Early detection and response to meningococcal disease epidemics in sub-Saharan Africa: appraisal of the WHO strategy

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Objective To assess the sensitivity, specificity and predictive value positive of the WHO threshold strategy for detecting meningococcal disease epidemics in sub-Saharan Africa and to estimate the impact of the strategy on an epidemic at district level.

Methods Data on meningitis cases at the district level were collected weekly from health ministries, WHO country and regional offices, and nongovernmental organizations in countries where there were epidemics of meningococcal disease in 1997. An epidemic was defined as a cumulative district attack rate of at least 100 cases per 100 000 population from January to May, the period of epidemic risk. The sensitivity, specificity and predictive value positive of the WHO threshold rate were calculated, and curves of sensitivity against (1 – specificity) were compared with alternatively defined threshold rates and epidemic sizes. The impact of the WHO strategy on a district epidemic was estimated by comparing the numbers of epidemic cases with cases estimated to have been prevented by vaccination.

Findings An analysis was made of 48 198 cases reported in 174 districts in Benin, Burkina Faso, the Gambia, Ghana, Mali, Niger, and Togo. These cases were 80.3% of those reported from Africa to WHO during the 1997 epidemic period. District populations ranged from 10 298 to 573 908. The threshold rate was crossed during two consecutive weeks in 69 districts (39.7%) and there were epidemics in 66 districts (37.9%). Overall, the sensitivity of the threshold rate for predicting epidemics was 97%, the specificity was 95%, and the predictive value positive was 93%. Taken together, these values were equivalent or better than the sensitivity, specificity and predictive value positive of alternatively defined threshold rates and epidemics, and remained high regardless of district size. The estimated number of potential epidemic cases decreased by nearly 60% in the age group targeted for vaccination in one district where the guidelines were followed in a timely manner.

Conclusion The use of the WHO strategy was sensitive and specific for the early detection of meningococcal disease epidemics in countries of sub-Saharan Africa during 1997 and had a substantial impact on a district epidemic. Nevertheless, the burden of meningococcal disease in these countries remains formidable and additional control measures are needed.

Keywords Meningitis, Meningococcal/epidemiology; Disease outbreaks/prevention and control; Meningococcal vaccines/therapeutic use; Immunization programs; Sensitivity and specificity; Predictive value of tests; Africa South of the Sahara (source: MeSH, NLM).

Mots clés Ménigite méningoccique/épidémiologie; Epidémie/prévention et contrôle; Vaccins antiméningoccociques/usage thérapeutique; Programmes de vaccination; Sensibilité et spécificité (Épidémiologie); Valeur prédictive tests; Afrique subsaharienne (source: MeSH, INSERM).

Palabras clave Meningitis meningocócica/epidemiología; Brotes de enfermedades/prevención y control; Vacunas meningocócicas/uso terapéutico; Programas de inmunización; Sensibilidad y especificidad; Valor predictivo de los tests; África del Sur (fuente: DeCS, BIREME).
of meningitis respectively in Africa (9). Case-fatality rates exceeded 10% during both years. The epidemic in 1996 was the largest ever recorded in a single year, and substantial underreporting of both cases and deaths probably occurred (10). Both epidemics were caused by the serogroup A III.1 clone, which has circulated throughout the region for over a decade (11, 12), but serogroup C meningococci have also caused or significantly contributed to other recent epidemics (13).

The WHO strategy for the control of epidemic meningococcal disease links the early prediction of epidemics with rapidly conducted mass vaccination campaigns (1). A threshold model of epidemic detection is used for early prediction. The threshold rate is 15 cases per 100 000 population per week averaged over two successive weeks. When the threshold strategy was first evaluated it was found to have reasonably good sensitivity (72–93%), specificity (92–100%) and predictive value positive (65–97%), and the population size considered most appropriate for epidemic prediction ranged from 30 000 to 100 000 (14). The potential impact of the strategy on epidemics depends on rapid detection and prompt mass vaccination campaigns. It has frequently been difficult to coordinate these activities in a timely manner in the meningitis belt (15).

