A Consensus Statement: Meningococcal Disease Among Infants, Children and Adolescents in Latin America

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Abstract: Invasive meningococcal disease is a serious infection that occurs worldwide. *Neisseria meningitidis* remains one of the leading causes of bacterial meningitis in all ages. Despite the availability of safe and effective vaccines against invasive meningococcal disease, few countries in Latin America implemented routine immunization programs with these vaccines. The Americas Health Foundation along with Fighting Infectious Disease in Emerging Countries recently sponsored a consensus conference. Six experts in infectious diseases from across the region addressed questions related to this topic and formulated the following recommendations: (1) standardized passive and active surveillance systems should be developed and carriage studies are mandatory; (2) a better understanding of the incidence, case fatality rates and prevalent serogroups in Latin America is needed; (3) countries should make greater use of the polymerase chain reaction assays to improve the sensitivity of diagnosis and surveillance of invasive meningococcal disease; (4) vaccines with broader coverage and more immunogenicity are desirable in young infants; (5) prevention strategies should include immunization of young infants and catch-up children and adolescents and (6) because of the crowded infant immunization schedule, the development of combined meningococcal vaccines and the coadministration with other infant vaccines should be explored.

Key Words: meningococcal disease, meningitis, surveillance, epidemiology, immunization

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Invasive meningococcal disease (IMD) is a serious infection that occurs worldwide, causing about 500,000 cases and 50,000 deaths yearly. *Neisseria meningitidis* remains one of the leading causes of bacterial meningitis in all ages.

To assess the epidemiology and disease burden of IMD, the national and regional surveillance systems are critical, since the epidemiology of IMD in Latin America has not been well-characterized and marked differences occur among countries.[1] Moreover, information is not uniform and the quality of the reported data is poor in many countries.

Despite the availability of safe and effective vaccines against IMD, few countries in the region have decided to implement a nationwide, routine immunization program with these vaccines. After several outbreaks, only Brazil and Cuba have implemented a routine meningococcal vaccination program with conjugated MenC and outer-membrane protein B vaccines. Although a few other nations in the region have meningococcal vaccination programs, those available are focused only on high risk groups and/or for controlling sporadic outbreaks.

To assess the current epidemiology and surveillance status of IMD disease in Latin America as well as to determine how best to protect the population from future outbreaks, the Americas Health Foundation and Fighting Infectious Diseases in Emerging Countries, recently sponsored a consensus conference to provide clarity and recommendations on these issues and to discuss how best to use public health resources and available vaccines to reduce the incidence of disease. A panel of 6 experts in infectious diseases (the authors of this article) from across the region conducted a comprehensive literature review to identify articles that (1) were published from 2000–2013, (2) covered aspects of meningococcal disease in Latin America and/or national and international guidelines for IMD disease prevention, (3) were based on clinical trials or were observational studies and (4) provided a clear and complete protocol as well as a description of the population studied. With this evidence base, the panel discussed the issues identified above and developed a consensus document.

The present report details the panel's response to six questions, which are explained below.

WHAT IS THE CURRENT STATUS OF MENINGOCOCCAL DISEASE SURVEILLANCE IN LATIN AMERICA?

The establishment of a national and regional surveillance system is critical to assess the epidemiology and disease burden of IMD. It is also of paramount importance to monitor the impact of vaccines.[2,3]

The gold standard for diagnosis is laboratory-based testing, relying on cultures of cerebrospinal fluid, blood or other normally sterile body fluids. IMD requires compulsory notification in Latin America; however, countries use different surveillance systems. The surveillance is mainly passive and many countries have a system with regular and detailed reporting, whereas other countries do not, thereby limiting the possibility of comparing incidence and prevalence rates.[4]

In countries with a well-established passive system, such as Argentina, Brazil, Chile and Uruguay, isolates from at least 50–60% of all reported cases in any given year are reported. In most of the other countries, only a small proportion of isolates are provided, limiting the epidemiologic evaluation of circulating strains.[5]

Laboratory-based diagnosis of suspected cases of IMD in Latin America occurs almost exclusively via culture, which has the advantage of allowing determination of serogroup and other characteristics of the meningococcal isolate. However, previous antibiotic use is a risk factor for culture negativity, contributing to an underestimation of disease burden.[1]

