



Response thresholds for epidemic meningitis in sub-Saharan Africa following the introduction of MenAfriVac®



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ARTICLE INFO

Article history:

Received 28 July 2015

Received in revised form

28 September 2015

Accepted 29 September 2015

Available online 14 October 2015

Keywords:

Meningitis

Epidemic thresholds

Meningitis belt

Africa

ABSTRACT

Background: Since 2010, countries in the African meningitis belt have been introducing a new serogroup A meningococcal conjugate vaccine (MenAfriVac®) through mass campaigns. With the subsequent decline in meningitis due to *Neisseria meningitidis* serogroup A (NmA) and relative increase in meningitis due to other serogroups, mainly *N. meningitidis* serogroup W (NmW), the World Health Organisation (WHO) initiated a review of the incidence thresholds that guide response to meningitis epidemics in the African meningitis belt.

Methods: Meningitis surveillance data from African meningitis belt countries from 2002 to 2013 were used to construct a single NmW dataset. The performance of different weekly attack rates, used as thresholds to initiate vaccination response, on preventing further cases was estimated. The cumulative seasonal attack rate used to define an epidemic was also varied.

Results: Considerable variation in effect at different thresholds was observed. In predicting epidemics defined as a seasonal cumulative incidence of 100/10⁵ population, an epidemic threshold of 10 cases/10⁵ population/week performed well. Based on this same epidemic threshold, with a 6 week interval between crossing the epidemic threshold and population protection from a meningococcal vaccination campaign, an estimated 17 cases per event would be prevented by vaccination. Lowering the threshold increased the number of cases per event potentially prevented, as did shortening the response interval. If the interval was shortened to 4 weeks at the threshold of 10/10⁵, the number of cases prevented would increase to 54 per event.

Conclusions: Accelerating time to vaccination could prevent more cases per event than lowering the threshold. Once the meningitis epidemic threshold is crossed, it is of critical importance that vaccination campaigns, where appropriate, are initiated rapidly.

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1. Introduction

For over 100 years the African meningitis belt, which runs across the continent from Senegal to Ethiopia, has been prone to devastating epidemics of meningococcal meningitis [1], mostly due to *Neisseria meningitidis* serogroup A (NmA). In order to guide emergency response and control, the World Health Organisation (WHO) defined operational thresholds that trigger the reinforcement of surveillance (the alert threshold) and the launch of vaccination

campaigns and antibiotic treatment protocols (the epidemic threshold). For areas of population greater than 30,000 WHO recommended an alert threshold of 5 cases/10⁵ inhabitants/week and an epidemic threshold of 10/10⁵/week when epidemic risk is high, or 15/10⁵/week otherwise [2]. For small populations, thresholds were defined by absolute numbers of cases. The current thresholds have been appraised as being both sensitive and specific for detection of NmA epidemics [3–5]. Reactive vaccination traditionally utilises polysaccharide meningococcal vaccines, which offer short term protection [6].

Since 2010, countries in the meningitis belt have progressively introduced a new serogroup A meningococcal conjugate vaccine (MenAfriVac®) through mass campaigns [7,8]. Conjugate vaccines, unlike plain polysaccharide vaccines, are longer lasting,

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more immunogenic in young children and able to prevent carriage thus leading to herd immunity [9]. Meningitis due to NmA has declined and the proportion of cases due to other Nm serogroups, predominantly NmW, has increased [10]. As the epidemiology of disease due to other serogroups may be different to that due to NmA, WHO instigated a review of epidemic meningitis guidelines that included operational thresholds. We analysed meningitis surveillance data in the African meningitis belt, focussing on the epidemiology of meningitis due to NmW. The analysis described in this paper was presented to the WHO guideline review group and used to inform decisions about alert and epidemic thresholds in the final guideline [11].

2. Methods

Multiple sources of meningitis surveillance data in the African meningitis belt countries from 2002 (the year of the first major NmW epidemic in the meningitis belt [12]) to 2013 in weeks 1–26 (to reflect the meningitis season) were used to construct a single database (Table 1). All data were at district level; we did not obtain data at finer resolution such as sub-district or health centre level. The primary data source was the WHO Inter-country Support Team for West Africa database on suspected cases, organised so that one row represented a single district year with weekly case counts in columns. Laboratory line lists of individual cases were matched to the WHO weekly suspected case data by district and year. District years with ≥ 2 laboratory confirmed NmW cases and $>50\%$ NmW out of all confirmed cases due to *N. meningitidis* were retained. District years were also included if a request had been made to the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG) for vaccines containing NmW. District years with a total of 20 or fewer suspected cases were excluded (33 district years).

