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Priorities for research on meningococcal disease and the impact of serogroup A vaccination in the African meningitis belt

Dakar discussion group on priorities for research on epidemic meningococcal disease in Africa

Abstract

For over 100 years, large epidemics of meningococcal meningitis have occurred every few years in areas of the African Sahel and sub-Saharan known as the African meningitis belt. Until recently, the main approach to the control of these epidemics has been reactive vaccination with a polysaccharide vaccine after an outbreak has reached a defined threshold and provision of easy access to effective treatment but this approach has not prevented the occurrence of new epidemics. Meningococcal conjugate vaccines, which can prevent meningococcal carriage and thus interrupt transmission, may be more effective than polysaccharide vaccines at preventing epidemics. Because the majority of African epidemics have been caused by serogroup A meningococci, a serogroup A polysaccharide/tetanus toxoid protein conjugate vaccine (PsA-TT) has recently been developed. Results from an initial evaluation of the impact of this vaccine on meningococcal disease and meningococcal carriage in Burkina Faso have been encouraging.

To review how the research agenda for meningococcal disease in Africa has been changed by the advent of PsA-TT and to define a new set of research priorities for study of meningococcal infection in Africa, a meeting of 41 scientists was held in Dakar, Senegal on April 24th and 25th 2012. The research recommendations developed during the course of this meeting are presented in this paper.

The need for enhanced surveillance for meningitis in defined populations with good diagnostic facilities in African countries at risk of epidemics was identified as the highest priority. This is needed to determine the duration of protection against serogroup A meningococcal disease provided by PsA-TT and to determine the risk of disease and carriage caused by meningococci of other serogroups. Other research areas given high priority included identification and validation of serological correlates of protection against meningococcal disease and carriage, development of improved methods for detecting carriage and epidemiological studies aimed at determining the reasons underlying the peculiar epidemiology of meningococcal disease in the African meningitis belt. Minutes and working papers from the meeting are provided in supplementary tables and

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some of the presentations made at the meeting are available on the MenAfriCar consortium website (www.menafriCar.org) and on the web site of the Centers for Disease Control (www.cdc.gov).

Keywords

Meningococcal meningitis; Africa; Vaccination; Surveillance

1. Introduction

For over 100 years, large epidemics of meningococcal meningitis have occurred every few years in countries of the Sahel and sub-Saharan, an area known as the African meningitis belt [1]. The unique epidemiology of meningococcal infection in this part of Africa includes the occurrence of epidemics every few years, which may result in tens of thousands of cases and thousands of deaths, severely disrupting routine health services. Subjects of all age may be affected but older children and young adults are the groups most at risk. Epidemics occur during the dry season, subsiding during the rainy season but sometimes recur in neighboring areas in the following dry season [2-4]. The majority of African epidemics have been caused by meningococci belonging to serogroup A but substantial outbreaks caused by meningococci belonging to serogroup C, W135 or X have also occurred [5-7].

Since the late 1970s, the main approach to epidemic control in the African meningitis belt has been reactive vaccination with a serogroup A + C or serogroup A + C + W135 polysaccharide vaccine after an outbreak has reached the World Health Organization (WHO) defined threshold [8]. When reactive vaccination is initiated early in the course of an epidemic, it can be effective in reducing morbidity and mortality but despite the administration of many millions of doses of polysaccharide vaccine over four decades, the frequency of epidemics in meningitis belt countries has not declined. This is because meningococcal polysaccharide vaccines induce only short lasting immunity, especially in infants and young children, do not induce immunological memory, may induce hyporesponsiveness when given repeatedly and, most importantly, have little or no impact on pharyngeal carriage and thus they are unable to prevent transmission [9]. Conjugate vaccines overcome many of these limitations as they are immunogenic in infants, induce immune memory and prevent transmission. Consequently conjugate vaccines are a more appropriate tool for effective prevention strategies than polysaccharide vaccines in sub-Saharan Africa as well as in other parts of the world.

