INTRODUCTION OF A SEROGROUP A MENINGOCOCCAL CONJUGATE VACCINE IN THE GAMBIA, WEST AFRICA

Background

Epidemics of meningococcal meningitis have occurred at frequent but irregular intervals in the dry savannah regions of countries forming the southern border of the Sahara, the African meningitis belt, for over 100 years. No reliable way of predicting when and where these epidemics will occur has been found. African epidemics are characterised by their large size, with nearly 100,000 cases being recorded in an epidemic in Nigeria in 1996, although the true figure was probably much larger. Epidemics begin at the start of the dry season and finish with the coming of the rains, often starting up again during the following dry season. During epidemics, cases may occur in subjects of all ages. Incidence is often highest in infants but the majority of cases are seen in older children and young adults. Large epidemics cause major disruptions to the health services.

Meningococci can be characterised by the composition of their capsular polysaccharide. Most African epidemics have been caused by meningococci belonging to serogroup A, a rare cause of meningococcal disease in industrialised countries for the past 50 years, and initially it was believed that all African epidemics were caused by meningococci belonging to this serogroup. However, in the 1970s epidemics due to serogroup C meningococci were recorded in Nigeria and Burkina Faso and, in 2002, the international community was taken by surprise when a large epidemic of meningococcal meningitis due to a serogroup W meningococcus occurred in Burkina Faso. In 2005/6 an outbreak of meningococcal disease due to a serogroup X meningococcus was reported in Niger and cases of both serogroup W and X have been reported in several countries within the African meningitis belt during the past few years. The period 2010 – 2012 was relatively quiet in the African meningitis belt with approximately 22,000, 30,000 and 28,000 cases being reported in 2010, 2011 and 2012 respectively. Serogroup A disease has been encountered only rarely in countries in the central part of the meningitis belt in recent years, even prior to the introduction of the new serogroup A conjugate vaccine. However, in 2011 and 2012 there were substantial outbreaks of predominantly serogroup A meningococcal disease in Chad and adjacent areas of northern Cameroun.

Prevention of epidemic meningitis by vaccination

Until recently, the mainstay of epidemic meningitis control in Africa has been reactive vaccination with polysaccharide vaccines after an outbreak has been detected. To be effective, this approach requires early detection of an outbreak, rapid diagnosis of its cause and a quick vaccination response. This approach has saved many thousands of lives and reduced the impact of major epidemics but, despite the deployment of millions of doses of polysaccharide vaccines in the African meningitis belt, epidemics of serogroup A meningococcal disease have continued to occur. The reasons why polysaccharide vaccines have not prevented epidemics are that they are poorly immunogenic in the very young, probably induce only transient protection in older children and, mostly importantly, have little or no effect on meningococcal carriage and are thus unable to prevent transmission of the infection.

Development of a conjugate vaccine

Studies conducted in The Gambia and in Burkina Faso 20 years ago showed that it was possible to develop meningococcal A and C polysaccharide protein conjugate vaccines which were safe and immunogenic in African children and which induced immunological memory. However, these early studies were not followed up by any of the major pharmaceutical companies which focussed on the development of monovalent serogroup C conjugate vaccines for use in Europe, where these vaccines have proved to be highly effective. It was not until 2001 when, with support from the Bill and Melinda Gates Foundation, a serious attempt was made to develop a serogroup A meningococcal conjugate vaccine that could be used in Africa. This initiative led to the establishment of the Meningitis Vaccine Project (MVP), a partnership between WHO and PATH, which has done a remarkable job in developing and deploying a monovalent serogroup A meningococcal conjugate vaccine PsA-TT(MenAfrivac™) within a period of 10 years.[1] The vaccine is manufactured, using a new conjugate technology, at the Serum Institute of India and produced at a price of approximately $0.40 per dose. Studies in Mali, Senegal and The Gambia have shown that the vaccine is safe and immunogenic in toddlers and adults and a study undertaken in Ghanaian infants indicates that it is also immunogenic in this age group.

In 2010, the vaccine was prequalified by WHO and vaccination of subjects aged 1-29 years commenced in Burkina Faso, Mali and Niger. In Burkina Faso, nearly 100% coverage was achieved in a six- week mass vaccination campaign.[2] In 2011, universal vaccine coverage of those aged 1-29 years was achieved in Mali, Niger and in several states in Nigeria. In 2012, Chad was fully vaccinated and additional states in Nigeria were also vaccinated. Plans are in place to roll out the vaccine across the rest of the African meningitis belt during the period 2013-2016. Sustaining the immune level of the population following these mass campaigns will be achieved either by introduction of PsA-TT into the routine infant immunisation programme, with one or two doses being given during the first two years of life, or by periodic mass immunisation programmes.

PsA-TT was pre-qualified on the basis of its safety and immunogenicity [3] and no phase 3 efficacy trial was done. Thus, evaluation of the efficacy of PsA-TT through phase 4 post-introduction studies is essential. In the meningitis season following the national immunisation programme in Burkina Faso, there was a marked fall in the number of cases of meningitis over previous years and only one serogroup A case was reported; [4] there was also a marked decline in the prevalence of serogroup A meningococcal carriage [5] suggesting that the vaccine is highly effective in preventing both meningitis and carriage. However, PsA-TT was introduced in Burkina Faso at a time when there was a very low level of transmission of serogroup A meningococci in the central part of the African meningitis belt as a result of natural fluctuations in the incidence of this infection. Evidence for an impact of PsA-TT on meningococcal meningitis and carriage has also been obtained in Chad. Although these initial results are very encouraging, more post implementation information is needed on the efficacy of PsA-TT in preventing cases and carriage, on its ability to provide herd protection among unvaccinated subjects and on the duration of protection that it provides.

In 2014, a decision will need to be made as to whether PsA-TT should be introduced in The Gambia.

THE GAMBIA

The Gambia is a small country on the west coast of Africa which is completely surrounded by Senegal, except for a short coastline. The country covers an area of approximately 11,000 km^2 and is mainly flat savannah with flood plains bordering the river. The climate is typical of the sub-Sahelian region of West Africa with a three to four month rainy season (July-October) and a long dry season during the remainder of the year. Average rainfall in recent years has been about 1,000 mm, although this used to be much higher. The population has increased rapidly in recent years and is now estimated to be about 1.7 million. The Gambia is occupied by people belong to several ethnic groups with Wollofs predominating on the coast and Mandinkas and Fulas up-country. The majority of the population still lives in rural areas and is engaged in farming although there is an increasing urban population in the areas around the capital Banjul where about 0.5 million people live. GDP is estimated to be about $2,000 per person. The country has an active tourist industry, most active during the dry season, focussed on the coast but with some tourist spending a period up country.

The Gambia

The Gambia has a relatively good health service and a well established EPI programme. Vaccine coverage in 2011 was estimated to be 96% for DPT3 and that 91% for measles vaccination. The Gambia was the first country in sub-Saharan Africa to introduce Hib vaccination into its routine immunisation programme and the second, after Rwanda, to introduce a pneumococcal conjugate vaccine. This was initially PCV-7 but this was replaced in 2011 by PCV-13.

The Gambia is on the margin of the African meningitis belt. In 1992/3 over 1,000 cases were reported, due predominantly to infection with serogroup A meningococcus and a large epidemic caused by a serogroup A meningococcus occurred in 1997 with over 1,000 reported cases. The Ministry of Health responded to these epidemics by reactive vaccination with serogroup A + C polysaccharide vaccination in affected areas. Between epidemics, a small number of cases have

been recorded in most years. In 2012, there as an outbreak of serogroup W meningitis in Upper River region with over 100 reported cases. Meningococcal disease in The Gambia shows the characteristic features of epidemic meningitis in Africa with outbreaks occurring during the dry season and with cases in all age groups but with the greatest number of cases occurring in older children and young adults.

Task

The Ministry of Health of The Government of The Gambia is considering whether or not it should introduce PsA-TT in The Gambia. Although large outbreaks have occurred in the country, these have been relatively infrequent and occasional outbreaks can be managed through reactive vaccination. Mounting a national campaign is a large and demanding process. Because of these uncertainties, the Minister of Health has set up a working group to advise him and the Minister of Finance on -

a. Whether The Gambia should introduce PsA-TT into its routine immunisation and, if so –
b. What kind of vaccination programme should be used?
c. Who should be vaccinated?
d. How should the impact of introducing the vaccine be monitored.

Instructions to the break out group

You are the working group established by the Ministry of Health to a advise the Minister of Health and the Minister of Finance, whose support will be needed for any large scale vaccination programme, as to whether PsA-TT should be introduced into the Gambia and, if so, how this would be done. If your decision is to support vaccination then you will need a strong case to back this argument and to persuade the Ministry of Finance to release the funds that this would require.

To move forward -

- Choose your chairman and rapporteur.
- Give each member of the group a role in the expert team.

You will be informed of how long you have for your discussions. After these have finished your rapporteur will be asked to make a presentation of your findings.

BACKGROUND PAPERS.

1. *Frasch C, Preziosi MP, Laforce FM. Development of a group A meningococcal conjugate vaccine, MenAfriVac (TM). Human Vaccine and Immunotherapeutics; 2012; 8; 715-724.*

Group A meningococcal disease has been an important public health problem in sub-Saharan Africa for over a century. Outbreaks occur there annually, and large epidemics occur at intervals ranging between 8 and 12 y. The Meningitis Vaccine Project was established in 2001 with funding from the Gates Foundation with the goal of developing, testing, licensing, and introducing an affordable group A meningococcal conjugate vaccine into Africa. From 2003 to 2009 a monovalent group A conjugate vaccine, MenAfriVac (TM), was developed at the Serum Institute of India, Ltd through an innovative public/private partnership. Preclinical studies of the new conjugate vaccine were completed in 2004 and a Phase 1 study began in India in 2005. Phase 2/3 studies in African 1-29 y olds were completed in 2009 showing the new meningococcal A conjugate vaccine to be as safe as currently licensed meningococcal polysaccharide vaccines, but much more immunogenic. After Indian market authorization (December 2009) and WHO prequalification (June 2010), MenAfriVac (TM) was introduced at public health scale using a single 10 µg dose in individuals 1-29 y of age in Burkina Faso, Mali, and Niger in December 2010. We summarize the laboratory and clinical studies leading to prequalification of MenAfriVac (TM) . The 2011 epidemic season ended with no reported case of group A meningitis in vaccinated individuals

2. *Djingarey MH, Barry R, Bonkoungou M, Tiendrebeogo S, Sebgo R, Kandolo D, Lingani C, Preziosi MP, Zuber PL, Perea W, Hugonnet S, Dellepiane de Rey Tolve N, Tevi-Benissan C, Clark TA, Mayer LW, Novak R, Messonier NE, Berlier M, Toboe D, Nshimirimana D, Mihigo R, Aguado T, Diomandé F, Kristiansen PA, Caugant DA, Laforce FM. Effectively introducing a new meningococcal A conjugate vaccine in Africa: the Burkina Faso experience.* Vaccine. 2012;Suppl 2: B40-45**.**

A new Group A meningococcal (Men A) conjugate vaccine, MenAfriVac™, was prequalified by the World Health Organization (WHO) in June 2010. Because Burkina Faso has repeatedly suffered meningitis epidemics due to Group A Neisseria meningitidis special efforts were made to conduct a country-wide campaign with the new vaccine in late 2010 and before the onset of the next epidemic meningococcal disease season beginning in January 2011. In the ensuing five months (July-November 2010) the following challenges were successfully managed: (1) doing a large safety study and registering the new vaccine in Burkina Faso; (2) developing a comprehensive communication plan; (3) strengthening the surveillance system with particular attention to improving the capacity for real-time polymerase chain reaction (PCR) testing of spinal fluid specimens; (4) improving cold chain capacity and waste disposal; (5) developing and funding a sound campaign strategy; and (6) ensuring effective collaboration across all partners. Each of these issues required specific strategies that were managed through a WHO-led consortium that included all major partners (Ministry of Health/Burkina Faso, Serum Institute of India Ltd., UNICEF, Global Alliance for Vaccines and Immunization, Meningitis Vaccine Project, CDC/Atlanta, and the Norwegian Institute of Public Health/Oslo). Biweekly teleconferences that were led by WHO ensured that problems were identified in a timely fashion. The new meningococcal A conjugate vaccine was introduced on December 6, 2010, in a national ceremony led by His Excellency Blaise Compaore, the President of Burkina Faso. The ensuing 10-day national campaign was hugely successful, and over 11.4 million Burkinabes between the ages of 1 and 29 years (100% of target population) were vaccinated. African national immunization programs are capable of achieving

very high coverage for a vaccine desired by the public, introduced in a well-organized campaign, and supported at the highest political level. The Burkina Faso success augurs well for further rollout of the Men A conjugate vaccine in meningitis belt countries.

3. *Sow SO, Okoko BJ, Diallo A, Viviani S, Borrow R, Carlone G, Tapia M, Akinsola AK, Arduin P, Findlow H, Elie C, Haidara FC, Adegbola RA, Diop D, Parulekar V, Chaumont J, Martellet L, Diallo F, Idoko OT, Tang Y, Plikaytis BD, Kulkarni PS, Marchetti E, LaForce FM, Preziosi MP. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. N Engl J Med 2011; 364: 2293-304.*

Background: Group A meningococci are the source of major epidemics of meningitis in Africa. An affordable, highly immunogenic meningococcal A conjugate vaccine is needed.

Methods: We conducted two studies in Africa to evaluate a new MenA conjugate vaccine (PsA-TT). In study A, 601 children, 12 to 23 months of age, were randomly assigned to receive PsA-TT, a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (Haemophilus influenzae type b conjugate vaccine [Hib-TT]). Ten months later, these children underwent another round of randomization within each group to receive a full dose of PsA-TT, a one-fifth dose of PsACWY, or a full dose of Hib-TT, with 589 of the original participants receiving a booster dose. In study B, 900 subjects between 2 and 29 years of age were randomly assigned to receive PsA-TT or PsACWY. Safety and reactogenicity were evaluated, and immunogenicity was assessed by measuring the activity of group A serum bactericidal antibody (SBA) with rabbit complement and performing an IgG group A-specific enzyme-linked immunosorbent assay.

Results: In study A, 96.0% of the subjects in the PsA-TT group and 63.7% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline; in study B, 78.2% of the subjects in the PsA-TT group and 46.2% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline. The geometric mean SBA titers in the PsA-TT groups in studies A and B were greater by factors of 16 and 3, respectively, than they were in the PsACWY groups ($P<0.001$). In study A, the PsA-TT group had higher antibody titers at week 40 than the PsACWY group and had obvious immunologic memory after receiving a polysaccharide booster vaccine. Safety profiles were similar across vaccine groups, although PsA-TT recipients were more likely than PsACWY recipients to have tenderness and induration at the vaccination site. Adverse events were consistent with age-specific morbidity in the study areas; no serious vaccine-related adverse events were reported.

Conclusions: The PsA-TT vaccine elicited a stronger response to group A antibody than the PsACWY vaccine. (Funded by the Meningitis Vaccine Project through a grant from the Bill and Melinda Gates Foundation; Controlled-Trials.com numbers, ISRCTN78147026 and ISRCTN87739946.).

4. *Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data.Novak RT, Kambou JL, Diomandé FV, Tarbangdo TF, Ouédraogo-Traoré R, Sangaré L, Lingani C, Martin SW, Hatcher C, Mayer LW, Laforce FM, Avokey F, Djingarey MH, Messonnier NE, Tiendrébéogo SR, Clark TA. Lancet Infect Dis 2012;12:757-764.*

Background: An affordable, highly immunogenic Neisseria meningitidis serogroup A meningococcal conjugate vaccine (PsA-TT) was licensed for use in sub-Saharan Africa in 2009. In

2010, Burkina Faso became the first country to implement a national prevention campaign, vaccinating 11·4 million people aged 1-29 years. We analysed national surveillance data around PsA-TT introduction to investigate the early effect of the vaccine on meningitis incidence and epidemics.

Methods: We examined national population-based meningitis surveillance data from Burkina Faso using two sources, one with cases and deaths aggregated at the district level from 1997 to 2011, and the other enhanced with results of cerebrospinal fluid examination and laboratory testing from 2007 to 2011. We compared mortality rates and incidence of suspected meningitis, probable meningococcal meningitis by age, and serogroup-specific meningococcal disease before and during the first year after PsA-TT implementation. We assessed the risk of meningitis disease and death between years.

Findings: During the 14 year period before PsA-TT introduction, Burkina Faso had 148 603 cases of suspected meningitis with 17 965 deaths, and 174 district-level epidemics. After vaccine introduction, there was a 71% decline in risk of meningitis (hazard ratio 0·29, 95% CI 0·28-0·30, p<0·0001) and a 64% decline in risk of fatal meningitis (0·36, 0·33-0·40, p<0·0001). We identified a statistically significant decline in risk of probable meningococcal meningitis across the age group targeted for vaccination (62%, cumulative incidence ratio [CIR] 0·38, 95% CI 0·31-0·45, p<0·0001), and among children aged less than 1 year (54%, 0·46, 0·24-0·86, p=0·02) and people aged 30 years and older (55%, 0·45, 0·22-0·91, p=0·003) who were ineligible for vaccination. No cases of serogroup A meningococcal meningitis occurred among vaccinated individuals, and epidemics were eliminated. The incidence of laboratory-confirmed serogroup A N meningitidis dropped significantly to 0·01 per 100 000 individuals per year, representing a 99·8% reduction in the risk of meningococcal A meningitis (CIR 0·002, 95% CI 0·0004-0·02, p<0·0001).

Interpretation: Early evidence suggests the conjugate vaccine has substantially reduced the rate of meningitis in people in the target age group, and in the general population because of high coverage and herd immunity. These data suggest that fully implementing the PsA-TT vaccine could end epidemic meningitis of serogroup A in sub-Saharan Africa.

5. *Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. Kristiansen PA, Diomandé F, Ba AK, Sanou I, Ouédraogo AS, Ouédraogo R, Sangaré L, Kandolo D, Aké F, Saga IM, Clark TA, Misegades L, Martin SW, Thomas JD, Tiendrebeogo SR, Hassan-King M, Djingarey MH, Messonnier NE, Préziosi MP, Laforce FM, Caugant DA. Clin Infect Dis 2013; 56: 354-363.*

Background: The conjugate vaccine against serogroup A Neisseria meningitidis (NmA), MenAfriVac, was first introduced in mass vaccination campaigns of 1-29-year-olds in Burkina Faso in 2010. It is not known whether MenAfriVac has an impact on NmA carriage.

Methods: We conducted a repeated cross-sectional meningococcal carriage study in a representative portion of the 1-29-year-old population in 3 districts in Burkina Faso before and up to 13 months after vaccination. One district was vaccinated in September 2010, and the other 2 were vaccinated in December 2010. We analyzed 25 521 oropharyngeal samples, of which 22 093 were obtained after vaccination.

Results: In October-November 2010, NmA carriage prevalence in the unvaccinated districts was comparable to the baseline established in 2009, but absent in the vaccinated district. Serogroup X N. meningitidis (NmX) dominated in both vaccinated and unvaccinated districts. With 4 additional sampling campaigns performed throughout 2011 in the 3 districts, overall postvaccination meningococcal carriage prevalence was 6.95%, with NmX dominating but declining for each campaign (from 8.66% to 1.97%). Compared with a baseline NmA carriage prevalence of 0.39%, no NmA was identified after vaccination. Overall vaccination coverage in the population sampled was 89.7%, declining over time in 1-year-olds (from 87.1% to 26.5%), as unvaccinated infants reached 1 year of age. NmA carriage was eliminated in both the vaccinated and unvaccinated population from 3 weeks up to 13 months after mass vaccination (P = .003).

Conclusions: The disappearance of NmA carriage among both vaccinated and unvaccinated populations is consistent with a vaccine-induced herd immunity effect.