Meningococcal polysaccharide vaccines have been available for several decades (16). Serogroups A and C are present in most such vaccines used in the region. These vaccines have repeatedly been shown to be more than 85% efficacious in the prevention of invasive meningococcal disease in Africa (17) and elsewhere. At least in developed countries, immunity lasts five years or longer among most healthy vaccinated adults (18).

Since the introduction of the threshold strategy in 1995 an intensive multinational effort has promoted its use through the improvement of epidemic detection and response capacity. However, severe epidemics of meningococcal disease have continued to occur and the effectiveness of the strategy has therefore been questioned. The aims of the present study were to determine whether the strategy was still sufficiently sensitive and specific for detecting epidemics in sub-Saharan Africa and to estimate its impact on an epidemic at the district level.

**Methods**

**Calculation of sensitivity, specificity and predictive value positive**

In 1997 we collected data weekly at the district level from health ministries, WHO country and regional offices, and nongovernmental organizations in every country where there were significant numbers of meningitis cases between January and May, the period of highest epidemic risk 1997. Incidence rates were calculated using denominators obtained from health ministries at the district, regional or national level. The districts were stratified into population quartiles.

On the basis of the threshold rate of 15 cases per 100 000 population per week and using data from all districts included in the analysis, we calculated sensitivity, specificity and predictive value positive as aggregate values. The WHO definition of a district epidemic as an overall attack rate of at least 100 per 100 000 population per year was used. Districts with incomplete surveillance data were excluded.

Two sets of curves of sensitivity against (1 – specificity) were constructed for different weekly incidence thresholds of meningitis. Data from all districts included in the analysis were used for the first set, whereas data from districts stratified by population quartile were used for the second. In order to assess whether alternative thresholds or epidemic definitions improved sensitivity or specificity relative to the WHO guidelines, sensitivity and specificity were compared graphically for threshold values ranging from 2 to 26 cases per 100 000 population per week in increments of 2 and for alternative epidemic definitions of 50 and 75 per 100 000 population per year. Sensitivity, specificity and predictive value positive were also calculated in relation to a threshold definition of ≥ 15 per 100 000 per week for two successive, not averaged, weeks.

**Cases prevented**

We collected data on weekly attack rates, vaccine coverage rates, and dates of a vaccination campaign in a medium-sized district (Reo District, Koudougou Region, Burkina Faso) in order to estimate the impact of the threshold strategy on an epidemic at this level. Meningococcal disease was defined as being present in persons with compatible symptoms and signs of meningitis and turbid cerebrospinal fluid (1). Confirmation by culture was not available. Coverage rates during the vaccination campaign were estimated on the basis of the proportion of control subjects vaccinated in a case-control study of vaccine efficacy conducted during April and May 1997 (19). The controls were persons aged at least 5 years who were matched to cases by age category and place of residence. Interviews with subjects were conducted in their native language 7–14 days after a mass vaccination campaign with bivalent A/C meningococcal polysaccharide vaccine. The subjects were asked about their meningococcal vaccination status, which was confirmed by the examination of vaccination cards if these were available. For comparison the proportion of cases prevented per epidemic was estimated on the basis of vaccine coverage rates obtained from district ministry of health sources.

The number of cases prevented by vaccination was estimated in the age group targeted during the vaccination campaign. This involved comparing attack rates among vaccinated and unvaccinated persons by means of the following equations (17).

Weekly overall AR = (VAR x PV)/(NVAR x PNV); VAR = 0.15 x NVAR; 0.15 = (1 – VE), AR is attack rate; VAR, attack rate among vaccinated persons; NVAR, attack rate among unvaccinated persons; PV, proportion of population vaccinated; PNV, proportion of population not vaccinated; VE, vaccine efficacy, defined as 85% for the purposes of this analysis.

The estimated numbers of cases prevented were summed two weeks after the end of the vaccination campaign in order to allow for the development of post-vaccination antibody responses (16). The proportion of the epidemic prevented was calculated as:

estimated cases prevented/epidemic cases + estimated cases prevented.