Most African epidemics of meningococcal disease have been caused by meningococci belonging to serogroup A but, until recently, there was no serogroup A conjugate vaccine available for use in Africa as the quadrivalent vaccines containing a serogroup A conjugate produced by major pharmaceutical companies are too expensive for use in the poorest countries in Africa. However, in 2009, a serogroup A polysaccharide/tetanus toxoid conjugate vaccine (PsA-TT) (MenAfriVac™) was licensed in India. This vaccine was developed by the Meningitis Vaccine Project (MVP) (www.meningvax.org), a partnership between WHO and PATH working in close collaboration with the Serum Institute of India,

the vaccine manufacturer [10]. In 2010, the vaccine was pre-qualified by WHO on the basis of its safety and immunogenicity and non-inferiority to a reference polysaccharide vaccine [11], a similar approach to the one adopted in Europe and North America for the licensure of other monovalent or multivalent meningococcal conjugate vaccines. At the end of 2010, immunization of the whole 1- to 29-year-old population of Burkina Faso was undertaken during a ten-day period to achieve a reduction in the circulation of the serogroup A meningococcus nationwide as quickly as possible and to directly protect the age group at highest risk of meningococcal disease [12]. Vaccination of a proportion of the 1- to 29-year-old populations of Mali and Niger was also accomplished in 2010. In 2011-2012, the remaining 1- to 29-year-old populations of Mali and Niger were vaccinated and vaccination commenced in Chad, northern Cameroon and in six states in northern Nigeria. PsA-TT will be rolled out progressively across the meningitis belt during the next four years. PsA-TT is also being evaluated in infants and, if it receives regulatory approval for use in this age group, it will be used to vaccinate new birth cohorts in meningitis belt countries and/or in catch-up campaigns.

Initial results from Burkina Faso suggest that PsA-TT has been highly effective at preventing invasive serogroup A meningococcal disease, reducing serogroup A disease by nearly 100%, eliminating district level serogroup A outbreaks [13] and causing a rapid reduction in serogroup A meningococcal carriage [14]. During the 2011 meningitis season, a few months after the 2010 PsA-TT vaccination campaign, the incidence of suspected bacterial meningitis in Burkina Faso was reduced in all age groups, including those too young or too old to have been vaccinated, suggesting an additional indirect herd effect. In the two years following the introduction of PsA-TT there have been no cases of serogroup A meningococcal disease in vaccinated subjects. The results of these studies in Burkina Faso suggest that if a high level of vaccine coverage can be achieved across the meningitis belt, PsA-TT will prevent or greatly attenuate serogroup A meningococcal epidemics in the Africa and this view is supported by preliminary data from the 2012 meningitis season with no cases of serogroup A meningococcal disease being reported from Burkina Faso, Mali or Niger where PsA-TT has been deployed. However, it should be noted that the vaccine was introduced at a time of low natural transmission of serogroup A meningococci in the central part of the meningitis belt. Despite this initial success of PsA-TT, a number of important challenges to the control of epidemic meningitis in Africa remain. These include:

- The need for high quality data on the long term impact of PsA-TT to ensure continuing political willingness to build an effective, sustainable meningococcal vaccination strategy for Africa.
- Determination of the mechanisms of indirect protection produced by PsA-TT.
- Assessment of the burden of disease due to other meningococcal serogroups, as a result of serogroup replacement or natural fluctuations in the prevalence of different serogroups, and hence the potential need for a more complex conjugate vaccine for the African meningitis belt.

To develop a plan to address these challenges, a meeting of experts was held in Dakar, Senegal on April 24th and 25th 2012. This report summarizes the key conclusions from this meeting.

