[1] (assuming proportion of NmW/Y among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmW/Y)	2 studies (1037 patients)	Observational studies	Serious	Serious	Not serious	Not serious	Not serious	176 (168 to 184) [3]	LOW
False negatives (patients incorrectly classified as not having NmW/Y)								24 (16 to 32) [3]	
True negatives (patients without NmW/Y)								784 (776 to 792) [4]	
False positives (patients incorrectly classified as having NmW/Y)								16 (8 to 24) [4]	

CERMES: Centre de Recherche Médicale et Sanitaire; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; LAT: latex agglutination; Nm: *Neisseria meningitidis;* No.: number; QoE: quality of evidence

1. Pastorex cannot differentiate between Nm W&Y.
2. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
3. Based on pooled sensitivity of 88% (95% CI: 84–92%).
4. Based on pooled specificity of 98% (95% CI: 97–99%).

2d BD Directigen meningitis LAT under laboratory conditions for *N. meningitidis* serogroup W (assuming proportion of NmW among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmW)	1 study (63 patients)	Observational study	Unable to assess [1]	Serious	Unable to assess	Not serious	Unable to assess	200 (186–200) [2]	VERY LOW
False negatives (patients incorrectly classified as not having NmW)								0 (0 to 14) [2]	
True negatives (patients without NmW)	1 study (63 patients)	Observational study	Unable to assess	Serious	Unable to assess	Serious	Unable to assess	320 (96 to 592) [3]	
False positives (patients incorrectly classified as having NmW)								480 (208 to 704) [3]	

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; LAT: latex agglutination; Nm: *Neisseria meningitidis;* No.: number; QoE: quality of evidence

1. Only results of this study were available to reviewers so methodological quality cannot be assessed.
2. Based on reported sensitivity of 100% (95% CI: 93–100%) and a disease prevalence of 20% (pretest probability).
3. Based on reported specificity of 40% (95% CI: 12–74%) and a disease prevalence of 20% (pretest probability).

2e BinaxNOW under laboratory conditions for *S. pneumoniae*   (no field studies found) (assuming proportion of Spn among CSFs tested = 20%)

Outcome	No. of studies(No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with Spn)	3 studies (1151 patients)	Observational studies	Serious [1]	Not serious	Not serious	Not serious [3]	Not serious [4]	198 (192 to 200) [5]	MODERATE
False negatives (patients incorrectly classified as not having Spn)								2 (0 to 8) [5]	
True negatives (patients without Spn)								768 (760 to 776) [6]	MODERATE
False positives (patients incorrectly classified as having Spn)								32 (24 to 40) [6]	

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; No.: number; Spn: *Streptococcus pneumoniae*; QoE: quality of evidence

1. High risk of bias regarding patient flow in one study.
2. Unclear risk of bias regarding index test in all studies.
3. Sensitivity and specificity of three studies were pooled separately. Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on pooled sensitivity of 99% (95% CI: 96–100%).
6. Based on pooled specificity of 96% (95% CI: 95–97%).

2f CERMES ICT under field conditions for *N. meningitidis* serogroup A (assuming proportion of NmA among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmA)	1 study (1632 patients)	Observational study	Serious [1]	Serious [2]	Not serious	Not serious [3]	Not serious [4]	174 (168 to 178) [5]	LOW
False negatives (patients incorrectly classified as not having NmA)								26 (22 to 32) [5]	
True negatives (patients without NmA)								632 (608 to 656) [6]	
False positives (patients incorrectly classified as having NmA)								168 (144 to 192) [6]	

CERMES: Centre de Recherche Médicale et Sanitaire; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; LAT: latex agglutination; Nm: *Neisseria meningitidis;* No.: number; QoE: quality of evidence

1. High risk of bias for flow and timing.
2. High concern regarding patient selection.
3. Sensitivity and specificity of three studies were pooled separately. Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on sensitivity of 87% (95% CI: 84–89%) and a disease prevalence of 20% (pretest probability).
6. Based on specificity of 79% (95% CI: 76–82%) and a disease prevalence of 20% (pretest probability).