**Statistical analysis**

EpiInfo (version 6.04) was used for data entry and analysis of weekly district-level meningitis cases, the case-control study of vaccine efficacy, and chi-square calculation for comparison of proportions of districts crossing the epidemic threshold stratified by population quartile. SAS (Release 6.12, SAS Institute, Cary, NC, USA) was used to construct tables of districts and thresholds, and curves of sensitivity against (1 – specificity).
Results

An analysis was made of 48,198 cases in 174 districts in Benin, Burkina Faso, the Gambia, Ghana, Mali, Niger, and Togo (Table 1). These cases amounted to 80.3% of those reported from Africa to WHO during the 1997 epidemic period (2). A total of 69 districts (39.7%) crossed the WHO threshold and 66 districts (37.9%) had epidemics, i.e. at least 100 cases per 100,000 population. Three districts (1.7%) with incomplete data were excluded from the analysis.

District populations ranged from 10,298 to 573,908 persons (median = 176,291); 33 districts (19%) had populations in the range 30,000 to 100,000; 75% had populations of at least 100,000, and 45% had populations of at least 200,000. The quartiles of district population in thousands were: <111 (n = 40), 111–<176 (n = 46), 176–<248 (n = 47), and ≥ 248 (n = 41). The proportions of districts crossing the epidemic threshold for at least two consecutive weeks were 18%, 43%, 49% and 39% in the respective quartiles (P = 0.04) (Fig.1).

Sensitivity, specificity and predictive value positive

Using districts with cumulative attack rates of at least 100 per 100,000 population as the standard, the overall sensitivity of the threshold was 97.0%, the specificity was 95.4% and the predictive value positive 92.8% (Table 2). These parameters were similar when data from each country, not shown here, were examined separately. The examination of weekly threshold values ranging from 2 to 26 cases per 100,000, averaged over two weeks, revealed that the threshold of 15 per 100,000 population had comparable or better specificity and predictive value positive for a given sensitivity than other thresholds for predicting yearly epidemics of 100 cases/100,000 population (Fig. 2). The values did not change significantly when the sensitivity, specificity and predictive value positive were calculated on the basis of a threshold rate of 15 per 100,000 population for two successive but not averaged weeks (Table 3). For districts of the second largest and largest quartiles of population size the sensitivity decreased to 88% and 80% respectively, whereas the specificity remained uniformly good for all districts regardless of population size (Table 4).

Cases prevented

A total of 2881 cases (attack rate for whole district = 1119/100,000) and 316 deaths (case-fatality rate = 11%) occurred during a 12-week meningococcal disease epidemic in Reo District, Koudougou Region, Burkina Faso (estimated 1997

Table 1. African countries with large-scale meningococcal disease epidemics, 1997

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases reported to WHO (up to 1 June 1997)</th>
<th>Number of cases analysed (% of total reported cases)a</th>
<th>Number of districts analysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>21,504</td>
<td>18,377 (84.5)</td>
<td>50</td>
</tr>
<tr>
<td>Ghana</td>
<td>18,551</td>
<td>12,531 (67.5)</td>
<td>24</td>
</tr>
<tr>
<td>Mali</td>
<td>10,960</td>
<td>10,178 (92.9)</td>
<td>45</td>
</tr>
<tr>
<td>Niger</td>
<td>3922</td>
<td>41,198 (107)</td>
<td>38</td>
</tr>
<tr>
<td>Togo</td>
<td>2619</td>
<td>2,072 (79.1)</td>
<td>3</td>
</tr>
<tr>
<td>The Gambia</td>
<td>913</td>
<td>807 (88.4)</td>
<td>1</td>
</tr>
<tr>
<td>Benin</td>
<td>360</td>
<td>35 (9.7)</td>
<td>13</td>
</tr>
<tr>
<td>Other countries</td>
<td>1,181</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Totala</td>
<td>60,010</td>
<td>48,198 (80.3)</td>
<td>174</td>
</tr>
</tbody>
</table>

Source: reference 2.

a Includes cases reported to WHO for the period after 1 June 1997. For complete 1997 case figures, see reference 9.