The use of molecular methods to detect meningococcal DNA from blood, cerebrospinal fluid, serum and other sterile fluids, using polymerase chain reaction (PCR) and real-time PCR (RT-PCR),

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has proven to be an important tool for surveillance (PCR) and to increase the accuracy of the diagnosis of bacterial meningitis used as a clinical tool (RT-PCR).[6–9]

In some developed countries like the United Kingdom, PCR is a routine diagnostic modality for patients with meningitis, with >50% of laboratory-identified meningococcal cases confirmed by PCR alone.[10] The value of RT-PCR when incorporated into routine public health in Latin America was demonstrated in São Paulo, Brazil showing an increase in the diagnostic yield of bacterial meningitis by 85% over what was estimated by culture alone.[11] In that study, the main risk factor for being culture negative and RT-PCR positive was prior antibiotic treatment. Results of other prospective, active surveillance systems in Mexico,[12,13] where a higher meningococcal incidence rate compared with previous published information was documented, reinforce the importance of a wider adoption of PCR into routine microbiological laboratory surveillance.

Although progress has been made, the panel believes that there is a clear need for better surveillance systems across the region. The establishment of sentinel-based active surveillance systems, along with passive systems, incorporating population-based data and an expanded use of molecular-based diagnostic techniques, will be crucial to ensure accurate estimates of disease burden.

WHAT IS THE EPIDEMIOLOGY AND BURDEN OF MENINGOCOCCAL DISEASES IN LATIN AMERICA?

N. meningitidis has become the leading cause of bacterial meningitis in children after the dramatic reductions in the incidence of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b infections resulting from corresponding vaccination.[14–17]

Although the annual incidence is relatively low, case-fatality rates (10–15%) and sequelae (11–19%) among survivors are appreciable. Significant sequelaes includes limb or digit amputation, skin scarring, neurologic disabilities and hearing loss. Although the incidence is highest in infants, the case-fatality rates in adolescents are significantly high (~20%).[2] The most important risk factors for the development of IMD include younger age, crowding, smoking, concomitant respiratory infection and immunodeficiency.

Investigations into meningococcal carriage are crucial to the understanding of transmission dynamics and epidemiology.

Meningococcal carriage is assumed to be common, with a population prevalence of 10% often quoted and varies with age and setting.[18] Age is the most important factor in establishing carriage prevalence and is low in young children, increasing to its peak in adolescents and young adults and subsequently declining in older ages. High rates of carriage have also been found in household contacts of people with the disease, in military personnel and in crowded living conditions (eg, student dormitories, prisons).[19] Information regarding carriage in Latin America is scarce. In contrast to other studies, a report from Mexico found low carriage rates in children and university students.[20] The relationship between meningococcal carriage rates and IMD outbreak has received considerable study. The important measure in terms of disease is the rate of acquisition of a meningococci hypervirulent strain, not the overall carriage rate.[21]

The epidemiology of IMD in Latin America has not been well-characterized but marked differences occur among countries.[1] The information is not uniform and the quality of the reported data is poor in the region. The overall incidence per year varied from <0.1 cases per 100,000 inhabitants in Mexico to 1.5 cases per 100,000 in Brazil, with greatest numbers in infants <1 year of age. In contrast to the epidemiology of *N. meningitidis* in the developed world, there is no apparent second peak of incidence in adolescents in the region. This difference may be due to the lack of crowding in this age group. While overall there has been a downward trend in disease incidence within the region during the last few years, inconsistencies in the quality of information suggest that the disease has been underestimated.

Many IMD cases in Latin America are caused by serogroups B and C, but the emergence of serogroups W and Y has been reported in some South American countries. Serogroup A disease is now rare in the region.

In 1993, Pan American Health Organization implemented a Latin American and Caribbean laboratory-based passive surveillance program, named SIREVA, initially for cases of invasive *S. pneumoniae* infection. This network was extended in 2000 to cases of *N. meningitidis*; SIREVA performs a standardized systematic analysis of isolates recovered by the epidemiological survey network from countries in the region.[4] Of note, not all countries participate in SIREVA and some are more active than others (Fig. 1).