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Effectively introducing a new meningococcal A conjugate vaccine in Africa: The Burkina Faso experience

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ABSTRACT

A new Group A meningococcal (Men A) conjugate vaccine, MenAfriVac™, was prequalified by the World Health Organization (WHO) in June 2010. Because Burkina Faso has repeatedly suffered meningitis epidemics due to Group A *Neisseria meningitidis* special efforts were made to conduct a country-wide campaign with the new vaccine in late 2010 and before the onset of the next epidemic meningococcal disease season beginning in January 2011. In the ensuing five months (July–November 2010) the following challenges were successfully managed: (1) doing a large safety study and registering the new vaccine in Burkina Faso; (2) developing a comprehensive communication plan; (3) strengthening the surveillance system with particular attention to improving the capacity for real-time polymerase chain reaction (PCR) testing of spinal fluid specimens; (4) improving cold chain capacity and waste disposal; (5) developing and funding a sound campaign strategy; and (6) ensuring effective collaboration across all partners. Each of these issues required specific strategies that were managed through a WHO-led consortium that included all major partners (Ministry of Health/Burkina Faso, Serum Institute of India Ltd., UNICEF, Global Alliance for Vaccines and Immunization, Meningitis Vaccine Project, CDC/Atlanta, and the Norwegian Institute of Public Health/Oslo). Biweekly teleconferences that were led by WHO ensured that problems were identified in a timely fashion. The new meningococcal A conjugate vaccine was introduced on December 6, 2010, in a national ceremony led by His Excellency Blaise Compaore, the President of Burkina Faso. The ensuing 10-day national campaign was hugely successful, and over 11.4 million Burkinabes between the ages of 1 and 29 years (100% of target population) were vaccinated. African national immunization programs are capable of achieving very high coverage for a vaccine desired by the public, introduced in a well-organized campaign, and supported at the highest political level. The Burkina Faso success augurs well for further rollout of the Men A conjugate vaccine in meningitis belt countries.
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1. Introduction

Burkina Faso is a landlocked country with a population of 15.7 million that sits in the heart of the meningitis belt surrounded by Mali, Niger, Benin, Togo, Ghana, and Côte d'Ivoire. All districts in Burkina Faso are at risk of meningitis epidemics. The last major meningitis epidemic occurred from 2006 to 2008 and caused over 45,000 cases of meningitis with about 90% of cases due to Group A *Neisseria meningitidis* (*NmA*; Fig. 1). Endemic meningococcal disease rates are also high, making meningitis one of the most important public health problems in Burkina Faso.

Over the last 20–25 years epidemic meningococcal meningitis epidemics in Africa have been managed using a reactive

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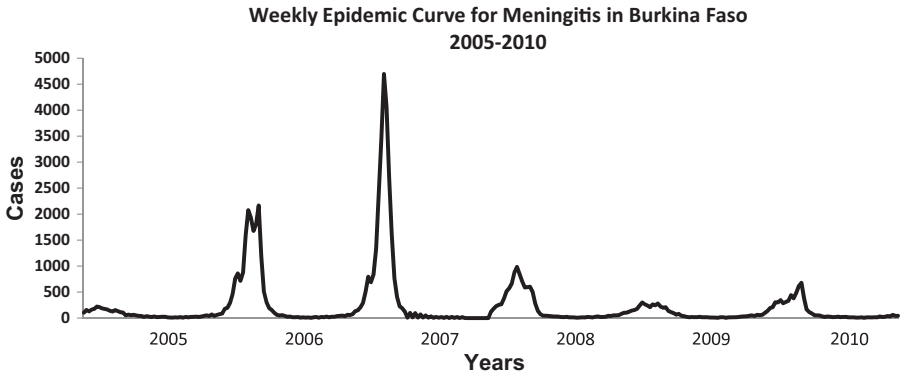

Fig. 1. Weekly reported meningitis cases – Burkina Faso 2005–2010.

strategy: i.e., when district meningitis rates exceed 10 cases per 100,000 population in a single week, reactive campaigns using polysaccharide meningococcal vaccines are implemented. These campaigns are logistically challenging, and often polysaccharide vaccines are given after epidemics are over. Moreover, polysaccharide vaccines have drawbacks since immunity wanes over three years, and the vaccine is not recommended for children under two years [1].

In 1996 and after a particularly severe *NmA* meningitis epidemic with over 180,000 reported cases African ministries of health (MoH) made a formal request to WHO for help in managing these epidemics. Three WHO-sponsored international consultations were held in 1999, 2000, and 2001; and all recommended that more potent meningococcal conjugate vaccines be developed for meningitis belt countries [2]. In June 2001, with funding from the Bill & Melinda Gates Foundation, PATH, a Seattle-based NGO, and WHO formed a partnership called the Meningitis Vaccine Project (MVP) with the specific goal of eliminating *NmA* epidemics by developing, testing, licensing, and introducing an affordable meningococcal A conjugate vaccine for use in the African meningitis belt [3]. Serum Institute of India Ltd. in Pune, India (SIIL), began developing a monovalent meningococcal A conjugate vaccine using a conjugation method originally discovered at the Center for Biologics Evaluation and Research laboratories at the US Food and Drug Administration in Bethesda, USA. Clinical trials of the vaccine were begun in 2005, and after the Drugs Controller General of India granted market authorization for the vaccine in December 2009 the dossier was submitted by SIIL to WHO for prequalification. Given the severity and magnitude of the meningitis problem in sub-Saharan Africa the prequalification of the Men A conjugate vaccine, now called MenAfriVac™, was granted "fast track" status by WHO, and after extensive review the vaccine was prequalified in June 2010 [3].

Burkina Faso, Mali, and Niger were chosen as "early introduction countries" because they are at high risk of *NmA* epidemics, had well-developed surveillance systems, and their respective ministries of health expressed interest in supporting the introduction of a new more potent vaccine to control the problem. Mali and Niger chose to introduce the new Men A conjugate vaccine in two stages, a first phase in 2010 and a second in 2011. Burkina Faso opted to immunize its entire 1–29-year-old population by the end of 2010. Consequently, efforts were begun in mid-2010 to plan for comprehensive immunization of 1–29-year-old Burkinabes in late 2010. This paper describes the steps taken that allowed for a highly successful immunization campaign to unfold in Burkina Faso in December 2010.

2. Vaccination strategy

The vaccination strategy was aimed at providing a single 10 mcg dose of MenAfriVac to all 1–29-year-old Burkinabes. Since 1–29-year-olds represent about 70% of the population, 11.6 million Burkinabes were targeted. From the outset a specific goal was the attainment of district-specific coverage rates greater than 90% to enhance the likelihood of herd immunity. Attaining herd immunity was very important because under ones were not included in the vaccination campaign. Studies conducted in the Netherlands after the introduction of meningococcal C conjugate vaccines have shown that under ones could be protected through herd immunity [4].

3. Regulatory issues

In December 2009 WHO's Global Advisory Committee on Vaccine Safety (GACVS) was updated on clinical safety data from studies of the new Men A conjugate vaccine and of plans for mass vaccination campaigns to be launched soon after the vaccine was prequalified by WHO [5]. The reactogenicity and safety of the vaccine had been evaluated in 7 clinical trials in 5 countries (Ghana, India, Mali, Senegal, and The Gambia). These included 1 study of children aged 14 weeks to 18 months while the other studies were conducted in participants aged 1–29 years, the target age group for the initial mass vaccination campaigns. The safety data from the clinical trials did not raise any particular concerns, but the committee highlighted the need for additional data from a larger population base to better assess the safety profile in particular with respect to potentially rare and delayed reactions [6]. In addition, the GACVS recommended that studies be done to evaluate vaccine safety in pregnancy because of the likelihood of administration of the vaccine to pregnant women during mass vaccination campaigns. The committee also highlighted the importance of gaining additional information on MenAfriVac with respect to the duration of protection; its effect on carriage of *NmA*; interactions with vaccines delivered by the Expanded Program on Immunization (EPI); any possible effect on the prevalence of other serotypes (serotype replacement); and the safety and immunogenicity of the vaccine in groups considered to be potentially at high risk, such as people infected with HIV and those who are severely malnourished.

While the clinical trial data did not show any significant safety issues with the vaccine, the GACVS committee also advised that, where possible, phased introduction of the vaccine would be desirable so that additional safety data could be accumulated before the vaccine was eventually used in large national mass campaigns. Consequently, three safety studies were done in September 2010 in Burkina Faso, Mali, and Niger in about 1.1 million persons. Districts

were chosen in each of the three countries, and between 300,000 and 400,000 1–29-year-olds in each country were given a single dose of the new vaccine. Passive surveillance systems were used to follow postimmunization complications. All serious adverse events were investigated and reviewed by national Adverse Event Following Immunization (AEFI) committees. Studies were begun in September, and data from the studies were reviewed by national committees in November, 2010.

GACVS was further updated on vaccine safety data relating to the introduction of MenAfriVac vaccine collected in the three early-adopter countries (Burkina Faso, Mali, and Niger). A total of 215 reports of AEFI, including 34 serious adverse events, were received after 1.04 million people were vaccinated. Based on reviews by national expert committees, only 1 serious AEFI (an anaphylactic reaction) was classified as related to vaccination. After review GACVS concluded that the new data did not suggest that there should be any special concern about safety [7].

The committee also addressed precautions about use of the vaccine in pregnant and lactating women. Given the potential benefits of the vaccine, the high risk of disease in the geographical area, and past experiences using similar vaccines in comparable conditions, GACVS supported WHO's position that the *NmA* conjugate vaccine should be offered to pregnant and lactating women residing in the meningitis belt during any stage of pregnancy or lactation. Nonetheless, GACVS recommended that MoHs develop plans to follow vaccinated pregnant women in antenatal or obstetric clinics and to monitor pregnancy outcomes by making appropriate comparisons with unvaccinated pregnant women.

In June 2011 the GAVSC Committee received new data on the safety profile of the Men A conjugate vaccine that now included data from active surveillance in one Burkina Faso district as well as the results from the enhanced passive surveillance [8]. There were 18 cases of urticaria and 14 episodes of bronchospasm noted in the district with active surveillance. GACVS Committee concluded that the surveillance data from the introduction of the Men A conjugate vaccine did not indicate any reasons for concern about the vaccine's safety but that the reports of bronchospasm and urticaria suggested hypersensitivity reactions to the vaccine and that a more indepth review of these cases be done to rule out anaphylaxis. GACVS also recognized that while it would not be practical to conduct widespread active AEFI surveillance there was utility in doing both active and passive surveillance to provide safety profile information [8].

Use of the vaccine in Burkina Faso required that the vaccine be registered in Burkina Faso, and members of the Burkina Faso National Regulatory Agency participated in a review of the Men A conjugate vaccine clinical dossier along with representatives from Mali and Niger in Geneva at WHO/HQ in June 2010. SIIL submitted an application to the Burkina Faso National Regulatory Agency that was reviewed, and the vaccine was formally licensed in Burkina Faso in November 2010.

4. Surveillance system

A properly functioning surveillance system is a fundamental prerequisite when introducing a new vaccine. This precondition was particularly important in Burkina Faso because it was to be the first of about 25 countries that were being considered for introducing the new Men A conjugate vaccine. There was need to ensure that the vaccine was safe and that impact could be measured on the incidence of *NmA* meningitis in Burkina Faso. In short, the challenge was to ensure that suspected cases of meningitis were reported and that sufficient spinal fluid samples were taken and available for microbiological studies. These were critical issues because the introduction of a new Men A conjugate vaccine was expected to alter the epidemiology of *NmA* in Burkina Faso, and it was important not only to document impact on the incidence of the disease but also to monitor whether the vaccination campaign had an impact on the distribution of men ingitis pathogens in the country.

Fortunately, major efforts had been expended over the last few years at improving meningitis surveillance in Burkina Faso. In 2003 several meningitis belt countries began implementing enhanced meningitis surveillance [9], an approach that focused on ensuring that suspected meningitis cases were reported on a weekly basis. In Burkina Faso the enhanced program emphasized systematic weekly data collection; compilation and analysis of epidemiological data; as well as the prepositioning of laboratory supplies and the adequate collection, transportation, and analysis of laboratory specimens. Standard Operating Procedures (SOPs) were developed by WHO in close collaboration with Meningococcal Collaborating Centres (CDC/Atlanta, NIPH/Oslo, and IMTSSA/Marseilles) and MVP. District health officers including laboratory officers were trained across the country; and lumbar puncture kits, trans-isolate media, and diagnostic reagents were provided to rural and reference health facilities.

In 2009 a more demanding but more informative surveillance system was introduced into selected districts in Burkina Faso. The new system was case-based and required that clinical and laboratory information were connected such that information could be related back to the individual—a process that facilitates person-specific analysis rather than grouped information. With the support of WHO and CDC/Atlanta progress was made in 2010 to shift district- to case-based reporting. Financial support for the purchase of laboratory supplies came from MVP and a special grant from the Michael and Susan Dell Foundation.

5. Laboratory confirmation

Pneumococci and *Hemophilus influenzae* type b can cause meningitis that is clinically similar to that seen in meningococcal meningitis. Hence, laboratory confirmation of the etiologic agent is an essential component of meningitis surveillance. Except for a single classic population-based study in Niger the standard laboratory methods used in Africa such as latex agglutination or culture have neither accurately measured the disease burden nor given good meningococcal serogroup distribution data [10]. Latex agglutination is expensive, and the test is a subjective one, often being performed by untrained staff. Furthermore latex agglutination tests do not identify Group X meningococci. Although culture and identification of the infecting organism continues to serve as the "gold standard" for diagnosis the number of positive cultures in most African surveillance systems has remained low because of antibiotic administration prior to collection of spinal fluid, delayed specimen transport, and the lack of properly standardized media. These problems are notoriously difficult to correct, and attempts at improving diagnostic capabilities have been an important goal of improving surveillance activities in Burkina Faso.

Use of the polymerase chain reaction (PCR) can solve many of the above problems. Real-time PCR (rt-PCR) is a closed system using fluorescent dyes to detect amplification. The dyes make rt-PCR more sensitive than conventional PCR, and the use of 2 primers and a probe can provide increased specificity as well. Because rt-PCR is a closed system the technique largely eliminates the risk of amplicon DNA cross-contamination in the laboratory.

During 2010–2011 rt-PCR was introduced in Burkina Faso, Mali, and Niger to detect and characterize *N meningitidis, Hs influenzae,* and *pneumoniae* (*Nm*, *Hi*, and *Sp*). Using standardized methods four reference laboratories did rt-PCR assays on DNA from spinal fluid and other clinical specimens from clinically defined bacterial meningitis patients [11–14]. The assays detect *Nm*, *Hi*, and

Sp as well as determining *Nm* serogroups A, B, C, W135, X, and Y. Up until this introduction, only Niger has been able to obtain laboratory confirmation for clinically defined bacterial meningitis at rates better than 1–2%. However, in 2011 and for the 4 laboratories using rt-PCR the confirmation rates with group determination approached 35%, a rate similar to that seen in Europe and North America. Internal and external quality control of testing was done within the countries and at CDC/Atlanta. The introduction of rt-PCR provided a sound platform for the study of etiologic agents in case of suspected meningitis but equally important has ensured that vaccine-induced changes in meningococcal strains will be reliably identified.

6. The meningococcal carriage study

As previously noted, a principal goal of the Burkina Faso introduction of a new Men A conjugate vaccine is the development of herd immunity that will protect unvaccinated individuals by reducing the circulation of *NmA* in the population. Given the importance of this phenomenon a major effort was made to study meningococcal circulation in the general population before and after the introduction of MenAfriVac.

With support from Norwegian Institute of Public Health (NIPH) and CDC/Atlanta, baseline meningococcal carriage prevalence was assessed by the MoH in 2009, using a multicenter, repeated cross-sectional study design with four sampling campaigns performed within a 4-week period every three months, covering both the epidemic and the nonepidemic season [15]. During each carriage study, over 5000 oropharyngeal samples were collected from a representative selection of 1–29-year-old volunteers living in three health districts in Burkina Faso—the urban district of Bogodogo and the rural districts of Dandé in the west and Kaya in the east. A questionnaire about risk factors for meningococcal carriage was administered to each participant or parent when the subject was less than 18 years of age. Isolation and identification of the meningococci were performed by national laboratories in Burkina Faso; while confirmation and molecular characterization, including genogrouping, multilocus sequence typing, and *porA*/*fetA* sequencing, were performed at NIPH in Oslo.

Analysis of the baseline meningococcal carriage in 2009 from a total of 20,326 samples showed an overall carriage prevalence of 3.96% [15]. *NmA* was carried by 0.39% of the population, and all the strains ($N = 80$) were identical; *NmA*, ST-2859, P1.20,9/F3-1. Carriage prevalence of *NmY* was 2.28%, *NmX* 0.44%, and *NmW*135 0.34%. There were geographic and seasonal variations of carriage prevalence with a higher prevalence in the rural districts compared to the urban districts and higher prevalence in the dry season, but serogroup distribution also varied by district. Male participants were more likely to carry meningococci with a maximum prevalence (7.5%) in the 15–19-year-olds, while the peak prevalence for female participants was in 10–14-year-olds (4.4%).

The carriage study district of Kaya was chosen as a site for the September 2010 safety study that was previously mentioned, and all 1–29-year-olds were given a dose of MenAfriVac from 18 to 24 September. A carriage study had already been scheduled for October–November 2010 which created an interesting situation whereby the 1–29-year-olds from Kaya would be vaccinated in September 2010, and 3–6 weeks later the same group of 1–29-year-olds would undergo nasopharyngeal cultures as part of the carriage study. Therefore, the results from the Kaya carriage study in October–November were of great interest. The results were dramatically positive; there were no *NmA* isolated from over 1700 throat cultures whereas prior carriage studies in Kaya had shown an *NmA* carrier rate of about 1%. These preliminary results provided strong early evidence that comprehensive coverage with the Men A conjugate vaccine would likely generate herd immunity.

The carriage study required that operational procedures be standardized and the quality of all reagents ascertained. Hence, a detailed quality control system was implemented [16]. In addition, joint training, supervision, and wrap-up meetings after each round were conducted to ensure high quality. A high level of coordination between local communities and the MoH along with WHO, CDC/Atlanta, NIPH/Oslo, and MVP has characterized this effort.

7. The communication plan

Informing all citizens that all 1–29-year-olds are to be immunized is no easy matter. Nonetheless, the communication plan that was linked to the introduction of the Men A conjugate vaccine proved to be flawless largely because it rested on years of prior work. Beginning in 2007 there were regular communications and briefings about the development of the Men A conjugate vaccine. These occasions included formal and informal press briefings that were linked to the initiation of clinical studies or international meningitis meetings held in meningitis belt countries. This early communication work was aimed at informing health professionals, communicators, and the public that a new, more potent vaccine against an important cause of epidemic meningitis was in the offing but that the vaccine would not prevent all cases of meningitis. As clinical trials unfolded each study was preceded by a detailed "crisis communication training workshop," an exercise which was repeated at international scale prior to the December introduction of the vaccine in Burkina Faso, Mali, and Niger. These exercises were very useful not only in informing clinicians and public health officials about the new meningitis A conjugate vaccine but also in codifying a response should questions about the vaccine arise either during the clinical trials or during vaccine introduction.

Once the Men A conjugate vaccine was prequalified by WHO, communication activities and social mobilization began addressing the challenge of informing all Burkinabes that a national vaccination program was imminent in December 2010 and that if they were in the age group 1–29 years, they ought to receive the vaccine. Prior measles campaigns had targeted those under 15 years of age, but increasing the target population to 29 years was a new challenge. Nonetheless, a Burkina Faso communication plan that comprised national, regional, and village outlets was devised, including town criers and community volunteers ("relais communautaires)." Traditional and religious leaders were also put to work communicating about the new more potent vaccine, the upcoming campaign, and the need to get vaccinated. Beginning on December 1 radio and television spots were broadcast in the national languages announcing the campaign that was to start on December 6. Messages emphasized that comprehensive coverage with this new vaccine could put an end to the annual meningitis epidemics that have been problematic for so long in Burkina Faso.

The success of the vaccination plan was due in no small measure to the scope and effectiveness of the communication and social mobilization plan. Particularly important was a national press conference on December 14 that was headed by the Minister of Health who was accompanied by representatives from WHO and UNICEF. The Minister emphasized that the campaign was going well and that a successful campaign was key in the goal to eliminate epidemic meningitis in Burkina Faso.