Table 2. Numbers of districts above and below weekly threshold of 15 per 100,000 averaged over two consecutive weeks vs yearly attack rate of 100 cases/100,000

<table>
<thead>
<tr>
<th>Threshold rate</th>
<th>Yearly attack rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 15</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>&lt;15</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
</tr>
</tbody>
</table>

Sensitivity: 64/(64+2) = 97.0%; 95% confidence interval = 88.5–99.5%.
Specificity: 103/(103+5) = 95.4%; 95% confidence interval = 89.0–98.3%.
Predictive value positive: 64/(64+5) = 92.8%; 95% confidence interval = 83.29–7.3%.
Predictive value negative: (103/103+2) = 98.1%; 95% confidence interval = 92.6–99.7%.

Fig. 1. Proportion of districts crossing meningitis epidemic threshold vs size: sub-Saharan Africa, 1997

Fig. 2. Sensitivity vs (100–specificity) of weekly thresholds and corresponding yearly attack rates (AR)
population = 257 367). The epidemic threshold was crossed in early February and the weekly attack rate peaked at 159 per 100 000 in mid-March. Vaccination campaigns were performed over a period of six days and were completed within two weeks after the epidemic threshold was crossed for the second consecutive week. The epidemic subsided in late April. Among the 120 control subjects in a case-control study of vaccine efficacy living in the village of Reo, vaccine coverage amounted to 86%.

A total of 4217 cases were estimated to have been prevented during the six weeks following the vaccination campaign while the epidemic subsided, allowing two weeks after the end of the campaign for the development of humoral immunity among vaccinated persons. This number represented nearly 1.5 times that of observed cases, or 59.4% of the total number of epidemic cases predicted in the absence of vaccination (Fig. 3). On the assumption that the observed case-fatality rate remained constant at 11% it was estimated that 464 deaths were prevented by vaccination. Alternative data for the entire district obtained from the health ministry, viz. the number of doses given divided by the estimated target population, indicated vaccine coverage to be 64%. The use of this value resulted in a lower estimate of the proportion of epidemic cases prevented, namely 46%.

Discussion

The WHO threshold strategy was found to be sensitive and specific in the prediction of epidemic meningococcal disease in seven African countries during 1997. No other threshold or epidemic definition performed as well or significantly better when sensitivity, specificity and predictive value positive were considered together. A number of thresholds were found to be reasonably sensitive and specific for predicting epidemics of various size, as has been suggested elsewhere (20, 21). It is possible that lowering the threshold from 15 to 10 per 100 000 per week in high-risk epidemic situations, e.g. for increases in incidence observed early during the meningitis season, would allow even higher sensitivity and earlier epidemic detection with minimal sacrifices in specificity and predictive value positive (21–24). However, the maximization of each of these parameters is critical. A reduction in sensitivity leads to delayed detection of epidemics and potentially reduces the number of cases and deaths averted through vaccination. Reductions in specificity and predictive value positive lead to vaccination campaigns of suboptimal impact in the absence of an ensuing, but predicted, epidemic. Such campaigns place considerable demands on human and material resources in countries where both are in very short supply.

The most appropriate denominator range for the use of the threshold in districts has been suggested as 30 000 to 100 000 persons (1, 14). In the present study, however, it emerged that sensitivity and specificity were very good in districts with populations of up to 175 000 and reasonably good even in very large districts. We found that districts with over 110 000 people were more likely to cross the threshold, suggesting that the transmission of meningococcal disease may be comparatively rapid and/or sustainable in areas of high population density. This finding should be interpreted cautiously, however, since surveillance may be more complete and timely in districts with relatively large populations.

By comparing actual and theoretical epidemic curves in one district experiencing a large-scale epidemic, we found that nearly three-fifths of meningococcal disease cases were prevented through the timely application of the threshold strategy. This number is close to a recently published estimate of the strategy’s potential impact (15). In the district analysed, vaccine coverage rates were higher and the vaccination campaign was conducted more promptly than in other districts studied during the past decade (17, 25). This explains the higher estimated impact of the strategy in our study, and refutes the notion that delays in implementation of the threshold strategy are inevitable in the region (26).