Serogroup distribution by region or country highlights the high diversity observed across Latin America in the last years.[5] Two examples of the dynamism of serogroup prevalence were seen in Colombia and in the Southern Cone. In Colombia, serogroup Y first emerged in 2003, and 3 years later was causing almost half of all infections. In 2007, serogroup W was causing <10% of the cases in Argentina and Chile. By 2012, this serogroup was the leading cause of invasive disease across all ages in both countries.[22,23]

The mechanisms that contribute to dynamic meningococcal epidemiology are related to microbial, host and environmental factors. An important microbial factor is capsular switching that is the mechanism by which *N. meningitidis* can change its capsular phenotype, as occurred with W, as mentioned above. Meningococcal outbreaks can also be started or sustained by capsular switching.

WHAT ARE THE AVAILABLE VACCINES FOR THE PREVENTION OF MENINGOCOCCAL DISEASE?

The development of meningococcal vaccines began in the 1960s with the most significant progress taking place during the past decade. Vaccines are now available against all meningococcal strains related to serogroups A, C, Y and W. Regarding protection against serogroup B, vaccines are available for specific strains and a broadly protective serogroup B recombinant vaccine has recently been approved in Europe and Australia.

Types of Vaccines

1. *Capsular polysaccharide vaccines*. These vaccines for serogroups A, C, Y and W are available in mono- and polyvalent formulations. They proved to be safe and effective in controlling outbreaks and epidemics. However, their immunogenicity in infants and young children is limited, especially against serogroup C, they exert only transitory and incomplete, if any, effect in reducing the colonization and the transmission of the meningococci in the vaccinated population and convey hyporesponsiveness after repeated doses compared with glycoconjugate vaccines. Therefore, these vaccines have been increasingly abandoned in the pediatric population.
2. *Glycoconjugate vaccines*. These vaccines are produced by coupling capsular polysaccharides to carrier proteins.[24] These conjugate vaccines elicit a higher antibody response than polysacharide vaccines and generate antibodies that have greater functional activity.

There are 2 meningococcal monovalent glycoconjugate vaccine formulations. One against serogroup A (currently being used in Africa) manufactured by Serum Institute of India and another against serogroup C, manufactured by 3 different