8. Cold chain and waste management

In May 2009, a WHO-sponsored in-depth assessment of vaccine logistics in Burkina Faso was conducted by an expert consultant, and a plan was formulated to address the problems noted during

the consultation. The good news was the availability of 6 functioning positive cold store rooms at the central level in Ouagadougou as well as 1 negative cold store room. Each of the 13 regions had a cold store room, and each district had at least 3 refrigerators with 165 liters capacity (Sibir^{TM} V170 EG) and 2 high-capacity freezers for ice packs (Vestfrost MF304 or Electrolux TFW800). About 98% of the peripheral health facilities had refrigerators (Sibir^{TM}). Thus, only 1 cold store room (40 m^3) was needed at central level in order that all 12 million doses of *NmA* conjugate vaccine could be safely stored at the central level before being sent to the periphery.

The plan also made recommendations on the distribution of vaccination materials by volume and weight and in accordance to the storage capacity of each region, district, and health facility. A computerized tool for the evaluation of vaccine storage capacities was introduced at all levels that estimated the frequency at which regions, districts, and peripheral health facilities should be supplied in vaccines and materials.

An assessment of the waste disposal capabilities identified major gaps, and with help from the Dell Foundation 13 high-capacity incinerators were purchased and installed in each of the 13 regions of the country. Burkina Faso has two industrial incinerators, one in Ouagadougou and a second in Bobo Dioulasso. In order to destroy the campaign waste in the 30 days following the campaign it was anticipated that 40% of waste material would be burned in the newly acquired 13 incinerators and the remaining 60% in the industrial incinerators. To facilitate this work a transportation system was developed to bring safety boxes to the incinerators. Unfortunately, because of fiscal constraints the waste management plan could not be fully implemented (see below).

9. Design and funding of the Burkina campaign

In Burkina Faso a National Organization Committee was formed in July 2010 to manage the national campaign to introduce the new *NmA* conjugate vaccine. WHO's Intercountry Support Team (WHO/IST) played a major role in coordinating planning activities in Burkina Faso, Mali, and Niger through a biweekly teleconference that included representatives from the three introduction countries plus all partners that continued until vaccine introduction in early December. The teleconferences required country-specific summaries describing the status of planning and an enumeration of constraints. Discussions ensued and led to the identification of logistic issues that sometimes required consultant assistance. An important outcome was that the planning process, over time, resulted in a harmonization of protocols through open discussions that candidly discussed problems that often spanned all three countries.

Burkina Faso's national plan was based on a district microplanning model for national measles immunization campaigns that had been originally developed by WHO and modified by the Burkina Faso EPI staff. Regional and district staff were familiar with these documents, and the planning and training processes flowed along familiar lines. By October 2010, the Burkina Faso EPI had completed their initial assessment of 1–29-year-olds who resided in 13 regions and 63 health districts.

Specifics on the funding of the Burkina Faso vaccination campaign are given in Table 1. The total budget for the Burkina Faso campaign was US$13,633,078. Of this sum about US$2 million from the Michael and Susan Dell Foundation was used to improve the cold chain capacity, to purchase refrigerated vans, to install 13 regional incinerators, and to buy laboratory supplies. Despite support from GAVI, WHO, and UNICEF the National Organizational Committee found itself short about US$1.3 million on December 5, the day before the campaign was to be launched. Rather than delaying the introduction of the vaccine the National Committee implemented a "Plan B," a rather daring maneuver that allowed the vaccination campaign to begin on December 6. Plan B included the following steps: (1) a decrease in the *per diem* paid to volunteers from US$5.31 to US$4.25 per day; (2) a decrease in the communication funds as well as funds allotted to waste disposal (pick-up and supervised destruction) and evaluation; and (3) a doubling of the work for all vaccination teams (fixed posts to vaccinate 600 instead of 300 persons per day; 500 persons per day instead of 200 for the advanced strategy sites, and having 1 supervisor per 10 instead of 5 teams).

10. The campaign

A total of 5328 vaccinators and an equal number of volunteers began the vaccination campaign after a national inaugural in Ouagadougou on December 6 that was presided by His Excellency Blaise Compaore, President of Burkina Faso. In 10 days, the campaign was completed and the 10,000 plus vaccinators and volunteers had performed superbly despite the conditions imposed by Plan B. A total of 11,425,391 of Burkinabes between the ages of 1–29 years were vaccinated in a hugely successful campaign. Community participation was extremely high. Citizens enthusiastically accepted the vaccine and referred to it as "the good vaccine". Regional administrative coverage by age group is summarized in Table 2 and showed that coverage was extremely high in all regions and in all age groups. When the campaign was finished and the coverage data analyzed the MoH concluded that the Nm A conjugate vaccine campaign was the most successful vaccination campaign that had been done in Burkina Faso. While care was taken to ensure that vaccine recipients were in the 1–29 year target range it is likely that some persons

Table 1
Funding the Burkina Faso campaign.

Costs and donors	Amount (US$)	Activities
Campaign budget		
Vaccine, syringes, needles, safety boxes	10,295,059	
Operational costs	3,338,019	
Total cost	13,633,078	
Donor resources		
GAVI contribution through UNICEF Supply Division	4,089,442	Purchase of vaccine, needles, syringes, and safety boxes
Dell Foundation through WHO	2,558,208	Vaccine, needles, syringes, and safety boxes
Dell Foundation through WHO and PATH	3,908,676	Material (cold chain support, waste disposal, and vaccination cards); and operational costs
GAVI through UNICEF Program Division	865,179	Communication and operational costs
Burkina Faso national budget	703,898	Operational costs
West African Health Organization (WAHO)	106,382	Operational costs
Lions Club (Italy)	77,767	Operational costs
Total resources mobilized	12,309,556	
Financial gap on December 6, 2010	1,323,522	

Table 2
Vaccination coverage by age and region in Burkina Faso (includes data from Kaya safety study in September and the December 6–16 national campaign [14]).

Region	1–4 years		5–14 years		15–29 years		Total	
	Number vaccinated	% of target	Number vaccinated	% of target	Number vaccinated	% of target	Number vaccinated	% of target
Boucle Mouhoun	248,093	101.80	482,282	102.13	414,618	105.05	1,144,993	103.09
Cascades	97,367	110.10	193,862	108.00	160,597	99.54	451,826	105.26
Centre	241,878	96.63	527,874	95.03	774,222	105.29	1,543,974	100.18
Centre Est	185,179	91.36	371,439	97.25	295,858	96.79	852,476	95.75
Centre Nord	145,995	109.32	260,698	104.11	199,760	100.02	606,453	103.91
Centre ouest	204,308	99.93	422,483	107.38	379,166	115.46	1,005,957	108.60
Centre Sud	106,109	99.91	213,442	105.72	189,558	102.88	509,109	103.40
Est	229,831	100.87	408,512	96.68	328,339	100.18	966,682	98.83
Haut Bassin	242,332	89.40	482,491	105.94	442,596	101.48	1,167,419	100.41
Nord	210,194	101.21	419,458	107.23	342,444	111.78	972,096	107.39
Plateau central	124,947	119.28	241,760	109.81	201,182	95.67	567,889	106.11
Sahel	181,399	107.31	317,260	99.27	295,279	108.66	793,938	104.41
Sud Ouest	103,745	109.32	198,757	104.11	190,682	100.02	493,184	103.91
Total	2,321,377	100.17	4,540,318	102.17	4,214,301	104.53	11,075,996	102.62

over 29 years received vaccine, we view this as a reasonable explanation for coverage over one hundred percent.

The implementation of Plan B did create some problems. The waste disposal targets were not met. The decreased funding from Plan B resulted in insufficient funds to transport safety boxes to incinerator sites. Only 56% of safety boxes were incinerated during the 30 days following the campaign. In addition, a formal evaluation of coverage using vaccination cards as the gold standard has not yet taken place.

11. Discussion

Safely vaccinating 11 million persons in 10 days is no easy task under the best of conditions, and the total success of the *NmA* conjugate vaccine introduction bears witness to the ability of the Burkina Faso MoH to plan and conduct an effective national vaccination campaign. MenAfriVac was the "right" vaccine being given at the "right" time. Burkinabes were very knowledgeable about epidemic meningitis, and their enthusiastic acceptance of the Men A conjugate vaccine is an excellent example of what can be achieved when products are highly sought by the population. While the implementation of Plan B raised concerns at the last minute, the vaccinators and volunteers took up the challenge and succeeded. Two important problems flowed from the lack of resources: (1) waste disposal was compromised, and over 40% of the safety boxes had not been in incinerated during the month following the campaign; and (2) a formal coverage evaluation has not yet been conducted [17]. While individuals are convinced of the reality of the high-coverage data it would be reassuring to have independent data confirming the coverage results.

Only time will tell whether MenAfriVac will eliminate *NmA* meningitis epidemics thus achieving the principal goal of the MVP. While early surveillance data from the 2011 epidemic season (January–April) suggest that the vaccine has had a major impact, more data and more time are needed before a firm and unambiguous conclusion on impact can be made [18].

Important lessons from the Burkina Faso introduction include the following: (1) the key role played by WHO a natural planning locus and as a focus for partner coordination; (2) the need for regular teleconferences with specific agendas to monitor progress and to identify problems; (3) the importance of a communication plan that begins at least two years prior to vaccine introduction; (4) early planning (2–3 years) on improving case and laboratory surveillance activities; and lastly (5) the challenge of identifying funding partners.

Conflict of interest statement

No author has a conflict of interest.

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Serogroup A meningococcal conjugate vaccination in Burkina Faso: analysis of national surveillance data

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Summary

Background **An affordable, highly immunogenic *Neisseria meningitidis* serogroup A meningococcal conjugate vaccine (PsA–TT) was licensed for use in sub-Saharan Africa in 2009. In 2010, Burkina Faso became the first country to implement a national prevention campaign, vaccinating 11·4 million people aged 1–29 years. We analysed national surveillance data around PsA–TT introduction to investigate the early effect of the vaccine on meningitis incidence and epidemics.**

Methods **We examined national population-based meningitis surveillance data from Burkina Faso using two sources, one with cases and deaths aggregated at the district level from 1997 to 2011, and the other enhanced with results of cerebrospinal fluid examination and laboratory testing from 2007 to 2011. We compared mortality rates and incidence of suspected meningitis, probable meningococcal meningitis by age, and serogroup-specific meningococcal disease before and during the first year after PsA–TT implementation. We assessed the risk of meningitis disease and death between years.**

Findings **During the 14 year period before PsA–TT introduction, Burkina Faso had 148 603 cases of suspected meningitis with 17 965 deaths, and 174 district-level epidemics. After vaccine introduction, there was a 71% decline in risk of meningitis (hazard ratio 0·29, 95% CI 0·28–0·30, p<0·0001) and a 64% decline in risk of fatal meningitis (0·36, 0·33–0·40, p<0·0001). We identified a statistically significant decline in risk of probable meningococcal meningitis across the age group targeted for vaccination (62%, cumulative incidence ratio [CIR] 0·38, 95% CI 0·31–0·45, p<0·0001), and among children aged less than 1 year (54%, 0·46, 0·24–0·86, p=0·02) and people aged 30 years and older (55%, 0·45, 0·22–0·91, p=0·003) who were ineligible for vaccination. No cases of serogroup A meningococcal meningitis occurred among vaccinated individuals, and epidemics were eliminated. The incidence of laboratory-confirmed serogroup A *N meningitidis* dropped significantly to 0·01 per 100 000 individuals per year, representing a 99·8% reduction in the risk of meningococcal A meningitis (CIR 0·002, 95% CI 0·0004–0·02, p<0·0001).**

Interpretation **Early evidence suggests the conjugate vaccine has substantially reduced the rate of meningitis in people in the target age group, and in the general population because of high coverage and herd immunity. These data suggest that fully implementing the PsA–TT vaccine could end epidemic meningitis of serogroup A in sub-Saharan Africa.**

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Introduction

For at least 100 years, the meningitis belt of sub-Saharan Africa—stretching from Senegal to Ethiopia (figure 1) and home to 430 million people—has had high endemic rates of meningitis, annual seasonal outbreaks, and explosive epidemics occurring every 5–12 years.[1,2] About 90% of cases during epidemics are attributable to *Neisseria meningitidis* serogroup A.[3] Burkina Faso, a landlocked west African country with a population of roughly 16 million, is one of the few countries entirely located within the meningitis belt and has hyperendemic rates of meningitis.[3,4] Annually, the government of Burkina Faso spends about 2% of its health budget on responding to epidemic meningitis.[5] During the 2007 epidemic, households with an affected family member incurred an average cost equivalent to a third of their household income.[6]

In late 2009, a novel meningococcal serogroup A polysaccharide–tetanus toxoid conjugate vaccine (PsA–TT, MenAfriVac) was licensed and subsequently prequalified by WHO—a requirement for purchase by UN agencies—based on results of clinical trials assessing safety and immunogenicity, but without efficacy trials.[7–9] After pilot implementation in the health district of Kaya in September, 2010, PsA–TT was introduced in the remaining 62 health districts through a national mass vaccination campaign in Burkina Faso. More than 11 million people were vaccinated in about 10 days in December, 2010, resulting in 11 466 950 vaccinees in the target population of people aged 1–29 years.[10] The vaccine and the aggressive strategy of rolling national vaccination campaigns in up to 26 at-risk countries within or bordering the meningitis belt (figure 1) over the next 5 years form an example of a new approach to control

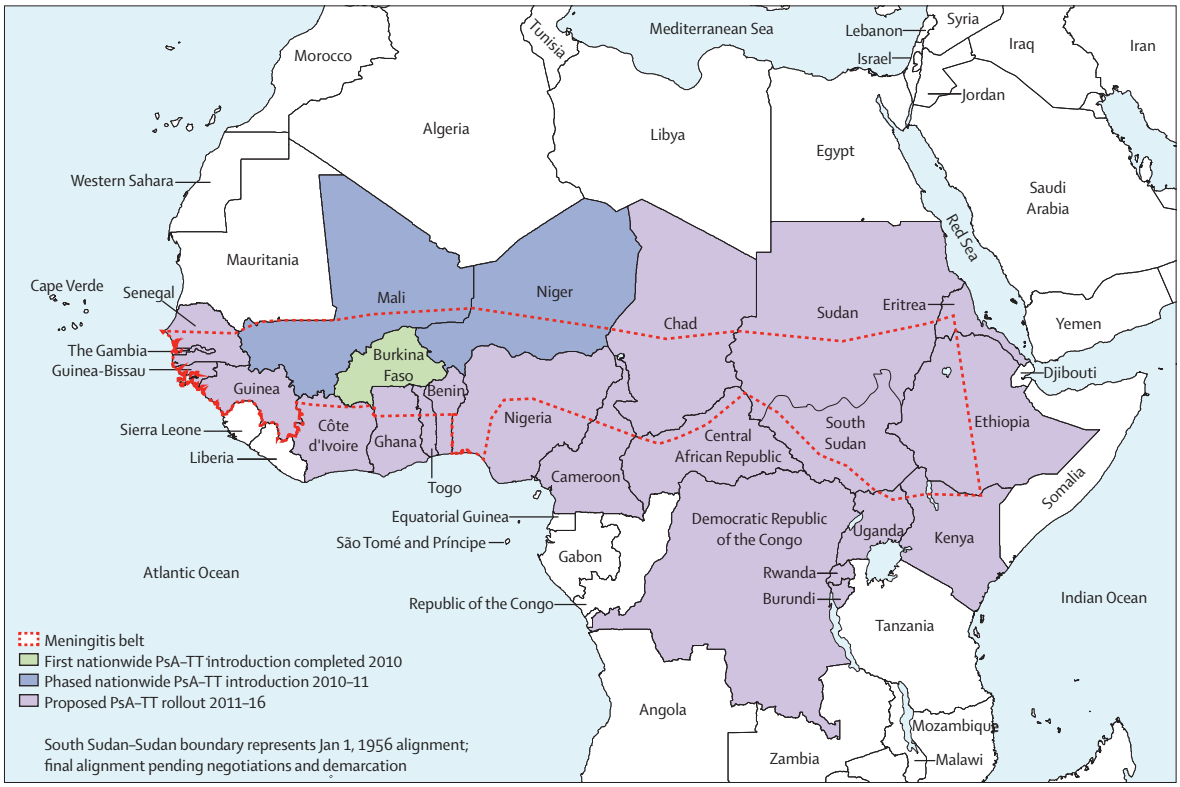

Figure 1: **The meningitis belt of Africa and meningococcal serogroup A conjugate vaccine (PsA–TT) rollout plan 2010–16**

epidemic-prone, orphan diseases.[11] Successful demonstration of the early effect of vaccination will validate this strategy and inform implementation plans for subsequent country campaigns. Toward this goal, we analysed national surveillance data around PsA–TT introduction and report the early effect of the vaccine on meningitis incidence and epidemics in Burkina Faso.

Methods

Data collection

In Burkina Faso, two complementary systems of population-based meningitis surveillance exist. Surveillance for reportable diseases is done by the *Télégramme Lettre Official Hebdomadaire* (TLOH), to which district-level aggregate reports of clinically defined meningitis cases and meningitis-related deaths are transmitted weekly. Functional since 1997, this system contains no identifying information or laboratory data, and only scarce demographic information. A second system—enhanced surveillance for *Maladies Potentiel Épidémie* (MPE)—was implemented in 2003, in response to the first large meningitis outbreak caused by serogroup W135.[12,13] This system collects enhanced case-level demographic information and results of cerebrospinal fluid examination and laboratory testing for a proportion of TLOH cases, using integrated disease surveillance and response instruments. The standard operating procedures for MPE surveillance have been modified over time, but were consistent between 2007 and 2010. In 2009, substantial efforts were made to improve specimen collection and transport to a national reference laboratory, pathogen confirmation, links between laboratory and demographic information, and case-based data management and quality (eg, completeness and timeliness)—these efforts to strengthen MPE surveillance were concentrated in ten districts. After the 2010 meningitis season and before the national PsA–TT vaccination campaign, revised case-based MPE surveillance standard operating procedures were implemented nationwide.

Cases were classified according to WHO case definitions.[14] Suspected cases of meningitis are defined as sudden onset of fever with a stiff neck or, in infants, a bulging fontanelle. Probable bacterial meningitis is a suspected case with turbid cerebrospinal fluid. A probable case of meningococcal meningitis is a suspected case with either a petechial or purpuric rash, Gram-negative diplococci on cerebrospinal fluid Gram stain, or in the setting of a continuing meningococcal meningitis epidemic. A confirmed case of meningitis is a suspected or probable case with *Neisseria meningitidis, Haemophilus influenzae* type b, or *Streptococcus pneumoniae* antigen detected in cerebrospinal fluid or isolated in culture from blood or cerebrospinal fluid. Beginning in 2010, real-time PCR capacity was implemented at the national reference laboratory level, and detection of *N meningitidis,*

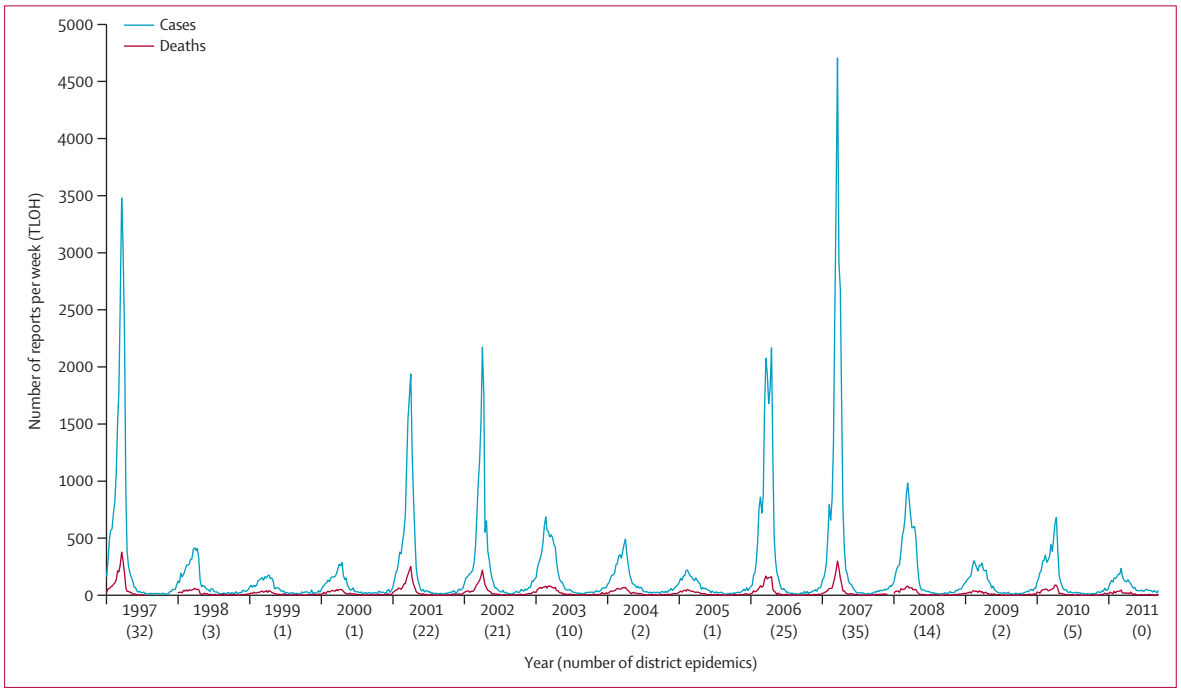

Figure 2: **Suspected cases of meningitis and deaths reported by the *Télégramme Lettre Official Hebdomadaire* surveillance system, by week, and number of health districts experiencing epidemics by year in Burkina Faso, 1997–2011**

H influenzae type b, or *S pneumoniae* genetic material by PCR was deemed confirmatory.[15,16] Serogroup determination was made either by antigen detection or PCR, with PCR deemed definitive.