Although the threshold strategy was a sensitive and specific predictor of district epidemics and had a significant impact on an epidemic at the district level, it has both theoretical and practical limitations. Assuming a vaccine efficacy of at least 85% (16) and optimal levels of achievable
vaccine coverage of 85%, as in the district studied, the threshold strategy’s maximum potential for epidemic reduction is approximately 72% (85 x 0.85), starting days to weeks after vaccination, depending on the humoral immune response. In a sub-Saharan African district of average size and weekly epidemic activity, numerous cases per week might still occur even with strict adherence to the threshold strategy. Besides the theoretical limits, in Africa there are formidable practical barriers to the control of epidemic diseases. Delays in communication between peripheral and national authorities increase the time between the detection of epidemics and the performance of vaccination. The inadequacy of vaccine supplies and logistics may decrease the effectiveness of the threshold even when an epidemic is rapidly detected. The threshold strategy is difficult to implement among sparsely scattered populations that are inaccessible by road. The strategy’s effectiveness is probably diminished more by these and other practical difficulties than by the theoretical limits.

Although routine immunization has been proposed as an alternative to the currently recommended WHO threshold strategy (27, 28), arguments have been made against the preventive use of meningococcal polysaccharide vaccines in developing and industrialized countries alike. Studies in sub-Saharan Africa and elsewhere have indicated that meningococcal polysaccharide vaccines are poorly immunogenic, especially so in areas with high rates of malnutrition, malaria and geohelminth infections (29, 30), and that they confer only evanescent protection among children aged under 4 years, among whom the risk is highest (31). They produce a limited booster effect and may attenuate serum bactericidal responses to meningococcal serogroups A and C upon revaccination (32, 33). In most settings they do not appreciably or durably alter nasopharyngeal carriage rates (34–36). Furthermore, even with antigens of longstanding use, routine EPI vaccine coverage rates rarely surpass 50–60% in sub-Saharan African countries (37).

Controversy exists concerning the potential cost-effectiveness of preventive meningococcal vaccination in sub-Saharan Africa. A simulated epidemic model suggested that routine vaccination might be more cost-effective than mass vaccination strategies (38), but an analysis of data from Burkina Faso indicated that four preventive doses of meningococcal polysaccharide vaccine would prevent only 30% of meningitis cases as opposed to 42% through the WHO strategy (39). Strategies other than preventive vaccination are clearly needed (40, 41).

The present study had several limitations. The sensitivity, specificity and predictive value positive of the threshold strategy were calculated using data collected during a large-scale epidemic; whether the strategy would be effective in the control of smaller epidemics or endemic disease is uncertain. Frequently, there is incomplete and late case-reporting from health centres, the most peripheral African health care access points, to district, regional and national health authorities. Over a quarter of the cases that occurred in six countries during 1997 were reported late, i.e. after a delay of at least three months, to national health authorities and WHO (2, 9). In order to maximize the number of districts analysed, data were obtained largely through national sources, which may not have reflected the true incidence of meningococcal disease at district level. This is evidently a problem in relation to other infectious diseases in Africa (42). In the almost complete absence of laboratory confirmation the strategy’s impact might have been underestimated if meningococcal disease cases were caused by other virulent serogroups, e.g. W-135, not included in the bivalent A + C vaccines used in most campaigns at district level (43–45). Finally, our estimated impact of the strategy on the basis of data from a single district with high vaccine coverage and minimal delay in vaccination may not represent the strategy’s impact on other district epidemics, as discussed above. Measuring the impact of the WHO strategy in sub-Saharan Africa requires a longitudinal sample of representative districts experiencing diverse epidemic conditions and response capacities (46).

Additional meningococcal disease control measures are needed in Africa. The identification of districts at high risk for epidemics (23) and the evaluation of preventive vaccination or other, e.g. treatment-based, strategies (47), are priorities for research. However, there is a paucity of data suggesting that preventive strategies significantly alter the epidemiology of meningococcal disease in actual African districts (48) and there is little evidence that improved control of epidemics can be expected through the use of alternatively defined thresholds or other strategies. Many investigators feel that strengthened implementation of the WHO threshold approach is critical for improved meningococcal disease control in this region (49, 50).