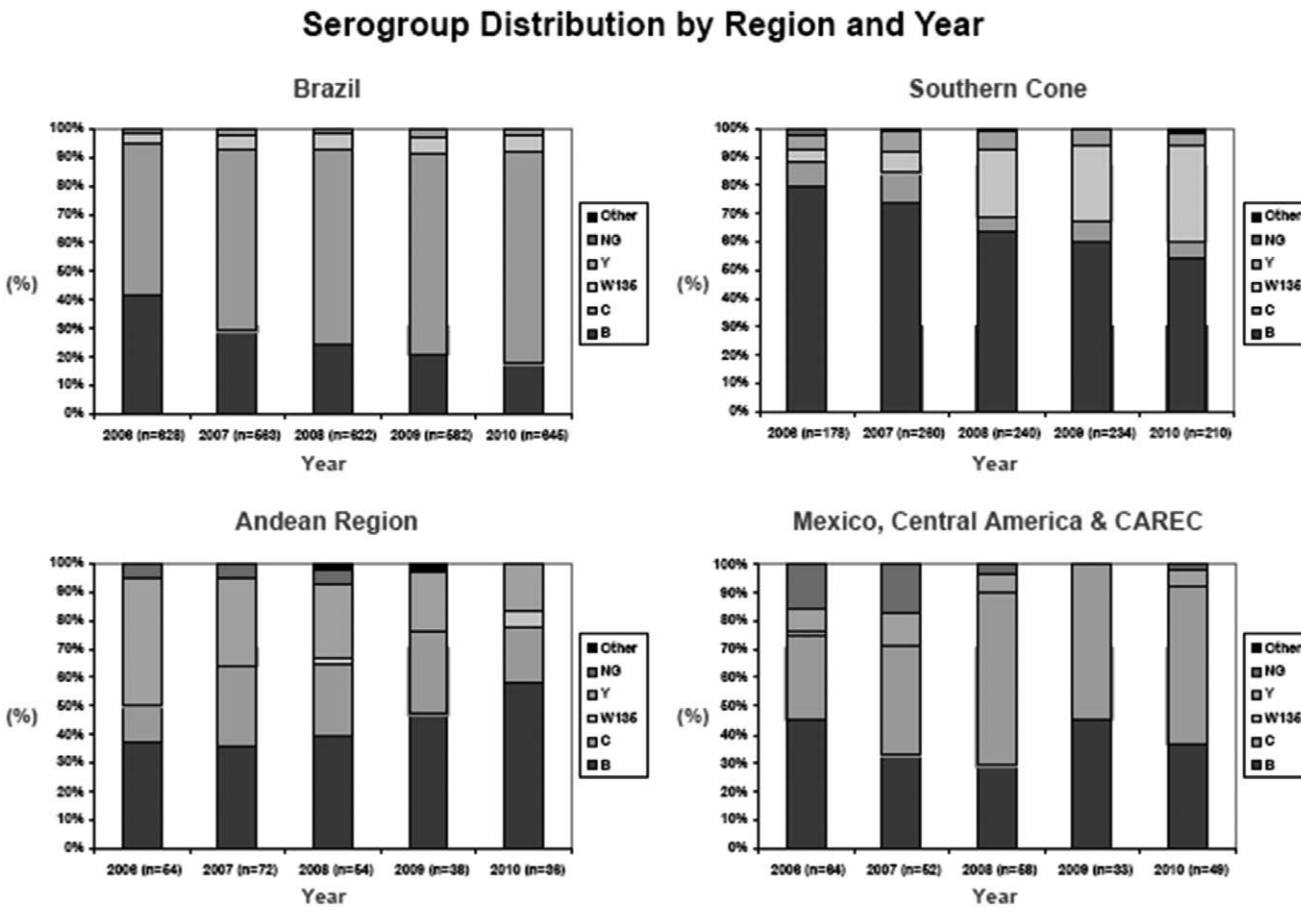

FIGURE 1. Laboratory-based Surveillance of Meningococcal Disease in Latin America and Caribbean Countries, SIREVA II 2006–2010.*Adapted from rapid changing in trends of meningococcal disease in Brazil from 2000 to 2010, Ana Paula Silva Lemos, Maria Cecilia Outeiro Gorla, Marta Galhardo, Conceicao Martins Zanelato, Maria Vaneide de Paiva, Marcelle Vicoso dos Santos and Maria Cristina de Cunto Brandileone. National Reference Laboratory for Meningitis, Bacteriology Branch, Adolfo Lutz Institute, Sao Paulo.

pharmaceutical companies (Novartis, Pfizer and Baxter), all proved to be safe and immunogenic in infants. One of the vaccines, conjugated to tetanus toxoid, appears to generate higher antibody titers than the others and may result in better priming and antibody persistence.[25]

Recently, a bivalent meningococcal polysaccharide protein conjugate vaccine that provides protection against meningococcal serogroups C and Y along with *H. influenzae* type b (Hib) was licensed in the United States for use as primary vaccination at 2-4-6 months with a booster dose in the 2nd year of life. Another bivalent HiB-MenC is used as a booster in the 2nd year of life in the United Kingdom.

Finally, there are quadrivalent vaccines against serogroups A, C, Y and W. Three glycoconjugate quadrivalent vaccines are available in Latin America. One is conjugated with denatured diphtheria toxoid (MenACYW-D) and is indicated for use in individuals 9 months to 55 years. The other vaccine is conjugated with a cross-reactive, nontoxic mutant of diphtheria toxoid (MenACYW-CRM197) and is indicated in Latin America for those >2 years of age.[26,27] More recent clinical evidence, which included a Latin American population, suggests MenACWY-CRM197 is immunogenic from 2 months of age; this vaccine is already approved for infants in the United States.[28] There is also a quadrivalent vaccine conjugated to tetanus toxoid approved in Europe for children from 1 year of age and was recently introduced in Chile, together with the other 2 quadrivalent conjugated formulations, for outbreak control.

With the availability of these quadrivalent vaccines, we now have the ability to vaccinate individuals at various young ages. The panel believes that all factors considered (eg, immunogenicity, safety, epidemiology of IMD) should vaccines be approved in Latin America in individuals as young as age 2 months, this change may make them the vaccines of choice.