This assessment was deemed to be a public health programme evaluation and was therefore exempted from ethical review by the US Centers for Disease Control and Prevention and Burkina Faso Ministry of Health.

Statistical analyses

To assess the effect of PsA–TT on epidemic meningitis, we compared national and district level incidence of meningitis, overall meningitis mortality rate, and occurrence of epidemics before and during the first year after PsA–TT implementation. Suspected cases and deaths reported through TLOH from 1997 to 2010 comprised the before PsA–TT period, and 2011 the after PsA–TT period. The analysis of these TLOH data was restricted to epidemiological weeks 1–24 (meningitis season) to represent the period of highest predictive value for serogoup A meningococcal infection in the absence of causal information in the dataset. Annual and weekly cumulative incidence rates were calculated with national and district population estimates from the *Institut National de la Statistique et de la Démographie* (INSD) census.[17] To account for redefinition of districts done during the assessment period, some health districts were combined, resulting in a total of 55 districts. District-level epidemics were defined by an annual incidence rate exceeding 100 per 100 000 population.[18–20] We defined an epidemic year as a year in which the national incidence rate exceeded 100 per 100 000 population; other years were defined as endemic years. We used a piecewise exponential model for grouped survival data to assess for significant differences in the risk of disease and death during the meningitis season between years. Hazard ratios (HR) were calculated comparing all years combined, epidemic years only, endemic years only, or each individual year compared with 2011.

To assess the age-specific and pathogen-specific effect of vaccination, we analysed MPE data for each year from 2007 to 2010 compared with 2011, excluding cases among known non-residents. PsA–TT was implemented in one district during epidemiological week 38, thus the analysis of MPE data was restricted to weeks 1–37. We calculated the population-weighted cumulative incidence of probable meningococcal meningitis by age group, using the age distribution from the 2006 INSD census applied to each year's estimated total population. These yearly age-specific incidence rates were compared by a log-Poisson regression model. We compared age-specific cumulative incidence rate ratios for each year compared with 2011. We used log-binomial regression to assess for differences in the proportion of bacterial meningitis cases attributed to *N meningitidis* serogroup A between years. To account for possible bias resulting from changes identified in *S pneumoniae* incidence over time, analyses were repeated excluding confirmed

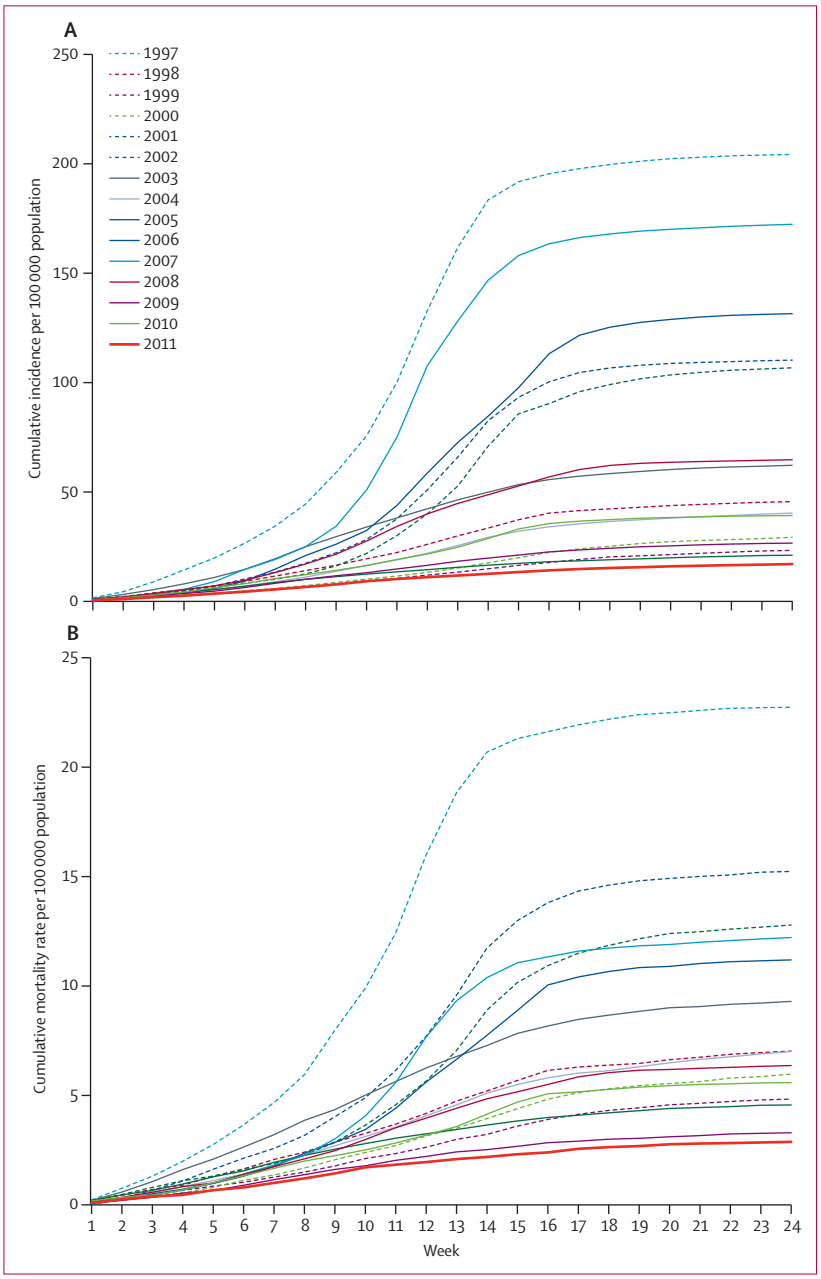

Figure 3: **Cumulative curves of rates per 100 000 population of suspect meningitis cases (A) and deaths (B) reported through *Télégramme Lettre Official Hebdomadaire* by week during the meningitis season in Burkina Faso, 1997–2011**

S pneumoniae cases from the yearly proportion denominators. We compared pathogen-specific cumulative incidence of confirmed meningitis disease by year using the same log-Poisson regression method described above, assuming that the distribution of laboratory results for meningitis cases with specimens collected but not sent for confirmatory tests was the same as the distribution for cases with laboratory test results available. We used SAS version 9.2 for analyses.

Role of the funding source

We had no external funding sources—the investigators were responsible for study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Jan 1, 1997, to Dec 31, 2010, 148 603 cases of suspected meningitis were reported through TLOH in Burkina Faso, with 17 965 deaths, corresponding to an annual median of 7757 cases (IQR 5082–13 886) and incidence of 61·0 per 100 000 population (IQR 37·8–117·3, figure 2). Overall, 92% (136 831 of 148 603) of cases occurred during the meningitis season (weeks 1–24). During this 14 year period, 174 district-level epidemics occurred; at least one district had an epidemic during each year (range 1–35). 5 epidemic years—1997, 2001, 2002, 2006, and 2007—accounted for 78% (135 of 174) of district-level epidemics, and 54 of 55 districts had at least one epidemic year during those 5 years. The median epidemic-year incidence was 131·5 per 100 000 individuals (IQR 117·3–179·1), and a median of 25 district epidemics (22–32) were recorded during these 5 years. By contrast, in the 9 endemic years the median incidence was 43·5 per 100 000 individuals (IQR 31·6–52·6), and a median of two districts had epidemics (IQR one to five).

In 2011, after the national PsA–TT campaign, 3875 suspected meningitis cases and 588 deaths were reported—the corresponding cumulative incidence of 24·1 per 100 000 individuals represented a decline of 60% from the median incidence 1997–2010. 71% (2748 of 3875) of cases occurred during the meningitis season, and no districts had epidemics in 2011—this finding was a break from the periodicity recorded in the previous 14 years. Comparing 2011 district-level meningitis season incidence to each of the 14 before PsA–TT years, incidence decreased in all health districts by a median of 79% (IQR 71–86% decrease).

With all 14 before PsA–TT years as a baseline (figure 3), risk of meningitis decreased by 71% (HR 0·29, 95% CI 0·28–0·30, p<0·0001) and risk of death decreased by 64% (0·36, 0·33–0·40, p<0·0001) after PsA–TT implementation. Significant declines in risk (p<0·0001 for all comparisons except p=0·04 for deaths in 2009) were identified when the analysis was repeated comparing 2011 to grouped epidemic years (88% disease, 80% deaths), grouped endemic years (54% disease, 51% deaths), and each year individually for both meningitis disease (range 21% [2005] to 92% [1997]) and deaths (range 13% [2009] to 87% [1997]).

From 2007 to 2011, 25 220 cases of suspected meningitis were reported through the MPE enhanced meningitis surveillance, compared with 51 700 meningitis cases through TLOH. During this time, the sensitivity of

	Cumulative incidence (n)					Baseline year*	2011 compared to baseline year		
	2007	2008	2009	2010	2011		CIR (95% CI)	p value	Relative risk reduction†
Age (years)									
<1	26·9 (167)	14·4 (92)	6·3 (42)	4·4 (30)	2·0 (14)	2010	0·46 (0·24–0·86)	0·02	54%
1–4	30·6 (652)	14·2 (312)	3·6 (83)	6·0 (140)	1·5 (37)	2009	0·43 (0·29–0·63)	<0·0001	57%
5–14	32·6 (1339)	15·3 (649)	5·5 (243)	10·9 (492)	2·0 (92)	2009	0·36 (0·29–0·46)	<0·0001	64%
15–29	11·6 (417)	5·3 (195)	1·9 (72)	1·8 (71)	0·7 (28)	2010	0·39 (0·25–0·6)	<0·0001	61%
≥30	4·8 (185)	3·3 (132)	0·7 (30)	0·6 (24)	0·3 (11)	2010	0·45 (0·22–0·91)	0·003	55%
Total (1–29)	24·4 (2408)	11·4 (1156)	3·8 (398)	6·5 (703)	1·4 (157)	2009	0·38 (0·31–0·45)	<0·0001	62%
Total (<1, ≥30)	7·8 (352)	4·8 (224)	1·5 (72)	1·1 (54)	0·5 (25)	2010	0·45 (0·28–0·73)	0·001	55%

CIR=cumulative incidence ratio. *The year with the lowest incidence before implementation was used as the baseline year for comparison to 2011. †Relative risk reduction indicates a decrease in risk of meningitis in the affected population relative to the baseline after vaccine introduction calculated as (1–CIR)×100.

Table: **Cumulative incidence per 100 000 population of probable meningococcal meningitis by age category reported through *Maladies Potentiel Épidémie* surveillance during weeks 1–37 in Burkina Faso, 2007–11**

MPE surveillance to detect suspected meningitis cases—with TLOH for comparison—improved from 41% (10 614 of 25 695) to 88% (3412 of 3875), the proportion of MPE-reported suspect cases with a cerebrospinal fluid specimen that was transported to a reference laboratory for confirmatory testing increased from 29% (2898 of 9824) to 99% (3399 of 3412), and the proportion of case-patient specimens with a bacterial meningitis pathogen identified increased from 7% (685 of 9824) to 35% (1157 of 3318).

When comparing 2011 to the lowest incidence year before PsA–TT (either 2009 or 2010), a 62% decline in risk of probable meningococcal meningitis was identified across the age group targeted for vaccination (cumulative incidence ratio [CIR] 0·38, 95% CI 0·31–0·45, p<0·0001; table). A statistically significant decline (p<0·0001) was also recorded for the comparison of 2011 to each age group individually, with the largest decline among people aged 5–14 years. Among age groups not eligible for vaccine, a 55% decline in risk of bacterial meningitis was indentified among people aged 30 years and older (p=0·003, table), and a 54% decline in risk among children aged younger than 1 year (p=0·02, table).

The overall proportion of confirmed cases of meningococcal meningitis during the before PsA–TT period was 68% (1020 of 1505), of which 86% (875 of 1020) were caused by serogroup A *N meningitidis* (figure 4). Among all identified pathogens, the proportion of serogroup A was higher during 2007–08 (80%, 771 of 965) than the subsequent endemic years (19%, 104 of 540, p<0·0001). In 2011, with cerebrospinal fluid obtained for laboratory confirmation from 99% of all patients with suspected meningitis, only one case of serogroup A meningococcal meningitis was confirmed among residents of Burkina Faso—who had not received PsA–TT—representing a decrease in serogroup A to less than 0·1% (one of 1157) of confirmed meningitis cases. This proportion was significantly (p<0·0001) lower than for each individual year from 2007 to 2010, whether *S pneumoniae* cases were included (relative risk range 0·005, 95% CI 0·0007–0·03 [2010] to 0·002, 0·0003–0·01 [2007]) or omitted (data not shown) from the proportion denominators.

In 2011, one confirmed case of serogroup A meningococcal disease was identified in Burkina Faso, resulting in an incidence of 0·01 cases per 100 000 individuals (figure 5). This finding represents a 99·8% decline in risk compared with 2010 (CIR 0·002, 95% CI 0·0004–0·02, p<0·0001). Among other meningococcal

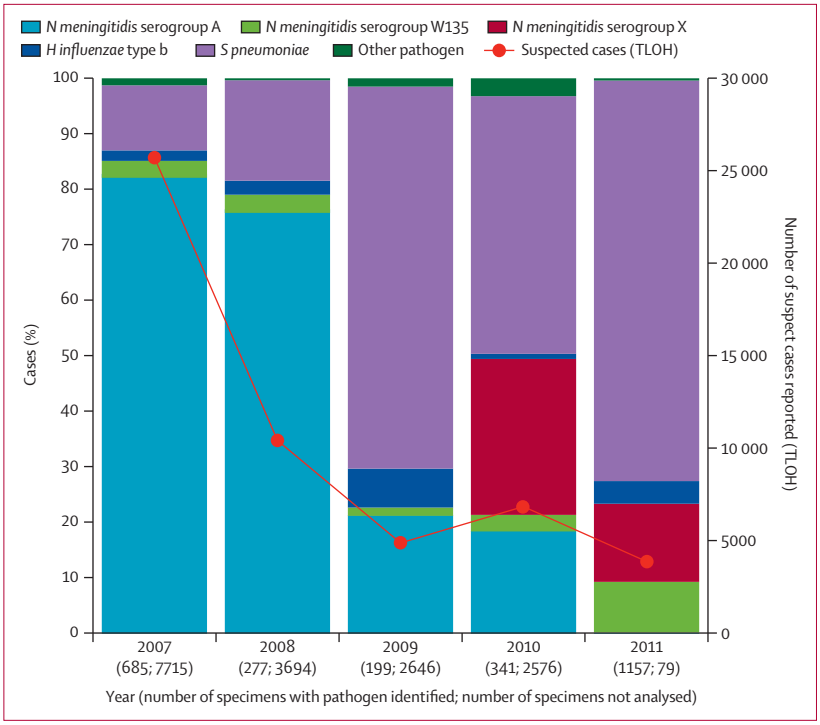

Figure 4: **Proportions of confirmed meningitis cases by year attributable to *Neisseria meningitidis*, *Haemophilus influenzae* type b, and *Streptococcus pneumoniae* from *Maladies Potentiel Épidémie* surveillance compared with suspected cases reported by TLOH in Burkina Faso, 2007–11**
TLOH=*Télégramme Lettre Official Hebdomadaire.*

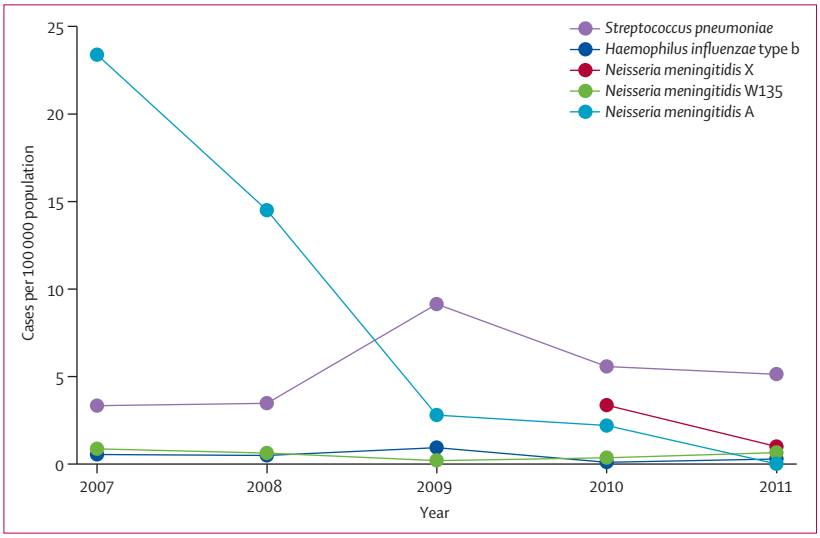

Figure 5: **Estimated annual incidence of confirmed meningitis by pathogen and year from *Maladies Potentiel Épidémie* surveillance in Burkina Faso, 2007–11**

serogroups, the incidence of serogroup W135 was fairly constant over time from 2007. Although serogroup X incidence declined in 2011, the number of districts with confirmed serogroup X cases increased from 6% (four of 63 districts, two epidemics) in 2010, to 67% (42 of 63 districts, no epidemics). By contrast, the mean incidence of pneumococcal meningitis increased from 3·4 (2007–08) to 6·6 per 100 000 (2009–11), and a slight seasonality was identified with a peak in February and March (data not shown).

Discussion

Observational data after the first national meningococcal A conjugate vaccination campaign provide evidence that serogroup A meningococcal conjugate vaccine has substantially reduced the burden of meningitis in Burkina Faso. Significant reductions were achieved both nationally and at the district level in the occurrence of meningitis epidemics and cases of suspected and probable meningococcal meningitis. The unprecedented low incidence of serogroup A disease in view of exceptional laboratory confirmation provides strong evidence for a great short-term vaccine effect.

Trials done before licensure showed that PsA–TT vaccination results in high titres of antibodies in both adults and children, which would be expected to lead to a high degree of direct individual protection.[8,9,21] Results from a coverage survey completed in December, 2011, showed national coverage of 95% among the target population of the 2010 PsA–TT campaign. Therefore, the 5 million individuals either too young or too old to be vaccinated were likely to indirectly benefit from high population immunity. The complete absence of confirmed serogroup A meningococcal disease among vaccine recipients is attributable in large measure to the immunogenicity of the vaccine. However, one serogroup A case was confirmed in an unvaccinated resident of Burkina Faso and three additional cases were confirmed in Burkina Faso among unvaccinated non-residents, showing that serogroup A has not completely been eradicated.

