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Stockpile needs for epidemic meningitis response 2018-2022

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Date: 8th December 2017

With thanks to: Dr Olivier Ronveaux, Katya Fernandez, WHO Geneva and Clement Lingani, WHO-IST Ouagadougou for providing data and expert advice.

Summary

Despite much progress in the control of epidemic meningitis through the roll-out of a group A meningococcal conjugate vaccine (MenAfriVac), other meningococcal groups and the pneumococcus continue to cause epidemics in the African meningitis belt. The emergence and spread of a new *N. meningitidis* group C (NmC) strain since 2013, in populations known to have low immunity to NmC, is particularly concerning.

There is considerable year-to-year variation in the incidence of meningitis in countries of the meningitis belt and in the size of populations affected by meningitis. The number of suspected meningitis cases reported ranges over an order of magnitude from <10,000 to nearly 100,000 cases per year over the period 2005-2017. MenAfriVac has reduced the burden of meningitis by around 60% and it is likely that control of NmA will be sustained over at least the next 5 years. As we do not fully understand the factors influencing epidemic risk, there are no suitable models that enable predictions of meningitis incidence in the period 2018-2022. Developing appropriate forecasts for vaccine stockpile requirements due to causes other than NmA is therefore challenging.

While recognising that reactive vaccination is a poor strategy for the control of meningitis epidemics compared to preventive vaccination, there are few alternatives until affordable multivalent (ideally pentavalent) meningococcal conjugate vaccines are available. To estimate the stockpile requirements for epidemic meningitis response in this intervening period, we examined different sources of data to quantify the past needs. We used WHO-IST surveillance data from 2005-2017 to estimate the number of district-years and corresponding populations where (1) the epidemic threshold was crossed for at least 2 weeks and (2) the cumulative seasonal incidence reached or exceeded 100 per 100,000. As laboratory data is inconsistently collected and reported at a district level, we do not include the ICG criterion for laboratory confirmation of the dominant strain in these analyses. To utilise data from across the whole time period, we reduced our disease burden estimates by 60% in unvaccinated populations to better reflect the post-MenAfriVac situation. We further assumed that vaccination campaigns would target 70% of the affected population. Data from an NmW-confirmed subset of the WHO-IST data and ICG vaccine requests and disbursements were also examined.

The target population at risk of non-A Nm disease per year (which can be used as a proxy for stockpile requirements) was estimated at a mean of 3 million (median 2.2 million) using method (1) and 1.9 million (median 1.3 million) using method (2). There was considerable heterogeneity and the maximum requirement was 10.6 million doses per year (method 1). A vaccine stockpile of 5 million doses would have been inadequate in 1/6 years (16.6%). There is a high risk of a major NmC outbreak over the next 4 years. A stockpile of **at least 5 million doses** and ideally **10 million doses** per year is recommended. A stockpile of 10 million doses will be insufficient for a catastrophic expansion across northern Nigeria and neighbouring countries.

The stockpile should consist of C and W containing vaccines, including monovalent group C conjugate vaccines. Conjugate vaccines should be procured in preference to plain polysaccharide vaccines, despite their higher price, as they can be repurposed or used in preventive campaigns. A stockpile of MenAfriVac should be considered separately as while there is a low risk of outbreaks, vaccine can be cycled into routine programmes. Ways of improving the speed of response should be investigated as timely immunisation will be much more effective.

Background

Epidemics of meningitis, primarily caused by *Neisseria meningitidis*, the meningococcus, continue to occur across the area of the Sahel and sub-Sahel known as the African meningitis belt[1]. Following the introduction of an effective[2] tailor-made vaccine[3] against *N. meningitidis* group A (NmA), the major cause of epidemic meningitis over the past 100 years, the burden of disease has been substantially reduced[4]. We estimate that after full vaccine-roll out, the incidence of suspected meningitis has declined by 57%, with an accompanying 59% decline in the risk of districts reaching the epidemic threshold[5]. Vaccine acceptance and uptake of MenAfriVac has been very high[6], reinforcing the success of a preventive strategy for epidemic meningitis.