3. *Serogroup B vaccines.* Tailor-made serogroup B vaccines have been developed, which are effective against outbreaks. These protein-based vaccines developed mainly with the immunodominant outer-membrane protein called porin A, which is retained in the outer-membrane vesicle (OMV).[29] This approach has been used to develop 3 different tailor-made vaccines to successfully control meningococcal B outbreaks caused by homologous strains in Cuba, New Zealand and Norway. The main limitation of OMV-B vaccines is their strain-specific response and inability to generate bactericidal antibodies against heterologous strains, particularly in infants.[30,31]

There has been much research to develop serogroup B vaccines based on other subcapsular proteins that will be broadly protective. By a technique known as "reverse vaccinology," a vaccine has been developed that contains 3 recombinant proteins, factor H

binding protein, Neisserial adhesin A and *Neisseria* heparin binding protein, which together are collectively expressed in the vast majority of serogroup B strains are immunogenic and elicited bactericidal activity. A four-component vaccine comprising the 3 previously mentioned proteins plus a detoxified OMV from a specific meningococcal B strain (NZ 98/254) has been developed. This 4CMenB vaccine was recently licensed for commercial distribution in Europe and Australia and has been found to be safe and immunogenic in a Latin American adolescent population.[32] Another recombinant, investigational, vaccine containing 2 factor H binding protein variants, expressed as lipoproteins in *Escherichia coli*, has been shown to be highly immunogenic in humans and to elicit broadly reactive anti-MenB bactericidal antibodies in phase 2 clinical trials in adolescents.[33]

In general, meningococcal vaccines can be administered concomitantly; however, they must be injected into different sites and not mixed with any other vaccines. Side effects from vaccination are rare. Mild and temporary local reactions, such as pain, erythema and induration, may appear 24–48 hours after administration. Moderate systemic reactions such as fever and irritability may be present in 10–30% of vaccines. Anaphylactic reactions after vaccination are rare.

General contraindications to vaccination apply to all meningococcal vaccines. There is no contraindication for meningococcal polysaccharide vaccines during pregnancy when the benefit of vaccination outweighs potential risks to the fetus. Conjugate vaccines are no longer contraindicated in individuals with history of Guillain-Barré syndrome.

WHAT IS THE CORRELATE OF PROTECTION, THE EFFICACY AND THE HERD PROTECTION GENERATED BY THE VACCINES?

Serum antibodies confer protection against IMD by activating complement-mediated bacteriolysis and by enhancing phagocytosis (opsonic activity).[34] In the 1960s, Goldschneider et al[34] using a serum bactericidal activity assay (SBA) found that military recruit with a titer ≥1:4 who were exposed during a group C meningococcal epidemic did not develop disease while virtually all cases occurred in individuals whose SBA titers were <1:4. In addition, SBA was rarely detected in children 2 months to 2 years of age, the age group with the highest incidence of disease. In contrast, many adults, in whom disease was rare, had SBA titers ≥1:4 measured against group A, B and C strains. It was also demonstrated that the meningococcal carrier state is an immunizing process and antibodies can be identified in many individuals within 2 weeks of colonization.

The Goldschneider study demonstrating a correlation between the SBA titer and protection, used human complement in the assay (hSBA). When measured with human complement, a SBA titer ≥1:4 is generally considered protective for serogroup C and A. Measurements of SBA are likely to be useful for evaluating immunization schedules for OMV vaccines,[35] but there are no confirmed immunological correlates of protection for serogroups Y, X and W. As it is now difficult to find sufficient amounts of human sera that lack antimeningococcal antibodies to serve as a source of exogenous complement, many laboratories now use infant rabbit serum (rSBA) because it is widely available and can be shared among laboratories for standardization of the assay.[36]

There are 2 possible approaches to establish a serological correlate of protection for a vaccine. One is based on immunogenicity data from individuals and the other is from a vaccinated population as a whole. To validate the use of rSBA as a correlate of protection in younger age groups, a population-based approach was selected in a UK study after the introduction of conjugate MenC vaccines. One month after vaccination, a rSBA threshold of 1:8 correlated best with observed efficacy, but this only applied to short-term efficacy and antibody values decreased markedly within 12 months of immunization.[37]