Epidemic waves are postulated to occur when epidemic cofactors increase and novel strains are introduced into an immunologically naive population.[22,23] The experience with *H influenzae* type b and meningococcal serogroup C clearly shows the substantial effect conjugate vaccines can have on nasopharyngeal carriage of bacteria, a necessary precursor to invasive disease.[24–28] Our finding of a significant reduction in risk of probable meningococcal meningitis not only in the vaccinated age group, but also in the population broadly suggests a herd effect resulting from reduction in carriage and interruption of transmission. Studies are underway in Burkina Faso to assess herd immunity, but this broad risk reduction is consistent with evidence of a substantial reduction in serogroup A carriage prevalence after the vaccination campaign (DA Caugant, Norwegian Institute of Public Health, a WHO Collaborating Centre for Reference and Research on Meningococci, personal communication).[29] The continued near elimination of the hyperendemic ST-11 serogroup C clone in the UK after its serogroup C vaccination programme might be largely attributable to a sustained herd effect despite waning titres of protective antibody among individual vaccinees.[30,31] Molecular subtyping of carriage and invasive isolates from Burkina Faso identified a high degree of homogeneity among serogroup A isolates in the past 5 years.[10] The potential for sustained reductions in carriage (or even elimination) of hyperendemic serogroup A meningococci is unclear.

2011 showed a break from the cyclic meningitis epidemic patterns recorded between 1997 and 2010. Improved surveillance nationally after the 2007 serogroup A epidemic has led to recognition that *S pneumoniae* was the most common cause of bacterial meningitis in recent endemic years—the proportion of *S pneumoniae* increased from less than 20% in 2007–08 to greater than 50% during 2009–11. This finding might be an actual increase in disease burden, potentially from the introduction of a more virulent serotype.[32,33] We compared these data to regional data from the endemic period before 2007, and identified similarities in both the relative rates of pneumococcal to meningococcal meningitis and the slight seasonality of pneumococcal meningitis.[34,35] Thus, the difference in incidence could equally be confounded by improved surveillance, with the most recent data showing the true endemic rate. Although we did not report pneumococcal serotype, data from one Burkina Faso region suggested that the seven-valent pneumococcal conjugate vaccine would only cover less than a third of serotypes identified in

children aged younger than 5 years, but ten-valent and 13-valent vaccines that are now becoming available could improve serotype coverage to 67%.[35] In-country capacity for molecular serotype determination is being established in Burkina Faso to assist the country in planning and assessment of the pneumococcal vaccine programme.

These data provide compelling first evidence of a substantial effect of serogroup A meningococcal conjugate vaccine when applied in a public health programme (panel). Although this is an observational study assessing only the first year of follow-up after implementation, a decrease in suspect cases and probable meningococcal meningitis in 2011 was identified even when compared with the lowest endemic years, suggesting an effect of vaccination as opposed to only secular variation in incidence. Strengthened surveillance provided early evidence of effective prevention of serogroup A disease and elimination of epidemics in the short term—continued investment to sustain high-quality surveillance in Burkina Faso is necessary to monitor vaccine effect and modification of secular epidemic trends over time. Although serogroup X has not been documented to cause epidemics similar in scale to serogroups A or W135, improved surveillance has detected the emergence and geographic expansion of serogroup X from four districts in 2010, to 42 in 2011.[36,37] Serogroup replacement has not been identified in countries that have used monovalent serogroup C conjugate vaccine. However, the recent localised epidemics of serogroups X and W135, and historically C are a cautionary reminder that maintenance of high-quality laboratory confirmation is crucial beyond the assessment of the immediate effect of the PsA–TT mass vaccination programme.[27] Other important assessments that should come from the first national implementation of PsA–TT include measures of vaccine effectiveness and causes of vaccine failures.[38,39]

Burkina Faso achieved high vaccine coverage in a period of only 10 days in December, 2010, as a result of experience in doing mass vaccination campaigns for meningitis epidemic response and other vaccine preventable diseases, and years of concerted effort to advocate with policy makers, sensitise the population, and organise the logistics necessary to fully implement the first national PsA–TT campaign. Surveillance systems in Burkina Faso can be viewed as an example of the high quality that can be achieved in developing countries through concerted collaboration. Although this effort is not warranted in all countries that implement the vaccine, other at-risk countries of the meningitis belt present logistical challenges to achieving full implementation of vaccination campaigns, and some degree of infrastructure strengthening of surveillance health systems is essential to show the effectiveness of the vaccine and effect of vaccination under variable conditions. Longitudinal surveillance should be sustained in some countries to measure long-term effect and assess the need for booster vaccination or other maintenance strategies. Without adequate surveillance infrastructure, system weaknesses could be interpreted as vaccine failure and threaten the implementation strategy.

Epidemic meningitis has been a devastating problem in Africa for the past century. The true goal must be to sustain its elimination. Future challenges such as accumulation of susceptible cohorts due to waning immunity, introduction across porous national borders of novel serogroup A strains, and the potential for other serogroups to emerge all argue for sustained investment in surveillance and response capacity. PsA–TT is not licensed for use in infants, and appropriate strategies for maintenance of epidemic elimination should be planned.[11,40] Affordable multivalent conjugate vaccines are needed, because other serogroups are proven causes of meningitis outbreaks. Despite these future challenges, this early success in Burkina Faso should strengthen momentum toward achieving the goal of ending epidemic meningitis as a public health concern in sub-Saharan Africa.

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms "MenAfriVac" OR "PsA–TT" OR "meningococcal A conjugate vaccine" OR "group A meningococcal conjugate vaccine" AND "epidemic meningitis" OR "epidemic meningococcal meningitis" AND "Africa" for reports from December, 2009, onward, since the first monovalent conjugate meningococcal serogroup A meningitis vaccine was licensed in 2009. The date of the search was May 15, 2012. We identified 32 articles but no population-based reports of the effect of vaccination on meningitis epidemics.

Interpretation

Our study is the first to report the effects of a national meningococcal serogroup A conjugate vaccination programme on epidemic meningitis at a population level. We have shown a substantial decrease in all-cause meningitis, meningitis epidemics, and serogroup A meningococcal disease in Burkina Faso after the implementation of the mass vaccination programme. Continued progress toward elimination of serogroup A meningococcal meningitis epidemics in sub-Saharan Africa will require high vaccination coverage in at-risk countries, adequate surveillance to monitor vaccine effect and the potential re-emergence of disease, and implementation of a vaccination programme to maintain epidemic elimination.

Contributors

RTN developed methods, led the analysis and interpretation of data, and drafted the paper. SWM contributed to the statistical analysis, and assisted with the review of available studies. JLK, FVKD, TFT, and SRT contributed to developing methods, study implementation, data collection, data interpretation, and critical revision of the paper for important intellectual content. RO-T, LS, CL, CH, LWM, FA, and MHD were involved in study implementation and data collection, primary data collection, and technical support. FML contributed to data interpretation and report revisions. NEM and TAC provided conceptual and technical guidance and contributed to critical revision of the paper for important intellectual content.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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MAJOR ARTICLE

Impact of the Serogroup A Meningococcal Conjugate Vaccine, MenAfriVac, on Carriage and Herd Immunity

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(See the Editorial Commentary by Maiden on pages 364–6.)

Background. The conjugate vaccine against serogroup A *Neisseria meningitidis* (NmA), MenAfriVac, was first introduced in mass vaccination campaigns of 1–29-year-olds in Burkina Faso in 2010. It is not known whether MenAfriVac has an impact on NmA carriage.

Methods. We conducted a repeated cross-sectional meningococcal carriage study in a representative portion of the 1–29-year-old population in 3 districts in Burkina Faso before and up to 13 months after vaccination. One district was vaccinated in September 2010, and the other 2 were vaccinated in December 2010. We analyzed 25 521 oropharyngeal samples, of which 22 093 were obtained after vaccination.

Results. In October–November 2010, NmA carriage prevalence in the unvaccinated districts was comparable to the baseline established in 2009, but absent in the vaccinated district. Serogroup X *N. meningitidis* (NmX) dominated in both vaccinated and unvaccinated districts. With 4 additional sampling campaigns performed throughout 2011 in the 3 districts, overall postvaccination meningococcal carriage prevalence was 6.95%, with NmX dominating but declining for each campaign (from 8.66% to 1.97%). Compared with a baseline NmA carriage prevalence of 0.39%, no NmA was identified after vaccination. Overall vaccination coverage in the population sampled was 89.7%, declining over time in 1-year-olds (from 87.1% to 26.5%), as unvaccinated infants reached 1 year of age. NmA carriage was eliminated in both the vaccinated and unvaccinated population from 3 weeks up to 13 months after mass vaccination ($P = .003$).

Conclusions. The disappearance of NmA carriage among both vaccinated and unvaccinated populations is consistent with a vaccine-induced herd immunity effect.

Keywords. *Neisseria meningitidis*; meningitis belt; conjugate vaccine; carriage; herd immunity.

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Meningococcal disease is a major public health challenge in countries of sub-Saharan Africa lying in the meningitis belt [1, 2]. The causative agent, *Neisseria meningitidis* normally lives in a commensal relationship with humans, colonizing the nasopharynx [1, 3, 4], and is transmitted between healthy persons by close contact. Only exceptionally it enters the bloodstream and causes meningitis and/or septicemia. In the meningitis belt,

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N. meningitidis of serogroups A (NmA), W135 (NmW135), and X (NmX) have caused outbreaks [5–7], but NmA has been responsible for all but one of the major epidemics.

In spite of extensive use of polysaccharide vaccines, epidemics are still occurring [8]. Conjugate vaccines, developed by coupling a carrier protein to the polysaccharide antigen, elicit strong and long-lasting immune responses, including children <2 years old [3, 9] and may confer herd immunity by interrupting transmission of the pathogens [10–14]. Meningococcal conjugate vaccines against serogroups A, C, Y, and W135 are marketed in industrialized countries [3], but for most African countries, they are not affordable [15].

MenAfriVac, a safe, immunogenic and affordable conjugate vaccine [16] was developed especially to eliminate NmA epidemics in the meningitis belt and was first introduced in Burkina Faso, Mali, and Niger in 2010 [15, 17, 18]. Mass vaccination of 10.8 million 1–29-year-olds was done in Burkina Faso from 5 to 15 December 2010. When vaccination coverage is not complete, however, the ability to achieve herd immunity in addition to protecting vaccinated individuals will be an essential benefit of the vaccine. Although many conjugate vaccines have been shown to interrupt carriage of the pathogen, this remained to be demonstrated for a NmA conjugate vaccine.

To evaluate the potential for herd immunity after MenAfriVac vaccination, we studied its impact on NmA carriage in a multicenter repeated cross-sectional carriage study in Burkina Faso. Baseline NmA carriage was estimated to 0.39% in Burkina Faso in 2009 [19]. The impact of MenAfriVac on NmA carriage up to 13 months after vaccination and evidence of a herd immunity effect is presented here.

METHODS

Ethics

The study obtained ethical clearance from the Norwegian Regional Committee for Medical Research Ethics, Southern Norway, the Ethical Committee for Health Research in Burkina Faso, and the Institutional Review Board at Centers for Disease Control and Prevention, Atlanta, Georgia.

Study Design and Oversight

The study was conducted as a multicenter repeated cross-sectional survey in 3 health districts in Burkina Faso; the urban district of Bogodogo, counting roughly 616 000 inhabitants and in 2 rural districts, Dandé (215 000 inhabitants) and Kaya (500 000 inhabitants), as described elsewhere [19]. Multiple sampling campaigns were conducted simultaneously in all 3 districts, and for each campaign a representative portion of the 1–29-year-olds was included within a 4-week period. We used a multistage cluster design and performed a new random selection of households for each sampling campaign. All healthy 1–29-year-olds residing the selected households were invited to participate in a survey and to provide a swab specimen, independently of vaccination status and participation in previous campaigns. Informed consent was obtained from each participant or guardian if the subject was <18 years old. Household leaders and participants answered a structured questionnaire that included information on risk factors for carriage and MenAfriVac vaccination. All data were entered on personal digital assistants.

Prevaccination carriage prevalence was determined in 4 sampling campaigns (S1–S4) performed every 3 months in 2009 [19]. As part of a phased vaccine introduction, a safety study of MenAfriVac was conducted in Kaya, one of the study sites, from 18 to 24 September 2010 when all 1–29-year-olds were immunized. Three weeks later, carriage study S5 started in all 3 districts and was conducted in October–November 2010; S5 documented the carriage prevalence in nonvaccinated districts immediately before vaccination and also represented the first postvaccination campaign in Kaya.

The 1–29-year-olds in the rest of Burkina Faso were vaccinated with MenAfriVac in the period of 5–15 December 2010 [17]. Four postvaccination carriage campaigns were then done in the 3 study sites every 3 months through 2011 in the same way as before vaccine introduction. Campaigns S6, S7, S8, and S9 were conducted in February–March, May, August, and October–November 2011, respectively.

Sample Collection and Analysis

Oropharyngeal samples were obtained from each participant and analyzed at the Centre Hospitalier Universitaire Pédiatrique Charles de Gaulle for the district of Bogodogo, at the Centre Hospitalier Régional de Kaya for the district of Kaya, and at the Centre Hospitalier Universitaire Souro Sanou for the district of Dandé, as described elsewhere [19]. The Norwegian Institute of Public Health (NIPH), Oslo, Norway, received all presumptive meningococcal isolates for confirmatory analyses. The serogroup of confirmed *N. meningitidis* was determined by slide agglutination using A, B, C, X, Y, Z, W135, and 29E antiserum (Remel). For nonserogroupable isolates, the serogroup obtained by capsule gene polymerase chain reaction [20] was used as the final result. The quality of the laboratory analysis in Burkina Faso was monitored through a laboratory quality control (QC) system, as described elsewhere [21]. In addition to internal QC of reagents, media, and incubation conditions, a subset of presumptive *N. meningitidis*–negative samples were retrieved from 2 of the analytical steps and controlled at the NIPH as part of the external QC [21].

Data Management and Statistical Analyses

Field and laboratory data were combined. Samples with missing or duplicate links between the person and the

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laboratory identification or between the person and the household were excluded. Data management was done with R v.2.14.1 and statistical analysis with Stata v.11.1. Bivariable comparisons were performed using Rao-Scott corrected χ^2 tests, and odds ratios were calculated by logistic regression, using survey methods accounting for the cluster sampling design. Statistical significance was defined as P values <.05 and as 95% confidence intervals not including null.

RESULTS

Study Population

During the sampling campaigns S5–S9, a total of 28 625 persons were asked to participate, and 27 012 (94.4%) accepted (Table 1). Of these, 25 940 (96.0%) reached the swabbing station where an oropharyngeal swab specimen was obtained from 25 726 (99.2%). A total of 205 (0.8%) samples were excluded due to lack of traceability. Among the 205 excluded participants 14 (6.8%) were carriers, but none were carriers of NmA (13 NmX and 1 NmY). Of the 25 521 participants with data correctly registered in all databases (range, 5071–5169 per campaign), 22 093 were enrolled after vaccine introduction and therefore included when comparing pre- [19] and postvaccination carriage prevalence. The remaining 3428 samples were taken from the districts of Bogodogo and Dandé in S5, just before vaccine introduction. With 20 326 samples obtained in the baseline study [19], the total sampling size of the carriage study reaches 45 847.

In the postvaccination sampling campaigns, 43.4% of the participants were male, and 51.9% were <10 years old. The overall vaccine coverage estimated from the participant's responses was 89.7% for the first assessments possible after mass vaccination (S6), but coverage varied by districts (93.6%, 83.8%, and 91.8% for Bogodogo, Dandé, and Kaya, respectively). Vaccine coverage was age dependent in a consistent way; coverage was lowest in the 16–29-year age group at about 85% but remaining stable over time, and coverage of 1-year-olds declined over time from 87.1% in S5 to 26.5% in S9, as unvaccinated children reached 1 year of age.

Overall Meningococcal Carriage Prevalence

A total of 1649 carriers were identified, of whom 1536 were from the 22 093 participants enrolled after mass vaccination (6.95%) (Table 2). Carriage prevalence in the 3 districts decreased gradually, from 10.31% in S5 to 3.29% in S9 (Figure 1). In each campaign, prevalence was highest in the district of Kaya, and lowest in Bogodogo. There was a higher prevalence during the 2011 dry season (S6 and S7) than during the rainy season (S8 and S9) ($P < .001$).

NmA Carriage Before and After Vaccination

In campaign S5, NmA carriage prevalence in Dandé (0.24%) was comparable to the overall 2009 prevalence (0.21%) in that district. In Bogodogo, no NmA was found in S5, but NmA carriage was also intermittent and low in the baseline study. Thus, campaign S5 demonstrated that NmA was still circulating in unvaccinated districts at the same magnitude as during the baseline study in 2009 [19].

Table 1. Enrolled Participants and Collected Samples in Carriage Study Performed in 3 Districts in Burkina Faso, 2009–2011

	Prevaccination		Postvaccination			
	2009	2010	2010	2011	Total S5–S9	Postvaccination Total[d]
	S1–S4[a]	S5 (Bogodogo, Dandé)[b]	S5 (Kaya)[c]	S6–S9		
No. of persons						
Asked to participate	23 097	3779	1877	22 969	28 625	24 846
Agreeing to participate	21 583	3567	1825	21 620	27 012	23 445
Meeting at swabbing station	20 676	3480	1716	20 744	25 940	22 460
Providing swab specimen	20 470	3444	1704	20 578	25 726	22 282
No. of samples						
Excluded[e]	144	16	61	128	205	189
Included in analysis	20 326	3428	1643	20 450	25 521	22 093

[a] Baseline study of meningococcal carriage [19].

[b] S5 in Bogodogo and Dandé: last carriage study campaign before vaccination.

[c] S5 in Kaya: first postvaccination carriage study campaign.

[d] Samples taken in Bogodogo and Dandé during S5 (before MenAfriVac vaccination in those districts) are not included.

[e] Samples without full traceability were excluded.

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Table 2. Meningococcal Carriage Before and After MenAfriVac Vaccination in Burkina Faso

		Sampling Campaign								
	Prevaccination Total[a] (n = 20 326)	S5 (B, D)[b] (n = 3428)	S5 (K)[c] (n = 1643)	S6 (n = 5169)	S7 (n = 5096)	S8 (n = 5106)	S9 (n = 5079)	Postvaccination Total[d] (n = 22 093)	OR (95% CI)	*P*
Serogroup										
A	80 (0.39)	4 (0.12)	0	0	0	0	0	0	NA[e]	.003
B	0	0	0	0	0	1 (0.02)	0	1 (0.01)	NA[e]	.341
C	4 (0.02)	2 (0.06)	1 (0.06)	1 (0.02)	0	1 (0.02)	0	3 (0.01)	0.69 (.11–4.53)	.697
W135	70 (0.34)	9 (0.26)	0	7 (0.14)	26 (0.51)	35 (0.69)	24 (0.47)	92 (0.42)	1.21 (.69–2.13)	.506
X	90 (0.44)	51 (1.49)	388 (23.62)	311 (6.02)	240 (4.71)	138 (2.70)	100 (1.97)	1177 (5.33)	12.65 (6.88–23.25)	<.001
Y	457 (2.25)	36 (1.05)	15 (0.91)	66 (1.28)	37 (0.73)	43 (0.84)	30 (0.59)	191 (0.86)	0.38 (.25–.57)	<.001
NG[f]	108 (0.53)	11 (0.32)	6 (0.37)	16 (0.31)	15 (0.29)	22 (0.43)	13 (0.26)	72 (0.33)	0.61 (.41–.90)	.014
Total	809 (3.98)	113 (3.30)	410 (24.95)	401 (7.76)	318 (6.24)	240 (4.70)	167 (3.29)	1536 (6.95)	1.80 (1.37–2.38)	<.001

Unless otherwise specified, data represent No. (%) of carriers.