2. Format of the meeting

Over forty delegates, including epidemiologists, clinicians, microbiologists, immunologists, vaccinologists, molecular biologists and public health specialists attended the meeting together with representatives of the World Health Organization, research donors and non-government agencies (Supplementary Table 1). Participants were invited so as to provide representatives from the main groups concerned with the control of meningococcal disease in Africa. The meeting was supported by the Bill & Melinda Gates Foundation. On the first day of the meeting, speakers reviewed progress with the introduction of PsA-TT, the challenges that have been encountered and overcome in rolling out the vaccine and plans for the future deployment of PsA-TT over the next four years. The first results from evaluation of the impact of PsA-TT on the incidence of meningococcal meningitis and meningococcal carriage in Burkina Faso were presented. The delegates then split into two working groups to identify the key research priorities in the new environment created by the successful introduction of PsA-TT. Working group 1 was asked to identify four key research areas relevant to the maintenance of epidemic control while working group 2 was asked to identify four key research questions related to the biology of meningococcal infections in African meningitis belt countries and how these might change now that a serogroup A meningococcal conjugate vaccine is being introduced. Summaries of the discussions of the two working groups were then presented in a plenary session during which the priorities of the working groups were refined and during which new research priorities emerged.

The outcome of these discussions, presented in this paper, is a first step in a process of defining the next priorities for research on meningococcal disease in the African meningitis belt in the era of meningococcal conjugate vaccines. It is acknowledged that some specialities were under-represented at the meeting, and that additional inputs, reviews and refinement of priorities will be needed during the coming years.

3. Presentations and working group discussions

A list of the speakers at the meeting and the topics of their presentations is shown in Supplementary Table 2. Minutes of the meeting, which summarize the presentations and the outcome of the discussion groups, are provided in Supplementary Table 3. Reports of the two working groups are presented in Supplementary Tables 4a and 4b. Powerpoint of presentations by some of the key speakers are available on the MenAfrican website (www.menafrican.org) and on the Centers for Disease Control website (www.cdc.gov).

4. Research priorities

Based on the output of the meeting, and subsequent work by the delegates, the following research priorities were identified as key to a better understanding of meningococcal disease in the African meningitis at a time when a conjugate vaccine is being deployed.

4.1. Development of an enhanced and sustainable surveillance system for meningococcal disease and carriage in the African meningitis belt

Establishment of enhanced and sustainable surveillance systems in a limited number of sites was identified as the key research priority, as this is essential if many of the questions related to the introduction of PsA-TT and its impact on the epidemiology of meningococcal disease and epidemics in the African meningitis belt are to be answered. Evaluation of the duration of protection provided by PsA-TT and accurate assessment of the magnitude of any replacement disease requires ongoing surveillance in a defined population where a high proportion of cases are laboratory confirmed, allowing incidence rates to be calculated. Added value is provided when disease and carriage are studied in the same community. Although there has so far been no evidence of serogroup replacement following the widespread deployment of serogroup C meningococcal conjugate vaccines in Europe, it cannot be assumed that the same will be the case following deployment of a serogroup A meningococcal conjugate vaccine in the very different environment of the African meningitis belt. Reassurance that prevention of serogroup A epidemics is long lasting and that serogroup replacement does not occur will help in ensuring the uptake of PsA-TT and in retaining support for the vaccine from the population, local leaders and health officials. An effective surveillance system forms the platform for detailed geospatial and risk factor studies and it also provides the platform for systematic strain collections, allowing the evolution of the meningococcus to be evaluated over time. Enhanced, population based laboratory confirmed surveillance has already been established at some sites in the meningitis belt and needs to be sustained but this is relatively costly if high quality data are to be obtained.

The establishment of defined areas where high quality surveillance is undertaken does not take away the need to maintain surveillance for outbreaks across the meningitis belt. Such systems need to be able to detect and report cases rapidly and to operate at the first health facility level where many patients with meningitis make their first contact with the health system. Surveillance at this level would be helped greatly by the development and increased availability of point of care tests for the diagnosis of meningococcal infection and determination of its serogroup, especially if these tests would obviate the need for lumbar puncture or for blood culture, which is rarely available in meningitis belt countries, and through the development of new methods of data capture such as the use of mobile phones. Research is needed to develop and evaluate the effectiveness, feasibility, cost effectiveness and sustainability of novel surveillance systems.