However, outbreaks due to group W (NmW) have frequently occurred over the past 15 years[7,8], and in 2013 a new group C (NmC) strain emerged in northern Nigeria[9], subsequently causing significant outbreaks in Niger in 2015 (9,300 cases)[10] and Nigeria in 2017 (14,500 cases)[11]. While the emergence of NmW and NmC is not related to MenAfriVac introduction[12], there is evidence that the incidence of disease due to groups other than A is increasing in the post-MenAfriVac era[4]. A WHO expert group met in September 2017 to review experience from the expansion of serogroup C meningococcal meningitis epidemics in Africa and to update recommendations. The group concluded that the risk of NmC epidemics is likely to persist in Nigeria, Niger and neighbouring countries and that the size of the 2018 vaccine stockpile is currently too low[12]. Although the limitations of reactive vaccination for meningitis emergency response are well recognised[13,14], there are few other tools available while we await the licensure of an affordable pentavalent meningococcal conjugate vaccine.

Outbreaks of meningococcal disease are notoriously unpredictable. Despite many years of research, the factors that influence the risk of epidemic meningitis – which include humidity, dust and population immunity[15-17 18]- remain relatively poorly understood. Although there has been progress in modelling the general epidemiological features of disease in the African meningitis belt (including peak size and irregular periodicity)[16] and in making predictions of the impact of MenAfriVac[19,20] there are certainly no models that can accurately forecast the epidemic risk over the next 5 years. This presents a challenge for defining vaccine stockpile requirements. Decisions must be informed by data from previous years, expert opinion on the scale of risk due to NmC expansion[12] and ICG expertise and experience. Here, we review data from meningitis surveillance and ICG requests, and make comparisons with previous stockpile estimates to inform such decision making.

Methods

We analysed past data from two primary sources: surveillance data from WHO-IST and ICG data on vaccine requests and disbursements. We compared our findings to that of Dalberg in 2016.

The surveillance data from WHO-IST are reported in weekly meningitis bulletins throughout the meningitis season, and consist of reports of suspected cases of meningitis at a district level, with supporting laboratory information. The surveillance system is described in detail by Lingani *et al*.[8] Nine countries are judged to have consistently reported data over the past 10-12 years[5], and here we also focus on these countries (Benin, Burkina Faso, Chad, Cote d'Ivoire, Ghana, Mali, Niger, Nigeria, Togo). Note that we exclude DRC. We evaluate vaccine needs independently (i.e. without reference to actual ICG requests) using two different metrics: (1) districts reaching the epidemic threshold of 10 per 100,000 for at least 2 weeks during the meningitis season and more conservatively (2) districts reaching a cumulative incidence of 100 per 100,000 over the year. In each case, we summed the population in the affected districts and multiplied this by 0.7 to create a 'vaccine target population' (usually 2-29 year olds). To make use of data from the pre-MenAfriVac era when NmA was predominant we multiply the vaccine target populations by 0.4 (to reflect a 60% reduction in the burden of disease consistent with our previous findings[5]) in unvaccinated districts. As laboratory data is inconsistently collected and reported at

a district level, we do not include the ICG criterion for laboratory confirmation of the dominant strain in these analyses.

We also examined a specific dataset on NmW affected districts that was used to evaluate epidemic thresholds in 2015[13], which is a subset of the WHO-IST database; this does require evidence of laboratory-confirmed NmW, which must be the majority serogroup. Note that these data were used to inform the Dalberg study.

ICG data on vaccine availability, requests and disbursements were available from 1997 onwards, with more detail available from 2009 onwards. We examined the size and composition of the stockpile per year and the ratio of disbursements relative to total stock.

Results

Vaccine stockpile size

First, we estimated the annual total population size of districts that reached or exceeded the epidemic threshold (an incidence of 10 per 100,000 per week) for at least 2 weeks. This shows that the maximum vaccine requirement was 10.6 million doses. A very similar estimate of around 10 million doses is obtained for both the adjusted 2009 NmA epidemic and the 2017 NmC epidemic (figure 1). The mean target population is 3 million (median 2.1million).