2g Pastorex under field conditions for *N. meningitidis* serogroup A

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients tested	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmA)	1 study (143 patients)	Observational study	Not serious	Not serious	Not serious	Serious [1]	Not serious [2]	130 (106 to 150) [3]	MODERATE
False negatives (patients incorrectly classified as not having)								70 (50 to 94) [3]	
True negatives (patients without)	1 study (143 patients)	Observational study	Not serious	Not serious	Not serious	Very serious [4]	Not serious [2]	672 (576 to 736) [5]	LOW
False positives (patients incorrectly classified as having)								128 (64 to 224) [5]	

DTA: diagnostic test accuracy; No.: number; QoE: quality of evidence

1. Wide confidence intervals.
2. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
3. Based on sensitivity of 65% (95% CI: 53–75%) and a disease prevalence of 20% (pretest probability).
4. Very wide confidence intervals.
5. Based on specificity of 84% (95% CI: 72–92%) and a disease prevalence of 20% (pretest probability).

2h CERMES ICT under laboratory conditions for *N. meningitidis* serogroup A (assuming proportion of NmA among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmA)	1 study (1616 patients)	Observational study	Serious [1]	Serious [2]	Not serious	Not serious [3]	Not serious [4]	172 (168 to 178) [5]	LOW
False negatives (patients incorrectly classified as not having NmA)								26 (22 to 32) [5]	
True negatives (patients without NmA)								616 (592 to 632) [6]	
False positives (patients incorrectly classified as having NmA)								184 (168 to 208) [6]	

CERMES: Centre de Recherche Médicale et Sanitaire; CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; ICT: immunochromatographic test; Nm: *Neisseria meningitidis;* No.: number; QoE: quality of evidence

1. High risk of bias for flow and timing.
2. High concern regarding patient selection.
3. Sensitivity and specificity of three studies were pooled separately. Small CIs.
4. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
5. Based on sensitivity of 86% (95% CI: 84–89%).
6. Based on specificity of 77% (95% CI: 74–79%).

2i Pastorex under laboratory conditions for *N. meningitidis* serogroup A (assuming proportion of NmA among CSFs tested = 20%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1000 patients	DTA QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with NmA)	3 studies (1521 patients)	Observational studies	Serious [1]	Not serious	Not serious	Not serious [2]	Not serious [3]	176 (170 to 180) [4]	MODERATE
False negatives (patients incorrectly classified as not having NmA)								24 (20 to 30) [4]	
True negatives (patients without NmA)								776 (768 to 784) [5]	
False positives (patients incorrectly classified as having NmA)								24 (16 to 32) [5]	

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; Nm: *Neisseria meningitidis;* No.: number; QoE: quality of evidence

1. One study high risk of bias for index test and reference standard; one study used different reference standard.
2. Sensitivity and specificity of three studies were pooled separately. Small CIs.
3. Although not formally found, publication bias cannot be excluded given the high levels of DTA. We did not downgrade the evidence however.
4. Based on calculated sensitivity of 88% (95% CI: 85–90%).
5. Based on calculated specificity of 97% (95% CI: 96–98%).

GRADE Evidence Profile 3: Proportion of cases due to Spn and Hib during epidemics of meningococcal meningitis

Author(s): Cibrelus L

Date: 2014–04–26

Question: Among cases in meningococcal meningitis outbreaks due to Nm A before MenAfriVac compared with outbreaks due to other Nm serogroups, what is the proportion of cases receiving "suboptimal" treatment, i.e. being caused by other pathogens than Nm?