Meningococcal disease occurs soon after mucosal acquisition of the bacteria. Once serum antibody values wane, the ability of an immunized person to mount a memory antibody response upon exposure to a pathogenic group C strain may not be rapid enough to prevent disease. Data showing decreased vaccine effectiveness between 1 and 4 years after immunization of infants and toddlers, at a time when they can mount robust memory antibody responses, suggest that serum antibody persistence is more important in protection than memory.[38] Enzyme-linked immunosorbent assay tests are also used to determine the serogroup C meningococcal polysaccharide specific IgG, which can be expressed as geometric mean titers or geometric mean antibody concentrations. Immunogenicity studies likely predict short-term effectiveness; however, their ability to determine long-term effectiveness is uncertain as antibody levels decline postvaccination within 6–8 months. It is hoped that higher postvaccination titers will correlate with a longer duration of protection, but evidence supporting this hypothesis is lacking.[39]

MenC Vaccine Effectiveness

It is generally not feasible to perform efficacy studies of meningococcal vaccines because the disease is relatively rare, and therefore large populations would have to be recruited. Thus, regulatory authorities established immunological criteria as correlates of protection from IMD, to use in clinical trials that compare new vaccines to those previously approved.

As discussed earlier, after introduction of glycoconjugate meningococcal group C vaccination in the United Kingdom, there was a significant decline in the number of cases and deaths caused by group C in infants, toddlers and adolescents targeted for immunization. Effectiveness after 1 year was approximately 90% for all vaccinated groups. However, between 1 and 4 years after vaccination, effectiveness declined in all age groups, along with a parallel decline in rSBA titer. The protection was lost in infants vaccinated at 2, 3 and 4 months of age, and protection declined approximately 40% in toddlers vaccinated with 1 dose.[40] To increase the magnitude and duration of protective serum antibody in infants, the immunization schedule was changed in 2006 to 2 doses given at 3 and 4 months of age and a booster at 12 months.

Another study assessed the effectiveness of vaccination on oropharyngeal carriage of meningococci in a large cohort of UK adolescents. Swabs were collected before vaccine introduction and again 1 and 2 years after introduction. There was a 66% decrease of group C meningococci colonization and no evidence of replacement by other serogroups. Of note, there also was a 66% decrease in the incidence of group C invasive disease in unvaccinated individuals, suggesting that vaccination also induced herd protection.[41] Further data from both epidemiological and other carriage studies showed evidence that long-term protection in those with waning or lost antibodies was most likely the result of herd immunity, generated by the entire immunization program including catch-up in older age groups.[42]

After a continued period of predominance of serogroup C disease, Brazil, in late 2010, introduced the MenC conjugate vaccine in the routine immunization program. Population-based surveillance data showed that in the first year after its introduction, a rapid and significant reduction in incidence rates of IMD was observed in children aged <2 years, the age group targeted. When an immunization program does not incorporate catch-up campaigns, early herd protection effects are not likely to be observed.[43]

Effectiveness data for quadrivalent MenACWY-D in the United States after 4 years of increasing coverage primarily in adolescents, showed few cases of IMD among individuals previously vaccinated and no evidence of herd protection. Results from

a vaccine effectiveness study demonstrate waning effectiveness, and many adolescents are not protected 5 years after vaccination. Results from a case control study in the United States among individuals 10–23 years of age, demonstrated 77% vaccine effectiveness for serogroup C (95% confidence interval (CI): 14–94%) and 88% vaccine effectiveness for serogroup Y (95% CI: −23 to 99%). These results indicate that vaccine effectiveness wanes over time when assessed up to 5 years postvaccination. Therefore, in the United States, a booster is now recommended for adolescents 5 years after the first dose.[44]