Using the second metric of annual total population size of districts that reached or exceeded a cumulative incidence of 100 per 100,000, the historical vaccine requirements are lower, with a maximum of 7.8 million, and only 5.2 million in 2017 (figure 1). Note that no account is taken of the impact of reactive vaccination campaigns that may have curtailed the final epidemic size. The mean target population is 1.9 million (median 1.2million)

Looking at the subset of NmW-confirmed affected districts that reached the epidemic threshold[13], the estimates are lower, with only 4 of 11 years of surveillance (2002-2013) registering a vaccine requirement; 2.9million in 2002. 0.4million in 2003, 1.0million in 2010 and 2.8million in 2012. This gives a mean annual requirement of 655,000 doses. Although there are many limitations to this particular dataset, this comparison is important as the Dalberg study focussed on this data.

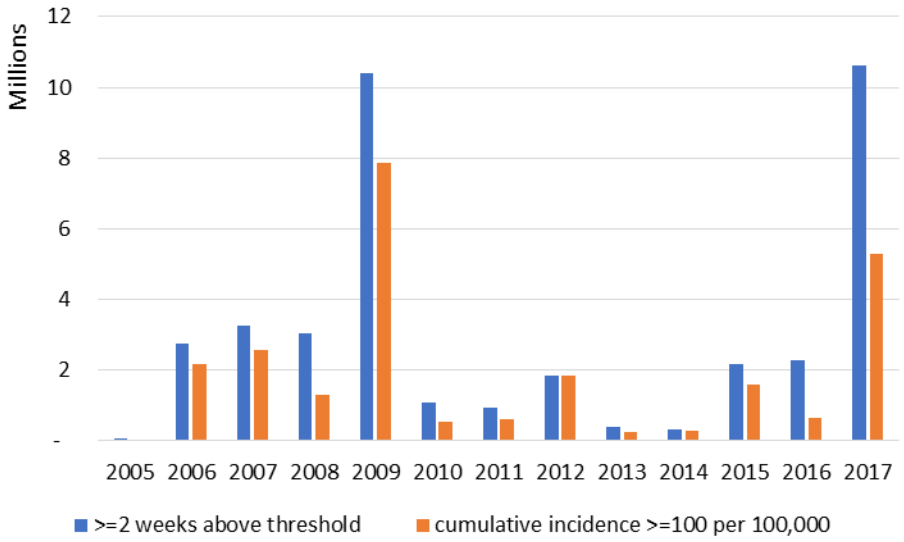

Figure 1: Estimates of target populations affected by meningitis outbreaks defined by 2 different criteria. Adjustments have been made for populations unvaccinated with MenAfriVac.

Data on ICG requests and disbursements were also evaluated. As ICG decisions are influenced by the reality of a limited vaccine supply, these data are not a reliable way to estimate the real need, nevertheless they provide useful context. In the pre-MenAfriVac era, ICG estimated needs of 12 million doses in 2009 and 2010. Estimates then fell as MenAfriVac was rolled out to 9.5 then 7 million in 2011-12 and 2013-14 respectively. However, fewer than 3 million doses each year 2009-2015 were W-containing vaccines. In terms of vaccine disbursements, excluding stocks of MenAfriVac, between 2009 and 2013 ICG disbursed between 5% and 60% of its vaccine supply. The ICG has considered the emergency stockpile as essential insurance in case of large epidemics, given the limited vaccine supply available in the global market.

Vaccine stockpile composition

The number of cases of suspected meningitis cases and the dominant meningococcal serogroup are shown in table 1, with variation in case numbers over an order of magnitude.

There is a clear shift in the dominant serogroup from NmA to NmW to NmC. As continued geographic expansion of NmC is expected, vaccine procurement should focus on C-containing vaccines, including monovalent serogroup C conjugate (MCC) vaccines. A priority should be given to conjugate vaccines over plain polysaccharide vaccines. There are clear advantages in procuring conjugate vaccines as they have the potential to be repurposed in the event they are not required for epidemic response or used in "reactive-plus" or preventive campaigns. The procurement of conjugates could help to generate a more stable demand and improve market shaping opportunities. (Note that modelling work is ongoing to investigate strategies for prevention or reactive-plus immunisation).