4.2. Understanding vaccine-induced meningococcal immunity

PsA-TT was licensed in India and prequalified by WHO on the basis of its ability to induce a high titer of serogroup A bactericidal antibodies, significantly superior to that induced by a reference polysaccharide vaccine, although the titer of serogroup A bactericidal antibodies that confers protection has not yet been defined. Nevertheless, measurement of the period after vaccination during which bactericidal antibodies remain above the level believed to provide protection together with data on the incidence of meningococcal disease may help in designing future vaccination strategies, for example the potential need for a booster dose and its timing. The efficacy of the vaccine in vulnerable populations also needs to be studied.

Several studies of antibody persistence in vaccinated individuals and populations following introduction of PsA-TT are ongoing but the question of what serological indicators to use remains open. Recent research, presented at the meeting, suggests that serogroup A bactericidal antibodies detected by current serological assays, especially those induced by natural infection, do not always reflect protective immunity in the meningitis belt and that further validation of current methods or alternative assays are needed. Determination of an immunological correlate of protection against carriage would help in understanding how meningococcal conjugate vaccines prevent transmission, when the indirect protective effects of the vaccine wanes and when there might be a risk of new strains of serogroup A meningococci becoming established. However, the mucosal immune response to the meningococcus has been little studied, in particular the cellular mucosal immune responses as this is difficult to do. Characterization of mucosal immune responses to natural meningococcal infection and to vaccination are key research priorities that need input from established mucosal immunologists. Another approach suggested in helping to define the mechanism of action of PsA-TT (and other meningococcal conjugate vaccines) is assessment of initial innate immune responses induced by the vaccine [15].

4.3. New approaches to the diagnosis of meningococcal carriage and disease and improved understanding of meningococcal biology and pathophysiology

Other basic research issues identified during the course of the meeting that need to be addressed to increase understanding of the epidemiology of meningococcal infection in Africa and how it might be affected by vaccination included the following:

4.3.1. The meningococcus—Delegates considered ways in which recent advances in microbial genomics could contribute to a better understanding of the epidemiology of meningococcal infection in Africa and how this information might be influenced by factors such as vaccination and increasing use of antibiotics. New genetic approaches could allow acquisition of information about the mechanisms by which commensal species become pathogenic, the role of genetic exchange across species and whether there is a risk of the emergence of entirely new meningococcal serogroups.

4.3.2. Carriage—Study of meningococcal carriage is key to understanding the epidemiology of meningococcal disease because carriage is the stage of the infection at which selective factors exert their effects and because generation of herd immunity through an effect on carriage is a major cost effective benefit of meningococcal conjugate vaccines. Thus, delegates recommended that a high priority should be given to development of more effective, sensitive and less time consuming methods of detecting meningococcal carriage. Areas suggested as being worth further exploration included (a) investigation of the use of microneedles or other technologies as potentially more sensitive methods for detecting the presence of meningococci in the pharynx, (b) the use of qPCR on samples taken directly from a swab, obviating the need for culture, and allowing detection of mixed cultures, (c) evaluation of the density of meningococcal carriage and how this might relate to the risk of disease and of transmission, and (d) study of the impact of indiscriminate use of antibiotics on meningococcal carriage, The influence of the oropharyngeal microbiota on meningococcal carriage, through competition for ecological niches, and of how seasonal

changes in the microbiota might influence the remarkable seasonal pattern of meningococcal disease in the African meningitis belt was suggested as an important area of research.