Abbreviations: CI, confidence interval; NA, not applicable; NG, nonserogroupable; OR, odds ratio.

[a] Baseline study of meningococcal carriage, campaigns S1–S4 in 2009 [19].

[b] S5 in Bogodogo and Dandé: last carriage study campaign before vaccination.

[c] S5 in Kaya: first postvaccination carriage study campaign.

[d] Samples taken in Bogodogo and Dandé on S5 (before MenAfriVac vaccination in those districts) are not included.

[e] Not applicable, because no NmB was found before vaccination, and no NmA was found after vaccination.

[f] Nonserogroupable *Neisseria meningitidis*.

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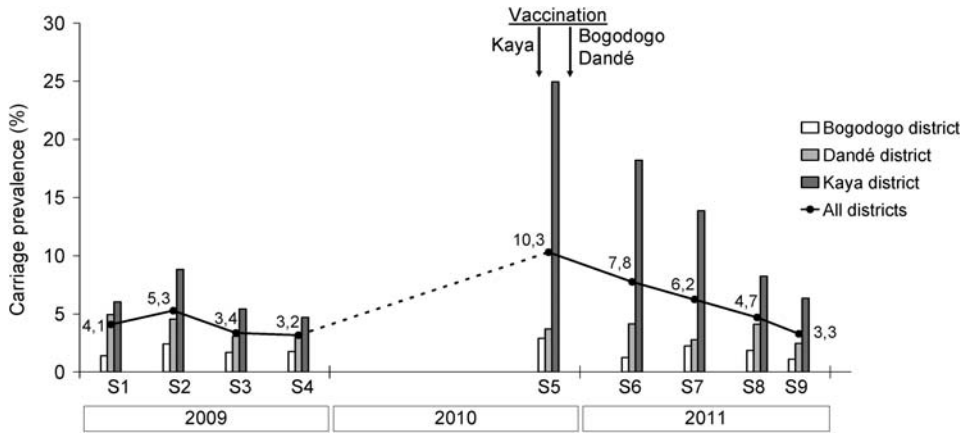

Figure 1. Carriage prevalence of *Neisseria meningitidis* in 3 districts in Burkina Faso at 9 sampling time points, S1–S9 (2009–2011) before and after MenAfriVac mass vaccination.

In the district of Kaya, where MenAfriVac vaccination campaign had ended 3 weeks before the carriage sampling S5 started, none of the 1643 persons enrolled during S5 carried NmA. The postvaccination carriage study campaigns S6–S9, conducted simultaneously in all 3 districts in 2011, enrolled an additional 20 450 persons, and none were carriers of NmA (Table 2; Figure 2). Elimination of NmA after mass vaccination was statistically significant when all 3 districts were considered together as well as when each district was considered separately ($P < .05$) (Figure 2).

Herd Immunity

Of 2241 unvaccinated participants, the expected number of NmA carriers was calculated to be 8.74 when we considered the overall baseline carriage of 0.39% or 6.84 when age-specific carriage prevalence was considered. No NmA carrier was found after vaccination and the difference was significant ($P < .05$).

Serogroup Distribution

In all 5 sampling campaigns S5–S9, NmX was dominant with an overall prevalence of 4.81%. NmX carriage decreased over time in all 3 districts and overall prevalence declined from 8.66% in S5 to 1.97% in S9 (Table 2). NmX was dominant in Kaya and represented 85.3%–94.6% of all meningococcal isolates; it represented 21.1%–63.3% of the isolates in Bogodogo and 9.5%–33.3% in Dandé (Figure 3). NmX prevalence was highest at S5 in Kaya (23.6%), but NmX was present in

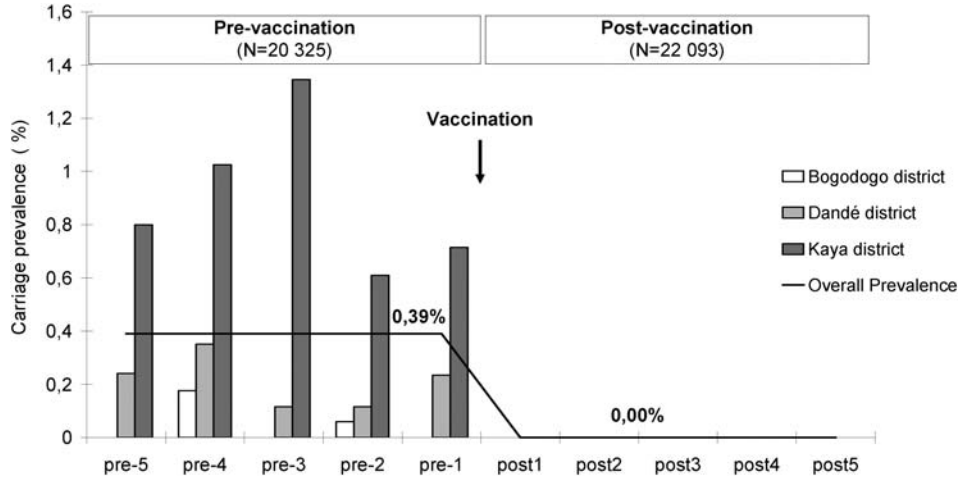

Figure 2. Carriage of serogroup A *Neisseria meningitidis* at 5 timepoints before (pre-5 to pre-1) and 5 timepoints after (post1 to post5) MenAfriVac vaccination.

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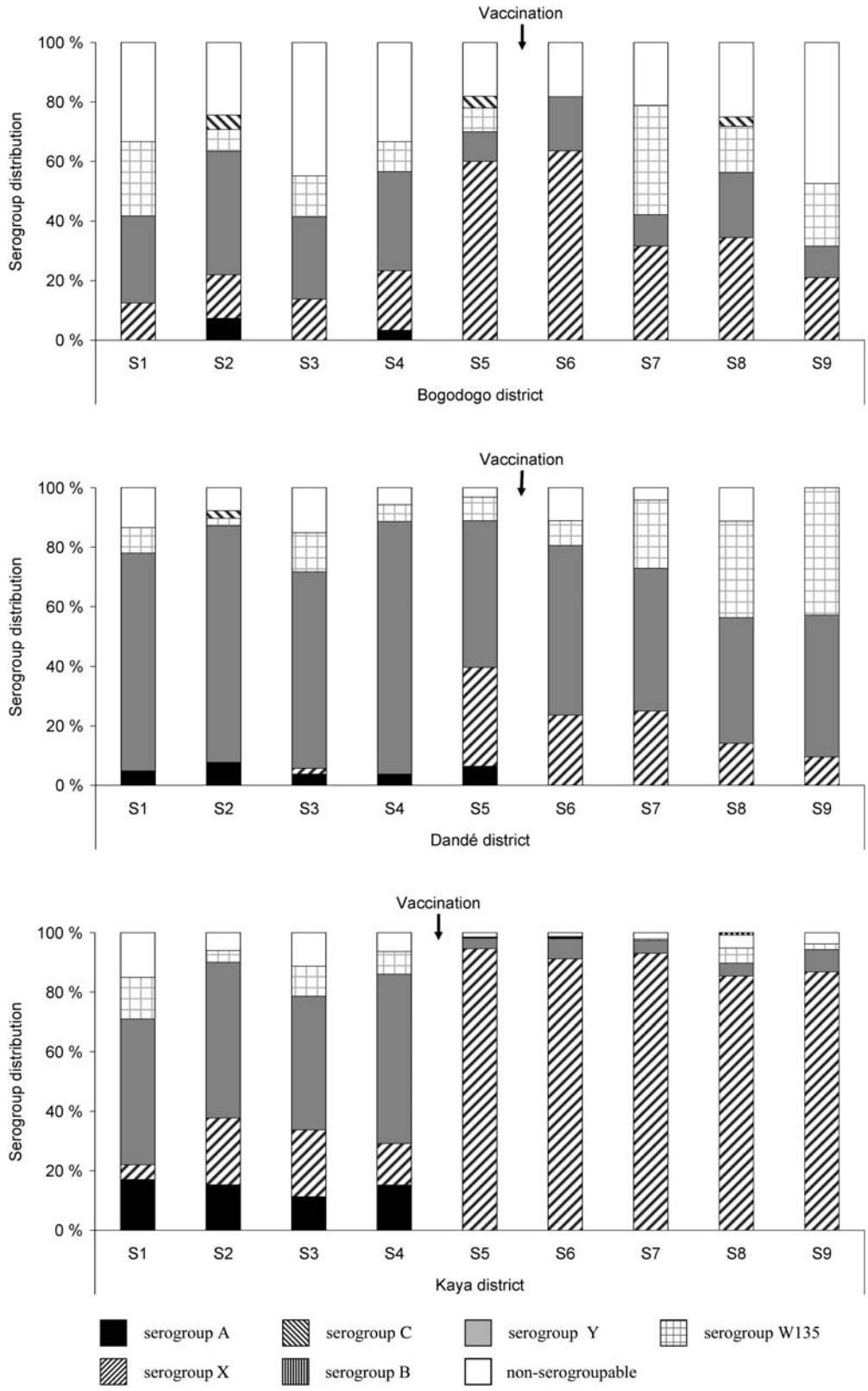

Figure 3. Serogroup distribution of meningococcal carriage isolates in 3 districts in Burkina Faso at 9 sampling time points, S1–S9 (2009–2011), before and after MenAfriVac mass vaccination.

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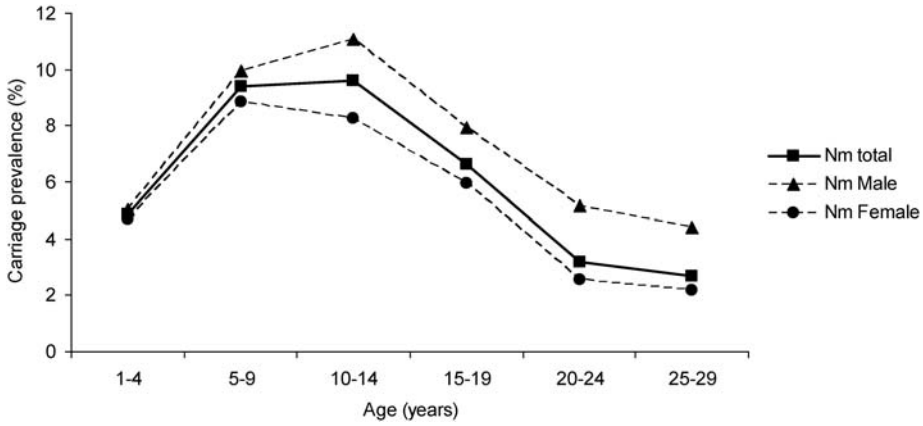

Figure 4. Carriage prevalence of *Neisseria meningitidis* by age group and sex. Abbreviation: Nm, *Neisseria meningitidis*.

unvaccinated districts (1.74% in Bogodogo; 1.23% in Dandé), at higher rates compared with 2009 data ($P < .001$ for both comparisons). NmX was the dominant serogroup in Bogodogo in S5 and S6 (Figure 3).

The proportion of nongroupable isolates was highest in Bogodogo, whereas NmY dominated in Dandé (Figure 3). Overall, NmY carriage was low (0.86%), and its prevalence by campaign declined through the study period (Table 2). NmW135 was almost nonexistent in Kaya, but it represented up to 36.8% and 42.9% of the isolates from Bogodogo and Dandé, respectively (Figure 3). Overall, NmW135 carriage prevalence reached a maximum in S8 (0.69%) and then declined in S9 (0.47%) (Table 2). Comparison of carriage prevalence before and after vaccination shows a significant reduction in NmA, NmY, and nonserogroupable carriage and a significant increase in NmX carriage (Table 2).

Age and Sex Distribution of Meningococcal Carriers

For the 20 092 participants providing swab specimens after MenAfriVac vaccination, carriage prevalence was higher for male participants (8.11%) than female participants (6.06%; $P < .001$). The highest prevalence was found among 10–14-year-olds for male and 5–9-year-olds for female participants (Figure 4). Carriage prevalence varied substantially with age only for NmX, with a maximum carriage in the age groups of 5–9 years (7.59%) and 10–14 years (7.48%) (Figure 5).

Laboratory QC

Five meningococcal isolates were found among the 1155 presumptive *N. meningitidis*–negative QC samples [21] retrieved from all the postvaccination campaigns. Of these 2 were NmX and 3 were nongroupable. Considering the proportion of samples tested in the 2 analytical steps included in the external

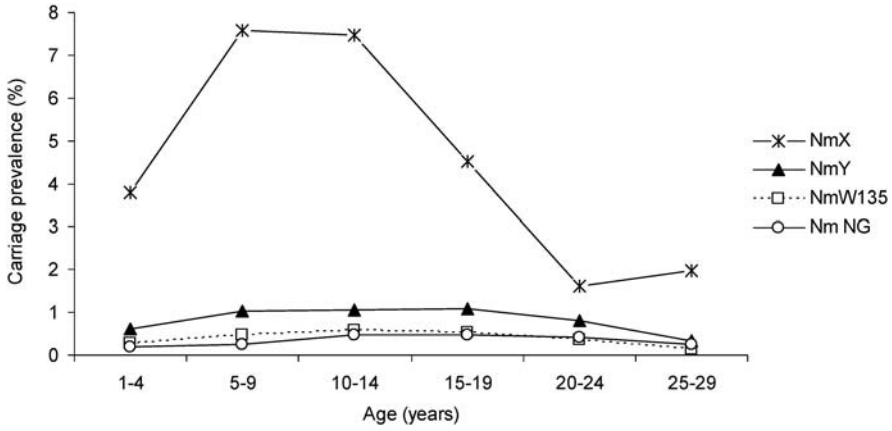

Figure 5. Carriage prevalence of dominating serogroups of *Neisseria meningitidis* by age. Abbreviations: NG, nonserogroupable; Nm, *Neisseria meningitidis*.

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QC, we extrapolated that the number of false-negative samples was 58, whereas the number of true-negative samples was 20 419. Of 1616 presumptive meningococcal isolates sent to the NIPH 1531 were confirmed as *N. meningitidis* (true positive) and 85 were not (false positive). Using standard formulas, the overall sensitivity of meningococcal isolation and identification in Burkina Faso after mass vaccination was 96.3% (range, 92.4%–100% for each campaign), and the overall specificity was 99.6% (range, 98.8%–99.8% for each campaign).

DISCUSSION

The study demonstrated that NmA carriage was eliminated after a successful mass vaccination campaign with MenAfriVac in Burkina Faso. The effect was seen in both vaccinated and unvaccinated persons and persisted throughout the 13-month postintroduction period.

The introduction of MenAfriVac, originally planned for the end of 2009, was delayed by 1 year. Because of lack of funds, we had to interrupt the repeated carriage samplings initiated in 2009 [19] until study S5, performed in October–November 2010, when NmA still circulated in unvaccinated districts at levels comparable to the 2009 baseline.

The age and sex of participants in the study were similar to those in the baseline study (43.7% male; 54% <10 years old) [19]; we assumed thus that the populations sampled were comparable. Study workers were largely the same as during the baseline study, the studies were identical in methodology, and retraining was provided before the study began. The QC system [21] documented excellent performance of the laboratories in Burkina Faso; the underestimation of meningococcal carriage was lower than during the baseline study (0.24% vs 0.49%), and 95% of the isolates sent to the NIPH were confirmed as *N. meningitidis*, compared with 77% in the baseline study. Moreover, none of the QC samples contained NmA. Hence, we feel confident that carriage prevalence before and after mass vaccination can be compared and that the disappearance of NmA carriage was not related to methodological changes or lapses in quality of the work performed.

We studied the 1–29-year-old age group, targeted for MenAfriVac vaccination. Consequently, some participants in the postvaccination carriage study were not vaccinated because they were either too young at time of vaccination or did not receive or accept the vaccine (mainly the 16–29-year-olds). If the vaccine did not interrupt transmission, the unvaccinated population would be at the same risk of carrying NmA as before vaccination. Our study demonstrated that NmA carriage was eliminated in the unvaccinated group. The herd effect was probably a result of high antibody titers demonstrated during the development and testing of the vaccine [16].

After the vaccination campaign, the dramatic decrease in NmA disease in Burkina Faso in 2011 and 2012 is also consistent with a strong herd effect [22]. In comparison, immunization of teenagers with NmC conjugate vaccines in the United Kingdom reduced carriage of serogroup C meningococci by 66% after 1 year [10], and the attack rate in unvaccinated was reduced by 66% [13]. Polysaccharide-protein conjugate vaccines against other pathogens have also been shown to reduce carriage and generate herd immunity. Vaccination of young children with pneumococcal conjugate vaccines has contributed to significant reduction of carriage and disease in older children and adults [14, 23, 24]. Conjugate vaccines against *Haemophilus influenzae* type b infection have enabled the control of this disease, and in some countries its elimination, an accomplishment partly attributed to the vaccine's ability to protect against colonization [11, 25]. Achieving herd immunity is an essential benefit of MenAfriVac and might contribute to significant reduction of meningitis epidemics.

Serogroup replacement, as demonstrated after the use of pneumococcal conjugate vaccines [24, 26], is always a concern when a new vaccine is introduced. A notable increase in NmX cases and a high NmX carriage prevalence was seen in 2011 [22]. However, NmX was already circulating in the eastern districts of Bogodogo and Kaya in 2009, occupying a larger ecological niche than NmA [19]. NmX started to cause disease in 2009 [27], and in the epidemic season of 2010, before vaccine introduction, about 20% of the tested isolates were confirmed as NmX [22]. The significantly higher NmX carriage prevalence in October-November 2010 seemed unrelated to vaccination as it was observed in both vaccinated and unvaccinated districts. Waning of NmX carriage in the course of 2011 suggests increasing immunity against this serogroup. Altogether, these data suggest that vaccine-induced serogroup replacement with NmX did not occur and that the increase of NmX cases in 2011 was due to a wave of NmX that had already started in 2009, as observed elsewhere [28].

Geographic variations in the meningococcal carriage rates were similar to those observed during the baseline study [19], with the district of Kaya having the highest prevalence. Seasonal variation was also similar, with lowest carriage in the rainy season.

The age distribution of meningococcal carriage, very much dominated by NmX, showed a maximum carriage in younger age groups compared with the prevaccination study [19]. Carriage of serogroups other than NmX varied little with age. Thus, age distribution of each serogroup was different from the baseline study, but in both studies, the dominant serogroup varied significantly by age, whereas the other serogroups did not. Age distribution of meningococcal carriage might therefore depend on the epidemiological context and the dominant serogroup.

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Our study showed no NmA circulation after vaccine introduction. We hypothesize that NmA colonization was impeded such that the effective reproduction number (R) fell to <1 and the pathogen disappeared [29]. Detailed analysis of the NmC circulation in the United Kingdom before the introduction of MenC conjugate vaccines estimated a basic reproduction number (R_0) at 1.36, lower than had been suspected [30]. Given the low NmA carrier rate in Burkina Faso before immunization it is likely that NmA R_0 in Africa may also be very low. If that supposition is correct, even modest coverage rates with NmA conjugate vaccine should have a major impact, assuming that complete population mixing is taking place [31]. Better data on NmA R_0 in Africa are sorely needed, as well as more detailed information on the length of protection after a dose of MenAfriVac.

The accepted theory for conjugate vaccines is that the high immunoglobulin G titers produced in blood leak onto the mucosal epithelium of the nasopharynx, thus preventing carriage acquisition [32]. Our study showed that MenAfriVac prevented acquisition but also possibly interrupted ongoing carriage, because unexpected rapid elimination of NmA carriage was seen in the district of Kaya. The possibility that MenAfriVac may be a therapeutic vaccine should be further explored.

In summary, NmA carriage was eradicated in both vaccinated and unvaccinated populations in Burkina Faso from 3 weeks up to at least 13 months after mass vaccination with MenAfriVac. Our findings are consistent with a vaccine-induced herd immunity effect. With herd immunity, the progressive implementation of MenAfriVac ultimately encompassing the whole of the meningitis belt may be expected to progressively eliminate NmA. Protecting the unvaccinated, especially the young children until the vaccine is integrated into child immunization programs, is clearly beneficial for the populations. To better understand the impact of a major public health intervention such as the introduction of MenAfriVac, in addition to continued surveillance, the dynamic of clearance, and the long-term protection of the vaccine against disease and carriage should be further explored.