OMV-B Vaccines Efficacy and Effectiveness

The effectiveness of tailor-made serotype B vaccines have not consistently been successful. The efficacy of an OMV-B vaccine was evaluated in Cuba in the late 1980s in children 10–14 years and was estimated to be 83%. Subsequently, the vaccine was introduced into the routine pediatric immunization schedule administered at 3 and 5 months of age. The current low level of disease incidence (0.2/100,000) has been attributed to the vaccine.[45] However, in Sao Paulo, Brazil, this vaccine was introduced in an attempt to control an outbreak in 1988. The efficacy of the vaccine varied greatly. Although the efficacy in children aged ≥48 months was similar to that of the Cuban experience in younger individuals, the vaccine was ineffective.[46] More recently, a tailor-made OMV vaccine has been used to control a specific outbreak of group B meningococcal disease in New Zealand. The vaccine was used in 3 doses, rather than 2, along with a booster given to infants only. In 2004, the vaccination campaign started to include individuals 6 months to 19 years of age. Postvaccination surveillance estimated the effectiveness as 80% in children between 6 months and 5 years of age in the first year after the vaccination.[47] We conclude from these reports that among various factors that could contribute to the results, the immunologic response is homologous to the circulating strain and the schedule of vaccine administration may be important.

Evidence is limited supporting a serological correlate of protection for meningococcal vaccines based on protein antigens. Nonetheless, an international consensus proposed that SBA is a suitable primary end-point for evaluating protein vaccines and would allow these vaccines to be approved without showing clinical efficacy.[48]

Vaccine manufacturers have developed new antigen–antibody binding assays to address the question of translating immunogenicity into a public health benefit. Pfizer has developed a meningococcal antigen surface expression (MEASURE) assay, based on flow cytometry using a monoclonal antibody to measure the amount of factor H binding protein from a collection of diverse meningococcal isolates. Similarly, Novartis has developed a meningococcal antigen typing system, where a capture enzyme-linked immunosorbent assay is employed to measure 3 vaccine components expressed in isolates from large collections of meningococci. These assays do not replace SBA as the correlate of protection and are neither standardized nor publicly available.[49]

Eventually, these assays might be used to obtain reproducible estimates of vaccine strain coverage in different geographical settings and to monitor meningococcal serogroup B strains over time. Some reference laboratories in Europe, Australia, North and South America have now tested >1000 MenB strains by meningococcal antigen typing system. Potential coverage was estimated at 78% (95% CI: 63–90%) for 4CmenB in Norway, United Kingdom, Germany, France and Italy. Among the strains predicted to be covered by the vaccine, 64% were positive for >1 antigen.[50]

Currently, Brazil is the only country in Latin America where coverage has been estimated by meningococcal antigen typing system. In a sample of 99 MenB invasive strains isolated in 2010, which accounts for approximately 53% of the MenB cases identified in Brazil, potential coverage of 4CMenB was 80.8% (95% CI: 70.7–94.9%), consistent with the results found in European countries.[51]

WHICH ARE THE BEST STRATEGIES FOR MENINGOCOCCAL DISEASE PREVENTION?

Because of budgetary constraints and the likely development of many new vaccines over the next few years, a rational choice of which vaccines to use and how best to use them is critical. Along with vaccine safety, it is imperative to have a robust disease surveillance system in place and a thorough understanding of cost-effectiveness to ensure a valuable and durable immunization program.

There is considerable variability in disease burden and serogroup distribution by region and over time. Furthermore, IMD can appear as an outbreak or an endemic, thus highlighting the need for country-specific strategies to make appropriate decisions. In Europe and in the Americas, the disease is mostly endemic.

In several European countries, Canada and Australia, immunization programs include universal vaccination of infants and/or toddlers with catch-up campaigns in children and adolescents, aimed at controlling disease caused by meningococcal serogroup C.[52,53] More recently, conjugate vaccines targeting disease caused by serogroups A, C, W and Y are being used in universal adolescent vaccination programs in the United States and Canada. A widespread immunization campaign against serogroup A disease has been also implemented in Africa.

In Brazil, from 2002 onward, a significant increase in the incidence rates of serogroup C disease has been observed, with various outbreaks reported in different regions of the country, associated to case-fatality rates as high as 20%. The highest incidence rates of IMD during this period were consistently observed in children under 2 years. In response, Brazil began to routinely immunize infants (2 doses at 3 and 5 months plus a booster dose at 12–15 months) and toddlers (1 dose between 12 and 23 months) with a meningococcal C conjugate vaccine in September 2010. Mathematical modeling has shown the routine immunization of Brazilian infants against serogroup C to be cost-effective,[54] but no catch-up campaign of older age groups was done due to cost and resourcing constraints.