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of lowering weekly thresholds (from 10 to 7, 5, 3 per 10^5) for detecting an epidemic based on different cumulative seasonal incidences (from 100 per 10^5 down to 20 per 10^5), were calculated. The different weekly and seasonal incidences were chosen to represent a higher than background incidence [13] and after initial exploration of the data. To further evaluate the thresholds, a 'post MenAfriVac® dataset', with suspected case counts by district year from Mali, Niger, Burkina Faso in both 2012 and 2013 and from Chad in 2013 only was used to estimate the number of times a specific weekly incidence threshold was crossed.

2.1. Estimating vaccine preventable cases

Cases occurring after applying different weekly incidence thresholds were calculated. The week that a given epidemic threshold was crossed (wt) was identified, and the cases that occurred in subsequent weeks were summed until weekly incidence declined to a 'normal' seasonal incidence of <2 per 10^5 [13] (noted as wn). Data from the ICG between 2006 and 2013 were used to determine the range, mean and median time taken from a request for vaccine to implementation of a reactive vaccination campaign.

An interval (lag) was calculated based on the number of weeks from crossing the epidemic threshold, to initiation of a reactive vaccination programme, with an additional 2 weeks to achieve population protection from vaccination (wt+lag, e.g. wt+6). The extra 2 weeks was included to allow for the estimated time taken to conduct a vaccination campaign (the median duration of vaccination campaigns in the ICG data was 4 days) and for development of a protective immune response (10 days). The number of vaccine preventable cases was estimated by multiplying the total number

of cases that occurred between wt+lag and wn by the effective vaccine coverage (V_{EC}), a composite variable of vaccine effectiveness and uptake. For example, vaccine uptake of 95% multiplied by vaccine effectiveness of 90% gives a V_{EC} of 86%; values of 75% and 90% were used in this analysis. Since children under 2 years of age may not be targeted in reactive vaccination campaigns because of low immunogenicity in this age group [6], the effect of excluding <2 year old children was also considered in the model by assuming that 16% of cases occurred in this age group. The number needed to vaccinate to prevent one case (NNV) was estimated by taking the inverse of the cases prevented divided by the population vaccinated ($1/(\text{preventable cases} \div \text{population vaccinated})$). The vaccinated population was assumed to be 75% of the mean district size, as an approximation of those aged less than 30 years old.

To investigate the robustness of these results, the distribution of the cases averted by outbreak was examined and to investigate any residual effects of vaccination triggered by the current threshold of $10/10^5$, the districts known to have been vaccinated with an NmW-containing vaccine were excluded from analysis.

3. Results

The final dataset used for analysis consisted of 136 district years with 20,777 suspected cases, of which 2318 (11.1%) were confirmed as NmW. Burkina Faso accounted for 82 (60%) of the district years, with Mali and Niger adding 14 and 17 district years, respectively, and four other countries (Benin, Chad, Ghana, and Guinea) contributing between 2 and 7 district years each (Fig. 1). District population sizes ranged from 59,330 to 884,859, with a median population of 263,110.

The total seasonal incidence ranged between 3 and 506 per 10^5 . Of 99 district years that exceeded a seasonal incidence of $20/10^5$, the peak weekly incidence ranged from 2.5 to 104 per 10^5 , with a median peak incidence of $6.2/10^5$ and the timing of the peak observed between week 2 and week 17 (median week 13). The performance of the weekly thresholds in predicting different definitions of an epidemic (based on seasonal cumulative attack rate) is shown in Table 2, and the combination of highest sensitivity and specificity for each definition of an epidemic is highlighted. The analysis was repeated for Burkina Faso only and for all others excluding Burkina Faso, although this did not markedly change the results (not shown). The post-MenAfriVac® dataset included 395 district years and the median cumulative seasonal incidence was $1.7/10^5$ ranging from 0 to 111 per 10^5 . Fewer than 10 cases per year were recorded in 237 of the 395 district years. Sixty-two districts reported a cumulative seasonal incidence of at least $20/10^5$. Only 3 districts reached a cumulative seasonal incidence in excess of $100/10^5$, all of which exceeded a weekly incidence threshold of $10/10^5$. Based on these data, in the post-MenAfriVac® era, 2, 3, 5 or 9 'events' per country would occur at thresholds of 10, 7, 5 or 3 per 10^5 per week, respectively, in a typical year.

3.1.1. Estimating vaccine preventable cases

Vaccines were released by the ICG to 151 districts (that had complete records of vaccination data) between 2006 and 2013. The time taken from crossing the threshold to the implementation of a reactive immunisation campaign was a mean of 26 days, median of 24 days (Fig. 2). The shortest response time, excluding those instances where vaccine stocks were already held in-country, was 10 days. Estimates of vaccine preventable cases were therefore based on two lag periods (6 and 4 weeks) from crossing the threshold to population protection.

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