Notes

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Development of a group A meningococcal conjugate vaccine, *MenAfriVac*™

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Keywords: meningitis, conjugate vaccine, meningococcus, development, immunity

Abbreviations: TT, unactivated tetanus toxoid; TT-H, hydrazide activated toxoid

Group A meningococcal disease has been an important public health problem in sub-Saharan Africa for over a century. Outbreaks occur there annually, and large epidemics occur at intervals ranging between 8 and 12 y. The Meningitis Vaccine Project was established in 2001 with funding from the Gates Foundation with the goal of developing, testing, licensing, and introducing an affordable group A meningococcal conjugate vaccine into Africa. From 2003 to 2009 a monovalent group A conjugate vaccine, *MenAfriVac*™, was developed at the Serum Institute of India, Ltd., through an innovative public/private partnership. Preclinical studies of the new conjugate vaccine were completed in 2004 and a phase 1 study began in India in 2005. Phase 2/3 studies in African 1–29 y olds were completed in 2009 showing the new meningococcal A conjugate vaccine to be as safe as currently licensed meningococcal polysaccharide vaccines, but much more immunogenic. After Indian market authorization (December 2009) and WHO prequalification (June 2010), *MenAfriVac*™ was introduced at public health scale using a single 10 μg dose in individuals 1–29 y of age in Burkina Faso, Mali and Niger in December 2010. We summarize the laboratory and clinical studies leading to prequalification of *MenAfriVac*™. The 2011 epidemic season ended with no reported case of group A meningitis in vaccinated individuals.

Introduction

Neisseria meningitidis (the meningococcus) is a particularly important cause of bacterial meningitis in children and adults because of its potential to cause epidemics. The relative importance of meningococcal disease as a public health threat varies greatly over time and geographic location, but the epidemic potential of meningococci confers a special public health concern whenever clinical cases of meningococcal disease occur.

Meningococci are divided into 12 different serogroups based upon the expression of chemically and serologically different capsular polysaccharides (PSs).[1] Virtually all meningococcal disease is caused by serogroups A, B, C, X, Y and W135. The relative importance of each serogroup varies with geographic region. Group A meningococcal disease is largely a problem in sub-Saharan Africa, while serogroups C and Y account for two-thirds of the meningococcal disease in the US. Group B *N. meningitidis* causes up to 90% of meningococcal disease in some European countries, while serogroups X and W135 have caused small- and moderate-sized outbreaks in Africa.[2-4]

Humans are the only natural host of meningococci, and about 5–10% of adults are asymptomatic meningococcal carriers. Recent data from sub-Saharan African have shown endemic carriage rates less than 1 percent for group A meningococci.[4]

Protective Immunity

Colonization can at times lead to invasive disease. Expression of a capsular polysaccharide is a requirement for invasion, but different strains of the same serogroup can differ greatly in their ability to invade and cause disease. Studies by Goldschneider et al. clearly showed that only individuals lacking bactericidal antibodies against the circulating virulent meningococcal strain go on to develop disease.[5]

Prior to development of antibiotics and effective vaccines, marked reductions in lethality of meningococcal infections were achieved using therapeutic sera. The success of serotherapy demonstrated the central role of humoral antibody in protection against invasive meningococcal disease.[6] The critical role of bactericidal antibodies has been further demonstrated in a number of ways: (a) the highest incidence of meningococcal disease occurs in individuals between 6 and 12 mo of age, at a time when bactericidal antibody levels are at their nadir; (b) studies in US Army recruits in the mid-1960s showed a direct correlation between susceptibility to meningitis and absence of serum bactericidal antibodies;[7] (c) individuals deficient in complement components C5, C6, C7 or C8 have an increased susceptibility to invasive meningococcal infection, even though they may have high levels of anti-meningococcal antibodies; (d) a correlation has been shown between the efficacy of meningococcal vaccines and persistence of vaccine-induced bactericidal antibodies.

Measurement of bactericidal antibody can serve as a surrogate for protective immunity, and in the development of meningococcal vaccines a primary requirement is the demonstration of the induction of bactericidal antibodies. Antibody responses can also

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be quantitated by ELISA, but IgG antibody titers are considered less important than bactericidal antibodies.[8]

Opsonophagocytosis has not been well studied, but is likely to be important in overall protection against meningococcal disease. Turbid spinal fluid specimens from meningococcal patients have many polymorphonuclear leukocytes with internalized meningococci. Vaccination with the A/C PS vaccine induces opsonic antibody.[9] Meningococci in phagolysosomes are rapidly killed, but they are protected from phagocytosis by their capsules in the absence of anticapsular or anti-outer membrane antibodies.

Need for a Meningococcal Serogroup A Conjugate Vaccine

Major African epidemics are associated with serogroup A meningococci.[10] Mongolia, Nepal and India have also reported group A meningococcal epidemics over the past 20 y, but the disease burden is much smaller when compared with sub-Saharan Africa.[11] The African "meningitis belt," with a population of about 350 million people, is a huge area stretching from Senegal in the west to Ethiopia in the east, and was first described in 1963 by Lapeyssonnie.[12] Meningitis epidemics characteristically occur in the hot, dry and dusty season from January to May and promptly cease with the onset of the rains. Focal epidemics occur nearly every year in one or more of the meningitis belt countries, and large outbreaks occur every 8–12 y.[12,13] These epidemic cycles likely reflect major changes in population immunity over time.[13]

In major African epidemics, attack rates range from 100 to 800 per 100,000 population, but individual communities have reported rates as high as 1%, caused almost entirely by serogroup A *N. meningitidis*.[10] These high rates have occurred despite using millions of doses of A/C polysaccharide vaccine that are administered in reactive campaigns, in response to outbreaks. An epidemic often lasts less than 2 mo and reactive campaigns require getting the infecting strain identified, finding vaccine and funding for vaccine purchase plus operational costs. This work takes time and more often than not, reactive campaigns are mounted late or even after a meningococcal epidemic has ended. In 1996–1997, West Africa experienced one of the largest recorded outbreaks of epidemic meningitis in history, with over 180,000 cases and 20,000 deaths registered. From 1998 to 2010 over 700,000 new cases of acute meningitis were reported to the World Health Organization.[14] The most affected countries include Burkina Faso, Nigeria, Chad, Ethiopia and Niger; in 2002, the outbreaks occurring in Burkina Faso, Ethiopia and Niger accounted for about 65 percent of the total cases reported in the African continent. In 2009 northern Nigeria reported over 70,000 cases of group A meningococcal meningitis. Furthermore, the meningitis belt appears to be extending further south. In 2004, over 11,000 cases of acute meningitis were reported from the Democratic Republic of Congo, a country heretofore not considered part of the "meningitis belt."

Meningococcal polysaccharide vaccines, like most other bacterial PS vaccines, do not effectively stimulate the immune system in young children and are largely non-immunogenic in infants. The exception is the group A meningococcal PS, which, for reasons not well understood, is immunogenic in infants as young as 6 mo of age, primes for a boosted response, and is effective when used in infants and toddlers in a two-dose immunization schedule.[15] Nonetheless and despite the use of tens of millions of doses of group A polysaccharide-containing vaccines in Africa over the past 20 y group A meningococcal epidemics have continued to occur. Development and use of meningococcal PS and conjugate vaccines have been reviewed in reference 16–18. The present review will focus on the need for, the development, and the clinical evaluation of a new group A meningococcal conjugate vaccine (PsA-TT), *MenAfriVac*™. A monovalent serogroup A conjugate vaccine was developed, because (a) the epidemiology of meningococcal disease in sub-Saharan Africa indicated that an effective monovalent Group A vaccine could prevent over 90% of endemic and epidemic meningococcal disease and (b) would be less expensive to develop that a polyvalent product.

Infants respond best to PS-protein conjugate vaccines because the immune response is more durable. Conjugate immunogens are PS-protein hybrids formed by the covalent attachment of a protein through its amino acid groups to a chemically modified, or "activated" PS. Attachment of the protein provides a number of T cell epitopes. These T cell epitopes interact with CD4 helper T cells greatly facilitating an antibody response to the attached PS. The T cell dependent response to a conjugate results in both serum IgG antibodies and memory B cells, even in infants. In general, immunogenicity of a PS-protein conjugate, in contrast to the native PS, does not depend upon the size of the conjugated PS; conjugates prepared with either PS or oligosaccharides may have similar immunogenicity. The size requirement for highly immunogenic serogroup A meningococcal conjugates has yet to be clearly demonstrated. Methods that have been used to prepare several meningococcal conjugate vaccines have been described in two recent reviews in reference 18 and 19.

Development of the Serogroup A Conjugate Vaccine for Africa

International meetings led by WHO explored whether expanded use of a Group A polysaccharide vaccine could be a useful strategy. Use of multiple doses of a group A meningococcal PS vaccine in the African Expanded Programme on Immunization (EPI) was a strategy that was discussed at length but not chosen because of the logistic demands that such a strategy imposes; rather, international groups including WHO recommended that a new Men A conjugate vaccine be developed.[20] In addition, African public health officials from affected West African countries indicated that to be affordable, the cost of a new meningococcal conjugate vaccine would need to be low, i.e., under US$0.50 per dose.[21] At this price, no large pharmaceutical manufacturer was interested in developing a monovalent serogroup A meningococcal conjugate vaccine for use in sub-Saharan Africa.

In 2001 the Bill and Melinda Gates Foundation awarded US$70 million to WHO and the Program for Appropriate Technology in Health (PATH) to establish the Meningitis Vaccine Project (MVP). The MVP grew out of a WHO-sponsored effort

to improve the public health response to meningitis outbreaks in sub-Saharan Africa after the devastating outbreaks in 1996–1997. The MVP goal was to eliminate epidemic meningitis in Africa as a public health problem through the development, testing, licensure and widespread use of conjugate meningococcal vaccines. After investigating different approaches, MVP chose to become a "virtual vaccine company" and to develop a serogroup A meningococcal conjugate vaccine in partnership with a developing-country manufacturer (Serum Institute of India Ltd., SIIL) with financing, technical assistance, and coordination by the MVP.[22,23] The MVP staff identified an initial source of vaccine-grade meningococcal A PS (SynCo. Bio Partners B.V.), a source of tetanus toxoid (SIIL), and a high-efficiency conjugation technology developed in the Laboratory of Bacterial Polysaccharides, Center for Biologics Evaluation and Research, US FDA. Production of the PS later shifted to SIIL. The MVP target was to be able to produce 25 million doses/year by 2009.

Vaccine Production and Quality Control

For a PS to be chemically linked to a protein, the PS must be activated, that is, chemically modified. The two primary methods currently used for PS activation are periodate oxidation and cyanylation.[24,25] Sodium periodate oxidizes diols (two adjacent carbons with hydroxyl groups) into aldehydes (C = O) and in the process breaks C-C bonds. Thus, depending upon the PS structure, periodate activation can fragment a PS and open the ring structures of sugars thus altering PS conformation. In the case of the serogroup A PS, only those repeat units lacking an O acetyl group on carbon 3 can be activated by the periodate treatment (see top diagram in **Fig. 1**) which is used in production of *MenAfriVac*™. The percent O acetylation in the purified group A PS is about 77–85%, and O acetylation is required for expression of protective epitopes on the PS.[26]

For most conjugates, the reactive aldehyde groups on the activated PS are condensed with free amino groups on the protein in the presence of sodium cyanoborohydride to form a stable secondary amine. Condensation of the aldehyde groups with the epsilon amino groups on lysine is a slow process, often taking a few days, with low conjugate yields. A new conjugation method was developed to decrease the conjugation time and increase conjugate yields.[27] The general conjugation scheme is shown in **Figure 2** and is described in detail in reference 27–30. Conjugation efficiency was improved for *MenAfriVac*™ by chemically activating both the PS and carrier protein (**Fig. 1**).[28] The protein was activated by introduction of hydrazide (-NH-NH_2) groups onto exposed aspartic and glutamic acids carboxyl groups by reacting tetanus toxoid with hydrazine using carbodiimide under acidic conditions. The activated protein was maintained soluble at about pH 10.5 until conjugation at pH 6.5–7.5 with periodate-activated aldehyde-containing serogroup A PS. The conjugate mixture was then reduced by sodium borohydride and diafiltrated to exclude the small molecules. The increased reactivity of hydrazine activated tetanus toxoid (TT-H) with the activated PS is shown in **Figure 3**. Activated serogroup A PS

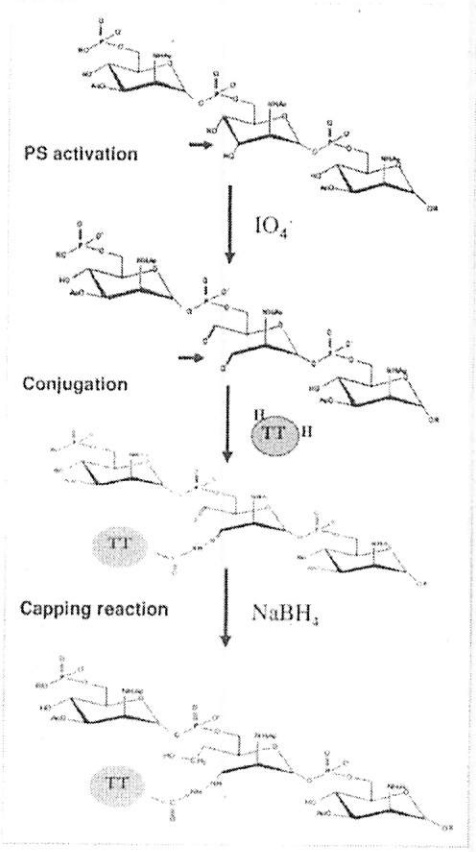

Figure 1. The group A meningococcal polysaccharide and schematics of polysaccharide activation and conjugation reactions.

was reacted with either tetanus toxoid (TT) or TT-H overnight (15–16 h) at room temperature. As seen in the figure the amount of high molecular weight conjugate obtained as measured by OD 280 absorbance was much greater when the activated PS was mixed with TT-H compared with TT.

Physico-chemical analyses are needed at different steps in the manufacturing process, and there are a variety of alternative methodologies. Studies by Silveira et al. in Brazil on a group C meningococcal conjugate using the TT-H technology showed that NMR could be used to show disappearance of the reactive aldehyde groups in the activated PS as a result of conjugation.[29] Additional advanced physico-chemical methods for characterization of meningococcal conjugates have been described, including determination of hydrazine content.[25,31]

The described conjugation method produces high molecular weight cross-linked lattice structures, due to multiple aldehyde groups on the PS and multiple hydrazide groups on the tetanus toxoid. Similar conjugates were produced in Brazil using the group C meningococcal PS, where they achieved 50% yields of conjugated PS.[29] Use of activated PS and TT-H has also been applied to serogroup W135 conjugate vaccines.[30]

Lot release testing of the different components of the meningococcal group A conjugate was done in reference to the 2006WHO recommendations for production of group A meningococcal conjugate vaccines.[32] The lot release tests shown in

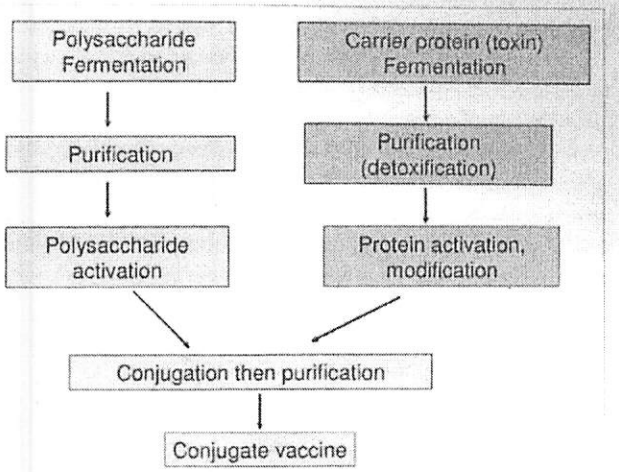

Figure 2. General process for manufacture of a conjugate vaccine.

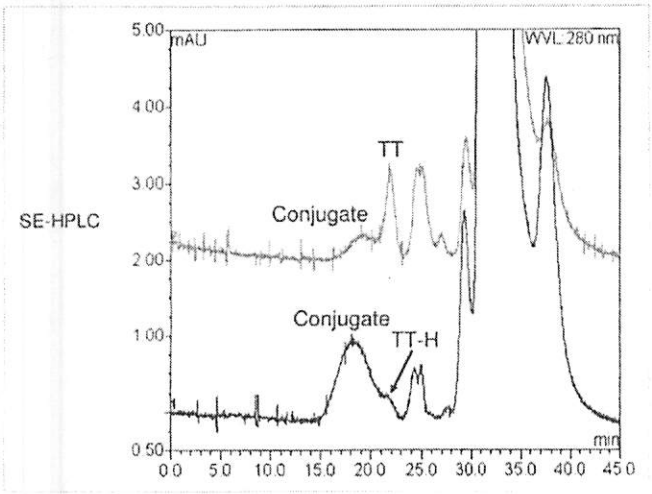

Figure 3. Improved conjugation efficiency when conjugates are prepared using the hydrazide activated carrier protein, tetanus toxoid.

Table 1 were performed on each bulk intermediate and on the final formulated vaccine.

Experimental group A meningococcal conjugate vaccine lots were evaluated in mice and rabbits. Initial studies showed that the conjugated group A PS was highly immunogenic in mice, inducing much higher bactericidal antibody (about 3 logs) compared with the PS alone.[27,28] Some conjugates were size-fractionated on the gel filtration matrix, Sephacryl S-400 HR. Different molecular size pools were used to immunize mice at 0.1 μg PS per dose in 3 weekly doses. Immunogenicity of the highest molecular weight pools as measured by both IgG antibody and bactericidal activity was significantly higher than for the lowest molecular weight conjugate pool.[27,28] The lowest molecular weight pool was, however, more immunogenic than a pure PS control vaccine.

Multiple lots of the serogroup A conjugate vaccine prepared at different manufacturing scales under cGMP conditions were characterized physicochemically and evaluated in mice and rabbits for both safety and immunogenicity prior to phase 1 trials in human adults.[28,33,34]

The *MenAfriVac*™ conjugate vaccine is a ten-dose lyophilized preparation that is reconstituted before injection.[34] The vaccine was formulated to contain per 0.5 ml dose 10 μg of group A PS conjugated to 10–33 μg of tetanus toxoid, and 0.06 mg Tris hydroxymethylamino ethane when reconstituted with saline containing 0.01% Thimerosal and 0.3 mg Al^{+++} as $AlPO_4$ per dose. The vaccine is administered intramuscularly.

Clinical Development and Licensure

The licensure plan for *MenAfriVac*™ was patterned on the successful introduction of the meningococcal serogroup C conjugate into the UK based upon demonstration of safety and functional immunogenicity in all targeted age groups from infants to young adults.[35,36] The efficacy of the C conjugate in the UK was inferred from induction of bactericidal antibody in most vaccine recipients (the SBA cutoff titer was 1:8 using rabbit complement). Presence of serum bactericidal antibody is accepted as a surrogate for protection against meningococcal disease[8] and efficacy studies are not required for licensing meningococcal conjugate vaccines.[37] The evaluation of the efficacy of *MenAfriVac*™ was based on its ability to induce levels of serum bactericidal antibodies sufficient and not inferior to those induced by licensed meningococcal polysaccharide vaccines. *MenAfriVac*™ was licensed by the Indian Drugs Controller General of India in December 2009 and received WHO prequalification in June 2010, which allowed for licensure in countries of the African meningitis belt followed by large-scale vaccine introduction to occur by the end of 2010. As of December 2011 MenAfriVac is licensed in Burkina Faso, Mali, Niger, Nigeria, Cameroon and Chad. Over the next five years the vaccine will be licensed in all meningitis belt countries.