Settings: Meningitis belt of sub-Saharan Africa

Bibliography: PICO 3 Report

Quality assessment						Summary of findings: Proportion of Spn and Hib in NmA cf NmW and NmX epidemics					
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Combined % Spn and Hib in Nm epidemics**	**NmA epidemics Overall % (95% CI)**	**NmW/X epidemics Overall % (95% CI)**	***Difference (NmW/X-NmA)**	**Certainty of the evidence**	**Importance**
Surveillance data and literature review	No serious limitations	Serious inconsistency (wide variability between studies)	Serious indirectness (changing epidemiology, changing vaccination status)	No serious imprecision	Serious risk of bias (towards reporting of larger epidemics)	*All ages**	12.9% (8.6–19.1%) (n=1874)	8.9% (6.3–12.4%) (n=1880)	**−4.0%**	⊕○○○ VERY LOW	
						2–23 months	19%*** (7–41%) (n=21)	22.4% (11–39%) (n=184)	**3.4%**		
						2–4 years	7.1%*** (1–24%) (n=28)	8.4% (3–20%) (n=261)	**1.3%**		
						5–14 years	6.3%*** (2–14%) (n=79)	6.4% (3–12%) (n=483)	**0.1%**	⊕○○○ VERY LOW	IMPORTANT
						15–29 years	0%*** (0–11%) (n=39)	10.1% (5–17%) (n=111)	**10.1%**		
						≥30 years	0%*** (0–32%) (n=10)	24.5% (12–42%) (n=43)	**24.5%**		
						Adverse effects of 5 days ceftriaxone	Not considered serious				

CI: confidence interval; Hib: *Haemophilus influenzae* type b; Nm: *Neisseria meningitidis*; Spn: *Streptococcus pneumoniae*

* No differences statistically significant; ** Different numerators and denominators used for all age analysis and for those with age breakdown according to availability of age specific data; *** Only one study

GRADE Evidence Profile 4a–c: Antibiotics and/or vaccine in preventing disease among household contacts of cases of meningococcal disease

Author(s): Telisinghe L
Date: 2014–04–23
Settings: Meningitis belt of sub-Saharan Africa
Bibliography: PICO 4 Report

4a: Should chemoprophylaxis be used to prevent meningococcal disease among household contacts of cases of meningococcal disease?

No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoprophylaxis	Control	Relative (95% CI)	Absolute	Quality	Importance
				Quality assessment				No. of patients		Effect		
Subsequent case of meningococcal disease (30 days) (follow-up 30 days; clinical judgement or PCR/culture)												
4	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	0/2322 (0%)	14/3353 (0.42%)	RR 0.16 (0.04 to 0.64)	4 fewer per 1000 (from 2 fewer to 4 fewer)	⊕○○○ VERY LOW	CRITICAL
Subsequent case of meningococcal disease (1 year) (follow-up 1 year; clinical judgement or PCR/culture)												
3	Observational studies	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	2/1629 (0.1%)	9/2174 (0.4%)	RR 0.34 (0.11 to 1.06)	3 fewer per 1000 (from 4 fewer to 0 more)	⊕○○○ VERY LOW	CRITICAL
Resistance to antibiotics (follow-up 14+ days)												
3	Randomized trials	Serious[4]	Serious[5]	No serious indirectness	Serious[3]	Resistance development was not detected for any antibiotic other than rifampicin. In 3 studies undertaken in a variety of settings, raised minimum inhibitory concentrations to rifampicin developed in 18.9%, 36.4% and 76.0% of the isolates tested.	–	–	–	–	⊕○○○ VERY LOW	CRITICAL

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoprophylaxis	Control	Relative (95% CI)	Absolute		
Adverse effects: rifampicin vs ceftriaxone (follow-up 6+ days)												
1	Randomized trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[3]	None	129/440 (29.3%)	88/416 (21.2%)	RR 1.39 (1.10 to 1.75)	83 more per 1000 (from 21 more to 159 more)	⊕⊕OO LOW	IMPORTANT
Adverse effects: rifampicin vs ciprofloxacin (follow-up 2 weeks)												
2	Randomized trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[3,6]	None	13/861 (1.5%)	15/737 (2%)	RR 0.75 (0.36 to 1.56)	5 fewer per 1000 (from 13 fewer to 11 more)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; No.: number; PCR: polymerase chain reaction; RR: relative risk

[1] No baseline demographic details provided; no adjustment for confounding in all studies; [2] All studies carried out in US or western Europe (non-epidemic situations); [3] Optimal Information Size (OIS) not met; [4] All studies high risk of bias; [5] One study in army recruits with very high percentage of rifampicin resistance; [6] CI includes both benefit and harm

4b: Should vaccination be used to prevent meningococcal disease among household contacts of cases of meningococcal disease?