One of the most promising prospects for improving the control of meningococcal disease involves using meningococcal capsular polysaccharide-protein conjugate vaccines (50, 51). In clinical trials in the Gambia (52), Niger (53), and the USA (54), meningococcal conjugate vaccines produced up to 20 times more serum bactericidal activity than polysaccharide vaccines. Direct evidence and experience with Haemophilus influenzae type b conjugate vaccines suggests that immunological memory and herd immunity, mediated via the interruption of nasopharyngeal carriage, are also possible advantages (55–58). Efforts should be made to expedite the licensing of meningococcal conjugate vaccines and to reduce their cost in order to permit their earliest possible use in developing countries.

Acknowledgements
The authors thank the following persons for technical assistance: Maria Santamaria, Evgeny Tikhomirov (WHO/ Geneva); Francis Varaine, Anne-Valerie Kaninda, Rosamund Lewis, Christophe Paquet (Epicentre, Paris); Felicity Curtts (London School of Hygiene and Tropical Medicine); Georges Soula (Centre Muraz, Bobo-Dioulasso, Burkina Faso); and Daniel Kertesz (WHO/Mali).

Conflicts of interest: none declared.
Résumé

Détectio n y respuesta précoce s en cas d’épidé mie de méningite à méningocoque en Afrique subsaharienne: évaluation de la stratégie OMS

Objectif Evaluar la sensibilidad, la especificidad y el valor predictivo positivo de la estrategia OMS para la detección de las epidemias de enfermedad meningocócica en el África subsahariana, y estimar el impacto de la estrategia en una epidemia a nivel de distrito.

Métodos Con periodicidad semanal se reunieron datos sobre los casos de meningitis a nivel de distrito a partir de los ministerios de salud, de las oficinas regionales y de países de la OMS y de organizaciones no gubernamentales en países donde había epidemias de enfermedad meningocócica en 1997. Se consideró que había epidemia cuando la tasa acumulativa de ataques por distrito alcanzaba al menos los 100 casos por 100 000 habitantes entre enero y mayo, el periodo de riesgo de epidemia. Se calcularon la sensibilidad, la especificidad y el valor predictivo positivo de la tasa umbral de la OMS y se compararon las curvas de sensibilidad frente al valor (1-especificidad) para diferentes umbrales y dimensiones de la epidemia. El impacto de la estrategia de la OMS en una epidemia de ámbito distrital se calculó comparando las cifras de los casos epidémicos y los casos que según las estimaciones se habían prevenido mediante la vacunación.

Resultados Se analizaron 48 198 casos notificados en 174 distritos de Benín, Burkina Faso, Gambia, Ghana, Mali, Niger y Togo. Estos casos representaban el 80,3% de los notificados por África a la OMS durante el periodo epidémico de 1997. La población de los distritos iba de 10 298 a 573 908 personas. La tasa umbral fue superada durante dos semanas consecutivas en 69 distritos (39,7%), y hubo epidemias en 66 distritos (37,9%). A nivel global, la sensibilidad de la tasa umbral para predecir las epidemias fue del 97%, la especificidad del 95%, y el valor predictivo positivo del 93%. Considerados conjuntamente, estos valores alcanzaban o superaban la sensibilidad, la especificidad y el valor predictivo positivo observados al definir de otra forma las tasas umbral y las epidemias, y seguían siendo altos con independencia del tamaño del distrito. El número estimado de casos epidémicos potenciales disminuyó casi en un 60% en el grupo de edad elegido para vacunación en un distrito donde se siguieron puntualmente las directrices. Conclusión La estrategia de la OMS funcionó como una alternativa sensible y especifica para detectar precozmente las epidemias de la enfermedad meningocócica en los países del África subsahariana durante 1997 y tuvo una repercusión sustancial en la epidemia de un distrito. No obstante, la carga de enfermedad meningocócica sigue siendo enorme en esos países, lo que hace necesarias medidas de control adicionales.