Table 1: Number of suspected meningitis cases and dominant pathogen by year. Note that numbers from 2005-2015 are taken from Trotter et al [5], and 2016 and 2017 from the WHO meningitis surveillance bulletin.

Year	Number of suspected cases of meningitis	Dominant meningococcal serogroup
2005	8595	NmA
2006	33775	NmA
2007	35487	NmA
2008	26050	NmA
2009	77562	NmA
2010	20315	NmW
2011	14242	NmW
2012	16068	NmW
2013	6631	NmW
2014	7232	NmW
2015	14451	NmC
2016	23119 (14232 excluding DRC)	NmC
2017 (to week 43)	28866 (23145 excluding DRC)	NmC

Discussion

We have examined surveillance data from the past 12 years and estimated previous vaccine needs. This was done independently from the ICG requests and processes as this system imposes additional requirements of laboratory confirmation (for which data are harder to acquire and curated less well) and involve implicit rationing (linked to the limited available vaccine supply). These analyses indicate that even in the context of NmA control, up to 10 million doses per year were required, although with marked variations in vaccine requirements per year. Clearly, not every district reaching the epidemic threshold

for at least 2 weeks will meet the ICG criteria, but this approach allows us to explore the upper limits of demand.

In order to use as much of the available information as possible, we retained data from the pre-MenAfriVac period, but made adjustments for the measured reductions in the burden of disease in the post-MenAfriVac era[5]. In extrapolating past experience to future requirements, we assume that there is no underlying change in the risk of disease, excepting NmA control. However, this may not be the case in the context of a geographical expansion of a novel and virulent NmC strain. There has been a clear shift from NmA as the dominant pathogen to NmW to NmC; vaccines in the stockpile should cover C and W, with current priority for C-containing vaccines.

In 2016, Dalberg conducted a study looking at meningitis outbreak response and the ICG[i]. They recommended that a vaccine stockpile of 5 million doses would cover 95% of outbreak scenarios. This analysis was based on a very limited dataset of 35 district years affected by NmW. This current analysis, which uses an expanded dataset and includes recent NmC outbreaks, suggests that 5 million doses would be insufficient in 1/6 years (16.6%). Dalberg recommended that further modelling be carried out to improve stockpile estimates. Here we prefer a more transparent approach and present the data that can inform stockpile requirements, recognising that there are no adequate models to forecast future meningitis risk. The mix of vaccines in the stockpile appeared to be driven by cost-minimisation. There are clear advantages in procuring conjugate vaccines as these have the potential to be repurposed in the event they are not required for epidemic response, or used in "reactive-plus" or preventive strategies. Modelling work is ongoing to investigate a range of strategies, including targeting of more limited age-groups and neighbours of affected districts.

These analyses can help to inform decisions about the stockpile needs for epidemic meningitis response. Expert opinion on the geographic expansion of NmC and future risk should also be taken into account, together with an assessment of the degree of acceptable risk to stakeholders.

Conclusions

There are no adequate methods for accurately forecasting the future risk of meningitis epidemics. For this reason, forecasting vaccine stockpile needs is challenging. Based on the experience of the recent past, the stockpile should be **at least 5million** doses per annum of C and W containing vaccines. As estimated stockpile requirements have already exceeded this level in 1 year of 6, and there is an expectation of continued expansion of NmC, it is recommended that a stockpile of up to **10 million doses** be considered. Conjugate vaccines, including monovalent C conjugate vaccines, should be procured in preference to plain polysaccharide vaccines.

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[i] In March 2016, the Bill & Melinda Gates Foundation solicited proposals to provide high-calibre strategic and analytical support to WHO to help define a 5-year strategic plan for meningitis outbreak response in Sub-Saharan Africa. The Dalberg Global Development Advisors company was contracted.