No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	An appropriate vaccine	Control	Relative (95% CI)	Absolute	Quality	Importance
Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Subsequent *definite* meningococcal disease (clinical features, culture, antibody and antigen test)												
1	Trial	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	0/520 (0%)	5/523 (0.96%)	RR 0.09 (0.01 to 1.65)	9 fewer per 1000 (from 9 fewer to 6 more)	⊕⊕○○ LOW	CRITICAL
Adverse effects												
0	–	–	–	–	–	None	–	–	–	–		IMPORTANT

CI: confidence interval; No.: number; RR, relative risk

[1] Unclear risk of selection, performance and detection bias; [2] Optimal Information Size (OIS) not met;

4c: Should chemoprophylaxis and vaccination be used to prevent meningococcal disease among household contacts of cases of meningococcal disease?

	Quality assessment						Summary of findings				Quality	Importance
							Number of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoprophylaxis and vaccination	Control	Relative (95% CI)	Absolute		
Subsequent case of meningococcal disease at ≤30 days												
0	–	–	–	–	–	None	–	–	–	–		CRITICAL
Subsequent case of meningococcal disease at ≤1 year												
0	–	–	–	–	–	None	–	–	–	–		CRITICAL
Resistance to antibiotics												
0	–	–	–	–	–	None	–	–	–	–		CRITICAL
Adverse effects												
0	–	–	–	–	–	None	–	–	–	–		IMPORTANT

CI: confidence interval; No.: number

Annex 5: Flow diagrams of searches in systematic reviews
(i) Rapid diagnostic tests: Search for primary articles

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┌─────────────────────────┐
│ Records identified      │
│ through database search │
│ N=3004                  │
└───────────┬─────────────┘
            ↓
┌─────────────────────────┐      ┌─────────────────────────┐
│ Titles screened n=3004  │─────→│ Records removed after    │
│                         │      │ title screen n=2871      │
└───────────┬─────────────┘      └─────────────────────────┘
            ↓
┌─────────────────────────┐      ┌─────────────────────────┐
│ Records remaining after │─────→│ Records removed after    │
│ title screen n=173      │      │ deduplication n=48       │
└───────────┬─────────────┘      └─────────────────────────┘
            ↓
┌─────────────────────────┐      ┌─────────────────────────┐
│ Abstracts screened      │─────→│ Records excluded         │
│ n=125                   │      │ following abstract       │
│                         │      │ screen n=70              │
└───────────┬─────────────┘      └─────────────────────────┘
            ↓
```

┌──────────────────────┐   ┌─────────────────────┐   ┌──────────────────────────┐
│ Additional articles │──→│ For full text screen│──→│ Unable to obtain   │
│ from reference   │   │ n=56   │   │ articles n=4   │
│ searches n=1   │   │   │   │   │
└──────────────────────┘   └─────────┬───────────┘   └──────────────────────────┘
                                     ↓

┌─────────────────────────┐   ┌─────────────────────────────┐
│ Full texts screened   │─────→│ Excluded n=36   │
│ n=52   │   │ *Review article (n=2)*   │
└───────────┬─────────────┘   │ *Not an RDT (n=3)*   │
            ↓   │ *Inappropriate ref standard*│
┌─────────────────────────┐   │ *(n=5)*   │
│ **Number of articles** │   │ *Inappropriate index test* │
│ **considered n=16**   │   │ *(n=4)*   │
└─────────────────────────┘   │ *Lack of data clarity (n=7)*│
                                 │ *Lack of detail on RDT (n=5)*│
                                 │ *Lack of detail on ref*   │
                                 │ *standard (n=1)*   │
                                 │ *Inappropriate pt group (n=2)*│
                                 │ *Not a DTA study (n=5)*   │
                                 │ *Not a CSF study (n=1)*   │
                                 └─────────────────────────────┘

CSF: cerebrospinal fluid; DTA: diagnostic test accuracy; pt: patient; RDT: rapid diagnostic test

(ii) Prophylaxis of household contacts: Search for systematic reviews

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┌─────────────────────────────┐
│  Records identified through  │
│  database search N=906       │
└─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│  Records remaining after     │───────▶│  Number of duplicates removed │
│  duplicates removed n=718    │        │  n=188                        │
└─────────────────────────────┘        └─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│  Titles screened n=718       │───────▶│  Number of records excluded   │
│                              │        │  following title screen n=522 │
└─────────────────────────────┘        └─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│  Abstracts screened n=196    │───────▶│  Number of records excluded   │
│                              │        │  following abstract screen    │
│                              │        │  n=128                        │
└─────────────────────────────┘        └─────────────────────────────┘
               │
               ▼
┌──────────────────────┐  ┌──────────────────────┐  ┌─────────────────────────────┐
│ Additional articles  │─▶│ For full text screen │─▶│ Unable to find articles n=16 │
│ reviewed based on    │  │ n=68+12=80           │  │ 3rd review by RJS            │
│ reference search     │  │                      │  │                              │
│ n=12                 │  │                      │  │                              │
└──────────────────────┘  └──────────────────────┘  └─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐        ┌─────────────────────────────┐
│  Full texts screened n=64    │───────▶│  Excluded                     │
│                              │        │                              │
│                              │        │  Not SR (i.e. reviews only)   │
│                              │        │                              │
│                              │        │  n=58                         │
└─────────────────────────────┘        └─────────────────────────────┘
               │
               ▼
┌─────────────────────────────┐
│  Number of articles considered │
│  n=4                          │
└─────────────────────────────┘
```