In general, however, universal infant vaccination programs are preferable to programs that target those at high risk. The potential for sustained reductions in disease arising from fewer doses of vaccine administered in infancy, a greater reliance on herd protection of infants through adolescent vaccination and inclusion of a booster dose at an older age should be explored in long-term studies.

For vaccination during outbreaks, a primary attack rate should be calculated and all confirmed cases of the same serogroup should be determined. Vaccination of the population at risk should be considered if the attack rate is >10 cases/100,000 persons during a 3-month period.[55] In a recent outbreak of serogroup W disease in Chile, this factor was considered for introduction of a quadrivalent conjugated vaccination program in children 9 months to 5 years of age. The usefulness of the above recommendations and the effectiveness of the vaccine are pending.

For Latin America, the panel believes that more research is clearly indicated to better delineate the epidemiology, true incidence, carriage rates and pattern of IMD in all ages before making a decision about universal or selective immunization. The likely new indication for 1 of the meningococcal conjugate vaccines (see above) and future availability of promising protein-based vaccines, highlights the importance of a better understanding of IMD and the need for cost-effectiveness studies in the region, before initiating widespread national immunization programs.

HOW DO YOU INTRODUCE A NEW VACCINE IN A CROWDED IMMUNIZATION PROGRAM?

In recent years, there has been a dramatic increase in the implementation of new vaccines in universal immunization programs. However, some of the already available vaccines are still underutilized. Building on the successes of routine immunization programs, the widespread use of new and underutilized vaccines has the potential to contribute significantly to reducing global childhood mortality.

The addition of new vaccines to routine childhood immunization schedules requires several critical issues to be addressed. These include: awareness of the burden of disease, availability of the vaccine, cost-effectiveness of the intervention, political will, a good communication plan and the means to introduce the new vaccine into the national immunization program.

In 2010, the implementation of the meningococcal C conjugate vaccination program in Brazil was done through a partnership between a pharmaceutical company (Novartis vaccines) and a Brazilian public-run vaccine manufacturer (Fundação Ezequiel Dias), including technology transfer for local production. Other recent vaccination programs in Brazil (Hib conjugate, rotavirus and pneumococcal conjugate vaccines) were implemented through technology transfer agreements.

Technology transfer from pharmaceutical companies to local vaccine manufacturers in Brazil has contributed significantly to increasing vaccine supply and access to many vaccines, with subsequent improvements in public health. In several cases, this technology transfer has also resulted in lower prices. It is also important to highlight that current technology transfer recipients may become suppliers in future transfers of technology. The 3- and 5-month visit schedule was chosen because many vaccines are already given at 2 and 4 months, making an additional vaccine at that time potentially burdensome and highlights the need to be able to combine different vaccines. The Brazilian experience may, therefore, serve as an important model for meningococcal vaccine development and introduction in other Latin American countries.

After vaccine introduction, surveillance is necessary to monitor the impact of the vaccine on the incidence of disease and to assess vaccine safety. Surveillance data provide decision makers with critical information before and after introducing a new vaccine.

RECOMMENDATIONS

(1) There is a clear need for better surveillance systems across the region. The establishment of sentinel-based active surveillance systems, along with passive systems, incorporating population-based data, will be crucial to ensure accurate estimates of disease burden. Standardized passive and active surveillance systems, with quality information, should be developed to acknowledge the burden of the disease, including incidence, case-fatality rates and prevalent serogroups in Latin America. Carriage studies are mandatory. (2) Countries should make greater use of the PCR assays to improve the sensitivity of diagnosis and surveillance of IMD. (3) All efforts should be made to provide adequate infrastructure conditions for early diagnosis and treatment and to reduce case-fatality rates and morbidity associated to meningococcal disease. (4) Development of vaccines with broader coverage and more immunogenic in young infants is needed. (5) Prevention strategies should include immunization of young infants and catch-up in children and adolescents, but these policies needs to be tailored according to individual country, cost-effectiveness studies and knowledge of disease burden, before initiating widespread national immunization programs. (6) Due to the crowded infant immunization schedule, the development of combined meningococcal vaccines and the coadministration with other infant vaccines should be explored. Alternative immunization schedules and partnership between private manufacturers and public institutions should be considered. The Consensus Panel believes that the implementation of the above recommendations will greatly reduce the adverse impact of IMD.

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