4.3.3. Meningococcal disease—There is still a need for further work to identify the host and environmental factors that contribute to the seasonality of meningococcal disease and predict or contribute to epidemics in the African meningitis belt. The results of this research could contribute to the design of more specific preventive strategies for meningitis in this area. Factors that might account for the current paucity of serogroup B disease, the appearance of serogroup X and W-135 outbreaks, localized epidemics and major, epidemic waves and for differences in incidence between rural versus urban populations and between age groups are still poorly understood. Appropriate study designs might include laboratory-based research using new animal or cell culture models and molecular studies of isolates, patient- or population-based risk factor studies and theoretical modeling. Factors to be investigated which could be associated with carriage, invasive disease, or epidemic occurrence, include co-infections (symptomatic or asymptomatic; viral or bacterial; inter- or intra-species competition), climate-related stresses (mechanical or immunologic stress), life-style-related stress (smoke exposure), and strain variations below current methods of pheno-/genotypic typing.

To understand better the pathophysiology of meningococcal infection, meningococcal disease syndromes, such as septicaemia, need to be studied.

Mathematical modeling studies should incorporate factors that influence the spatial, seasonal and year to year differences in risk of meningococcal disease, dynamic transmission models, and the development of predictive models for epidemics.

Changing behavior and health care in the meningitis belt populations, such as increased antibiotic use, introduction of *Haemophilus influenzae* type b, pneumococcal and influenza virus vaccines and urbanization may have an important impact on the epidemiology of bacterial meningitis and other disease syndromes in the future. Research is needed to determine role of such interventions in the epidemiology of meningococcal infections in the African meningitis belt.

4.4. Assessment of the need for a polyvalent meningococcal conjugate

Outbreaks of meningococcal disease caused by meningococci belonging to non-serogroup A meningococci continue to occur across the African meningitis belt [16] and establishing effective surveillance across the belt will allow the relative importance of these outbreaks and those caused by other bacteria, such as the serotype 1 pneumococcus, to be determined. These data will be essential in determining whether the burden of non-serogroup A meningococcal disease is sufficient to warrant universal immunization with a polyvalent conjugate vaccine and whether this would be cost effective. The best strategy for the manufacture and use of a polyvalent conjugate meningococcal vaccine for Africa requires further study. In the meanwhile, non-serogroup A vaccines, preferably conjugate vaccines, will be needed to contain outbreaks caused by meningococci belonging to serogroups C, W and Y but currently, no serogroup X vaccine is available.

5. Conclusions

Although the development and successful deployment of PsA-TT is a major achievement that is likely to have a dramatic impact on epidemic serogroup A meningococcal disease in countries of the African meningitis belt, the ways in which the meningococcus will adapt to this changing situation are uncertain. It is, therefore, important that the health authorities of affected countries and WHO (both AFRO and Geneva) recognize that despite the successful introduction of PsAA-TT, the battle against epidemic and sporadic meningococcal disease in the African meningitis belt is far from over and that a coordinated programme of research on this disease is still needed which is sufficiently rigorous to attract financial support from international donors. Sustained investigation will be needed to monitor the duration of protection provided by PsA-TT and to determine how disease due to meningococci of other serogroups changes over time. Many questions about the factors determining the transmission and invasiveness of meningococci in meningitis belt countries and about the mechanisms of protection against this bacterium remain. Studies to assess the interaction between the meningococcus and its host will generate knowledge about host-pathogen-environment interactions that will go beyond the specific problem of epidemic meningitis in the African meningitis belt. The successful introduction of PsA-TT has changed the public health priorities of research for meningococcal disease in Africa. However, decades of research have demonstrated that the behavior of the meningococcus in the African meningitis belt is dynamic and unpredictable. Consequently, delegates to the meeting emphasized the need to sustain an effective surveillance system for epidemic meningitis with strong laboratory support in countries where this has been established and, as an urgent priority, to establish effective surveillance in countries where there this is currently weak but which plan to introduce PsA-TT in 2013-2016. Research is still needed to find ways of ensuring that devastating outbreaks of meningococcal disease caused by meningococci of any serogroup are finally eliminated from Africa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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