* n=27 (39.7%) had no abstracts; SR: systematic review

(iii) Prophylaxis of household contacts: Search for primary articles

```
┌─────────────────────────┐
│ Records identified through │
│ database search N=2936   │
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐        ┌─────────────────────────┐
│ Records remaining after  │───────▶│ Number of duplicates     │
│ duplicates removed n=2381│        │ removed n=555            │
└─────────────────────────┘        └─────────────────────────┘
            │
            ▼
┌─────────────────────────┐        ┌─────────────────────────┐
│ Titles screened n=2381   │───────▶│ Number of records excluded│
│                          │        │ following title screen   │
│                          │        │ n=1754                   │
└─────────────────────────┘        └─────────────────────────┘
            │
            ▼
┌─────────────────────────┐        ┌─────────────────────────┐
│ Abstracts screened n=627 │───────▶│ Number of records excluded│
│                          │        │ following abstract screen │
│                          │        │ n=562                    │
└─────────────────────────┘        └─────────────────────────┘
            │
            ▼
┌──────────────────────┐   ┌─────────────────────────┐
│ Additional articles  │──▶│ For full text screen     │
│ reviewed based on    │   │ n=65+12=77               │
│ reference search n=12│   └─────────────────────────┘
└──────────────────────┘
            │
            ▼
┌─────────────────────────┐        ┌─────────────────────────┐
│ Full texts screened n=77 │───────▶│ Excluded                 │
│                          │        │                          │
│                          │        │ No relevant information  │
│                          │        │ for PICO n=72            │
│                          │        │                          │
│                          │        │ (Includes studies or     │
│                          │        │ reviews of vaccine or    │
│                          │        │ antibiotic effectiveness │
│                          │        │ in non-household setting; │
│                          │        │ outbreak reports;        │
│                          │        │ antibody response studies;│
│                          │        │ carriage studies;        │
│                          │        │ acceptability studies;   │
│                          │        │ economic evaluations)    │
└─────────────────────────┘        └─────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ Articles included n=2    │
│                          │
│ 1=chemoprophylaxis;      │
│ 1=vaccines               │
└─────────────────────────┘
```