The clinical development plan of the PsA-TT conjugate vaccine included a phase 1 study in adult healthy volunteers in India, followed by five phase 2 and 3 studies to assess safety, immunogenicity, immune memory and persistence in the target age population (1–29 y old) living in countries included in the African meningitis belt. This review will summarize data from three published studies in references 34, 37 and 38. All clinical studies were conducted in compliance with ICH/GCP and all applicable ethical and regulatory requirements.

The serological assays used to assess the immunogenicity of the PsA-TT vaccine are a serum bactericidal assay using baby rabbit complement (rSBA) to measure functional activity against MenA and an ELISA to measure total MenA IgG serum anticapsular antibody concentrations. Both assays have been standardized to yield reproducible data. The WHO recommendation for the evaluation of meningococcal polysaccharide vaccine immunogenicity is the use of endpoints based on both standardized assays: ELISA and SBA with baby rabbit complement.

Table 1. WHO recommendations for control testing of meningococcal Group A PS-protein conjugate vaccines*

Polysaccharide
Identity
Moisture content
O acetyl content
Purity
Molecular size
Size modified polysaccharide
If size reduced before activation then average molecular size
size distribution
Activated polysaccharide
Extent of activation
Size of activated polysaccharide
Carrier protein
Identity
Purity
SEC-HPLC or SDS-PAGE profile
Extent of activation (if applicable)
Bulk conjugate
Identity of polysaccharide and carrier protein (immunological for example)
Freedom from residual conjugation reagents
Polysaccharide and protein quantitation
Polysaccharide—protein ratio
Show free of unreacted functional groups on either the protein or the polysaccharide
Unbound (free) polysaccharide
Molecular size distribution, monitoring both protein and polysaccharide
Sterility
Stability of conjugate
Molecular size
Follow free polysaccharide or conjugated polysaccharide

*WHO Technical Report Series WHO/BS/06.2041-Final. Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines, 2006.

Clinical Phase 1 Study (PsA-TT-001)

This phase 1 clinical study[34] was performed in India from August 18, 2005 to October 3, 2006. The study was a double-blind, randomized, controlled study to assess safety and to obtain preliminary information on immunogenicity of the PsA-TT vaccine when administered to healthy adult volunteers from 18 to 35 y of age. Of the 74 male subjects enrolled into the study, 24 subjects received the PsA-TT conjugate vaccine, 25 an A/C polysaccharide vaccine, and 25 a tetanus toxoid vaccine. Subjects were followed up for safety evaluation for 4 weeks, and they had one blood draw just before immunization, and the second 4 weeks later. All subjects were subsequently followed up for safety evaluation (occurrence of serious adverse events [SAEs]) for a total duration of 48 weeks (1 y), and they had two more blood draws at 24 weeks (6 mo) and at 48 weeks (1 y) to evaluate antibody persistence.

In the three vaccine groups, local solicited reactions were mild and transient and resolved without sequelae. The commonest solicited reactions were pain (75% in PsA-TT group; 64% in PsAC group; 68% in TT vaccine group), redness (13% in PsA-TT group; 16% in PsAC and TT vaccine group) and swelling (8% in PsA-TT and PsAC group; 20% in TT vaccine group). Systemic solicited reactions were also mild and transient and resolved without sequelae. All non-solicited adverse events (AEs) resolved without sequelae and were unrelated to the vaccines.

Four weeks after vaccination 83% of subjects in PsA-TT group had a ≥ 4-fold increase in rSBA titers, 72% in the PsA/C group, and 12% in the TT vaccine group. rSBA GMTs were 8,192 in the PsA-TT group, 5,257 in the PsA/C group, and 217 in the TT vaccine group. All (100%) of the 24 subjects in PsA-TT group had a 4-fold increase in ELISA IgG concentrations, 80% in the PsA/C group, and none in the TT vaccine group. ELISA GMCs were 110 in the PsA-TT group, 44 in the PsA/C group, and 5 in the TT vaccine group (**Tables 2 and 3**).

Twenty-four weeks (6 mo) and 48 weeks (1 y) after vaccination, all initial rSBA ≥ 4-fold responders, i.e., 83% of the subjects four weeks after vaccination, remained 4-fold responders in the PsA-TT group. 64% and 56% remained 4-fold

Table 2. Clinical immunogenicity among 1 to 29 y-olds: MenA antibody percentage ≥ 4 fold-rise, 28 d after a single dose

Secondary endpoint difference Δ (95% CI) %PsACWY - %PsA-TT	% (95% CI) ≥ 4-fold rise MenA IgG ELISA concentrations	Number tested/ vaccinated MenA IgG ELISA concentrations	Primary endpoint noninferiority (CI% 95) difference Δ %PsACWY - %PsA-TT	% (95% CI) ≥ 4-fold rise MenA rSBA titers	Number tested/ vaccinated MenA rSBA titers	Vaccine group	Study ID	Age group (years)
-21 (-28, -16)	100 (97–100) 78 (72–84) 4 (2–7)	198/201 194/200 194/200	-32 (-40, -25)*	96 (92–98) 64 (57–71) 36 (29–43)	198/201 193/200 194/200	PsA-TT PsACWY Hib-TT	PsA-TT 002-	1 < 2
-17 (-29, -10)	98 (91–100) 83 (71–91) 10 (4–21)	58/63 63/66 60/66	-25 (-38, -12)**	98 (91–100) 86 (75–93) 60 (47–72)	57/63 64/66 60/66	PsA-TT PsACWY Hib-TT	PsA-TT -002	2 < 3
-29 (-35, -23)	89 (86–91) 60 (54–65)	599/604 289/296	-32 (-39, -25)*	78 (75–82) 46 (40–52)	602/604 290/296	PsA-TT PsACWY	PsA-TT -003	2–29
Not applicable (Phase I)	100 (86–100) 80 (59–93) 0.0 (0.0–14)	24/24 25/25 25/25	Not applicable (Phase I)	83 (63–95) 72 (51–88) 12 (3–31)	24/24 25/25 25/25	PsA-TT PsAC TT	PsA-TT 001-	18–34

*p < 0.001 for both comparisons, supported a claim of superiority for the PsA-TT vaccine, see references 39 and 40; **Study secondary endpoint (refer to the row above for study primary endpoint).

Table 3. Clinical immunogenicity among 1 to 29 y-olds: MenA antibody geometric mean, 28 d after a single dose

P-value* PsA-TT vs. PsACWY GMC	28 d Post-vaccination geometric mean concentration GMC (95% CI) MenA IgG ELISA	Baseline Pre-vaccination geometric mean concentration GMC (95% CI) MenA IgG ELISA	P-value* PsA-TT vs. PsACWY GMT	28 d Post-vaccination geometric mean titer GMT (95% CI) MenA rSBA	Baseline pre-vaccination geometric mean titer GMT (95% CI) MenA rSBA	Vaccine group	Study ID	Age group (years)
< 0.001	18 (16–21) 2 (1–2) 0.1 (0.1–0.1)	0.1 (0.1–0.1) 0.1 (0.1–0.1) 0.1 (0.1–0.2)	< 0.001	6235 (4948–7856) 365 (249–537) 61 (40–93)	14 (10–21) 16 (11–24) 13 (9–18)	PsA-TT PsACWY Hib-TT	PsA-TT 002-	1 < 2
< 0.001	15 (12–20) 2 (1–3) 0.2 (0.1–0.2	0.1 (0.1–0.2) 0.1 (0.1–0.2) 0.2 (0.1–0.2)	< 0.001	9343 (7044–12392) 1562 (958–2548) 268 (128–562)	43 (20–89) 66 (31–142) 51 (24–112)	PsA-TT PsACWY Hib-TT	PsA-TT -002	2 < 3
< 0.001	66 (60–72) 13 (11–15)	2 (2–3) 2 (2–2)	< 0.001	4713 (4336–5122) 1191 (969–1465)	223 (181–275) 316 (240–415)	PsA-TT PsACWY	PsA-TT -003	2–29
0.007	110 (68–174) 44 (26–71) 5 (3–8)	4 (3–7) 5 (3–8) 5 (3–8)	0.173	8192 (5221–12855) 5257 (2798–9878) 217 (73–644)	228 (84–617) 422 (191–929) 347 (140–861)	PsA-TT PsAC TT	PsA-TT -001	18–34

*Student's t-test.

responders in the PsA/C group as compared with 72% initially, and 4% remained 4-fold responders in the TT vaccine group as compared with 12% initially.

In summary, the phase 1 results in healthy adult volunteers showed that PsA-TT vaccine was safe, immunogenic, had a boosting effect in antibody concentrations against tetanus, and induced a persistent antibody response.

Clinical Phase 2 Study in African 12 to 23 Month Olds (PsA-TT-002)

This pivotal study began on 18 September 2006 and was completed on 6 April 2009 at Bamako, Mali and Basse, The Gambia.[37] The study was designed as a phase 2, double-blind, randomized, active controlled study to assess safety, immunogenicity and

induction of immunological memory of the PsA-TT vaccine when administered to healthy toddlers from 12 to 23 mo of age.

A total of 601 subjects were enrolled from 18 September to 6 November 2006 and were randomly allocated to one of the three study groups: 201 received the PsA-TT study vaccine, 200 received the ACWY reference PS vaccine, and 200 received the Hib-TT control vaccine. Subjects were followed up for safety evaluation for 4 weeks and for SAEs for the entire study duration. At week 40 post-primary immunization, the 589 subjects remaining in the study received a within-group randomly allocated "booster" dose of one of the three following vaccines: PsA-TT, 1/5th PsACWY or Hib-TT vaccine. All subjects allocated to one of the above final nine study groups were followed up for safety evaluation for 4 weeks post-booster immunization. They had three blood draws: one just prior to booster immunization, a second at week 1, and a third at week 4 post-booster immunization. Remaining subjects were subsequently under follow up for the evaluation of SAEs and of antibody persistence up to a period of at least two years post-primary immunization.

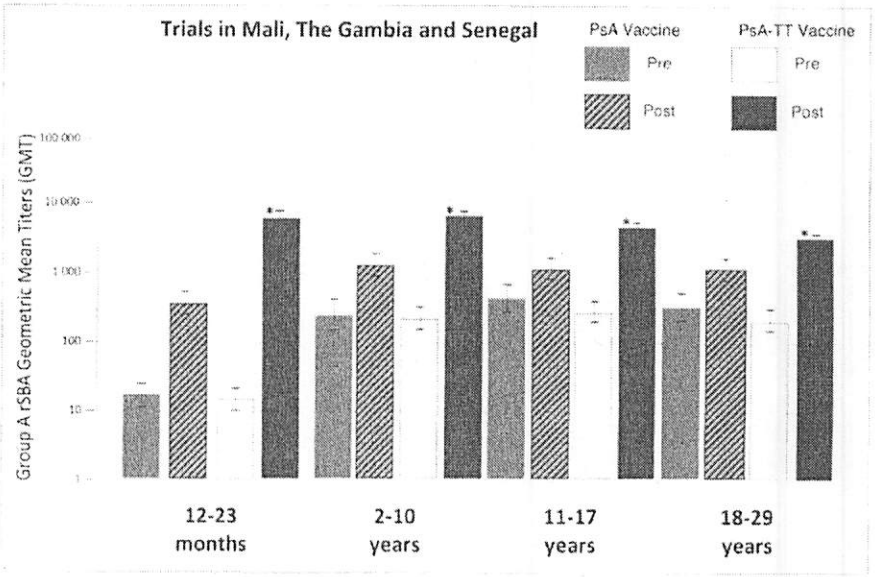

Figure 4. Geometric Mean rSBA TIters prior to and 28 d after a dose of either PsA-TT or PsA vaccine in African toddlers, adolescents and young adults.

Safety in the 12 to 23 mo Olds

There was no immediate safety issue after immunizations. At week 4 post-primary immunization, local reactions were transient and resolved without sequelae in the three vaccine groups. More indurations were reported in the PsA-TT vs. the PSACWY group ($p = 0.01$); the indurations were transient, mild and resolved without sequelae. Rates of adverse events were similar between vaccine groups and unrelated to the study vaccines. The most common AEs were malaria, respiratory infection, gastroenteritis and conjunctivitis. All reported AEs and SAEs were unrelated to the study vaccines.

Immunogenicity

Four weeks after vaccination 96% of subjects in the PsA-TT group had a ≥ 4-fold increase in Men A rSBA titer, 64% in the PsACWY group and 36% in the Hib-TT vaccine group. Men A rSBA GMTs were 6,235 in the PsA-TT group, 365 in the PsACWY group and 61 in the Hib-TT vaccine group; while at baseline Men A rSBA GMTs were similar in the three vaccine groups (**Tables 2 and 3**). In the PsA-TT group, 98% of the subjects had Men A rSBA titers ≥ 1:128 vs. 80% in the PsACWY group and 57% in the Hib-TT group; while at baseline those proportions were similar in the three vaccine groups: respectively 35%, 34% and 31%. **Figure 4** summarizes GMTs prior to and 28 d after immunization with either PsA-TT or PsA. In 12–23 mo olds GMTs (rSBA) were 16 times greater after PsA-TT when compared with PsA vaccine recipients.

Anti-polysaccharide IgG Antibody responses were also measured. All but one subject in the PsA-TT group had a ≥ 4-fold increase in ELISA IgG concentrations, 78% in the PsACWY group, and 4% in the Hib-TT group. ELISA geometric mean concentrations (GMCs) were 18 in the PsA-TT group, 2 in the PsACWY group, and 0.1 in the Hib-TT group; while at baseline (before vaccination), ELISA GMCs were similar in the three vaccine groups (**Tables 2 and 3**). The immune responses for subjects who received their first dose of conjugate or polysaccharide vaccine at between age 2 and 3 y (study week 40) were consistent with the above and are also presented in **Tables 2 and 3**. Overall, the study vaccine PsA-TT was found to be highly immunogenic; and the primary study objective, to demonstrate that the PsA-TT vaccine elicits antibody responses that are not inferior to those achieved by the PsACYW vaccine in subjects 28 d after a single dose, was achieved.

Antibody Persistence

At week 40 post-primary vaccination, 82% (95% CI 76–87) of subjects in the PsA-TT group still showed a ≥ 4-fold increase in rSBA titer with respect to baseline pre-immunization titers vs. 38% (95% CI 31–46) in each of the PsACWY and the Hib-TT group. rSBA GMTs were 1168 (95% CI 874–1,561) in the PsA-TT group, 47 (95% CI 31–72) in the PsACWY group and 53 (95% CI 34–81) in the Hib-TT vaccine group. In the PsA-TT group, 92% (95% CI 88–96) of the subjects had Men A rSBA titers ≥ 1:128 vs. 55% (95% CI 47–62) in the PsACWY group and 54% (95% CI 47–61) in the Hib-TT group. Similarly, 77% (95% CI 70–83) of subjects in the PsA-TT group still had a 4-fold increase in ELISA specific IgG concentrations with respect

to baseline pre-immunization titers vs. 47% (95% CI 40–54) in the PsACWY group and 9% (95% CI 5–14) in the Hib-TT group. ELISA GMCs were 1 (95% CI 0.9–1.3) in the PsA-TT group, 0.4 (95% CI 0.4–0.5) in the PsACWY group and 0.1 (95% CI 0.1–0.2) in the Hib-TT group. A single dose of PsA-TT received at age 12 to 23 mo, the youngest age group of the target population, was found to induce sustained and significantly higher rSBA titers 10 mo after immunization as compared with subjects who received a licensed polysaccharide vaccine.

Immunological Memory

At week 1 post-booster immunization, among subjects who received 1/5th of PsACWY vaccine dose, rSBA GMTs were 8,679 (95% CI 7,135–10,557) in the group primed with the PsA-TT vaccine vs. 2,295 (95% CI 1,800–2,925) in the group primed with the PsACWY vaccine. Among subjects who received a PsA-TT vaccine dose, rSBA GMTs were 21,721 (95% CI 17,706–26,646) in the group primed with the PsA-TT vaccine vs. 12,214 (95% CI 9,436–15,811) in the group primed with the PsACWY vaccine. We concluded that a single dose of PsA-TT received at age 12 to 23 mo, the youngest age group of the target population, was found to induce immunological memory.

In summary, the PsA-TT vaccine was safe and showed the characteristics of a conjugate vaccine with superior immunogenicity, effective inducement of immunological memory and inducement of bactericidal antibodies persisting at sustained levels up to 10 mo after a single vaccine dose in African toddlers 12 to 23 mo of age as compared with the current licensed tetravalent polysaccharide vaccine.

Clinical Phase 2/3 Study in African 2–29 Year Olds (PsA-TT-003)

The study was designed as a phase 2/3, double-blind, randomized, active controlled study to assess safety and immunogenicity of the PsA-TT vaccine when administered to healthy children and adults from 2 to 29 y of age.[37] A total of 900 subjects enrolled in the study (300 in Bamako, Mali; 300 in Basse, The Gambia; 300 in Niakhar, Senegal) were immunized at age 2–10 y (302), 11–17 y (301) and 18–29 y (297) after informed consent and assent procedures. The 900 subjects, of whom 372 were females (41%), were randomly allocated to one of the two vaccine groups: 604 to the PsA-TT study vaccine group and 296 to the PsACWY reference vaccine group. Subjects were followed up for safety evaluation for 4 weeks and for SAEs for the entire study duration. They had two blood draws: one just prior to immunization and a second at week 4 post-immunization. All subjects were under follow up for the evaluation of SAEs and of antibody persistence up to a period of at least one year post-immunization.

Safety in the 2–29 Year Olds

There was no immediate safety issue after immunizations. Rates of local and systemic reactions, AEs and SAEs were similar between vaccine groups overall, within each age group, and within each study site. All AEs were unrelated to the study vaccines. No SAEs and no deaths were reported in the first 28 d post-immunization. All fevers were <40°C. Other reactions were of mild or moderate intensity, transient and resolved without sequelae. Overall a total of 96 AEs were reported for 84 subjects aged 2 to 29 y. They all resolved without sequelae. During the one-year follow up, a total of five SAEs were reported in five subjects, they were unrelated to study vaccines.

Immunogenicity in the 2–29 Year Olds

Four weeks after vaccination 78% of subjects in the PsA-TT group had a ≥ 4-fold increase in rSBA titer vs. 46% in the PsACWY group (see **Fig. 4 and Table 2**). Thus, the primary objective of non-inferiority of the PsA-TT study vaccine to the PsACWY reference vaccine was achieved. Furthermore, this primary objective was achieved in a similar manner within each of the three age sub-groups (2–10 y, 11–17 y and 18–29 y olds).

rSBA GMTs were 4,713 in the PsA-TT group and 1,191 in the PsACWY group; while at baseline (before vaccination) rSBA GMTs were similar in the two vaccine groups (**Table 3**). **Figure 4** presents GMT data by age group and these results clearly indicate that the enhanced immunogenicity with PsA-TT extends to all age groups. In the PsA-TT group, all but one subject, i.e., 99% (95% CI 99–100) of the subjects had rSBA titers ≥ 1:128 vs. 95% (95% CI 91–96) in the PsACWY group; while at baseline those proportions were similar in the two vaccine groups: respectively 76% and 83% of the subjects had titers ≥ 1:128.

In the PsA-TT group, 89% of the subjects in the PsA-TT group had a ≥ 4-fold increase in ELISA IgG concentrations vs. 60% in the PsACWY group. ELISA Men A GMCs were 66 in the PsA-TT group vs. 13 in the PsACWY group; while at baseline (before vaccination), ELISA GMCs were similar in the two vaccine groups (**Tables 2 and 3**).

Over the one-year follow up, antibody decay was observed in both vaccine groups. Nonetheless, subjects vaccinated with PsA-TT had a significantly higher sustained MenA antibody persistence than those who received PsACWY vaccine as confirmed by both antibody assays.

Publications are being prepared summarizing immune persistence in the above study populations as well as safety, immunogenicity and immune persistence of the PsA-TT and PS ACYW vaccines in 2–10-y-old Indian children (including lot consistency) and large scale safety among the entire target population of 1 to 29 y-olds. Dose finding and schedule evaluation studies, including concomitant administration with routine Expanded Program of Immunization (EPI) vaccines, are still ongoing in the infant population and are expected to be fully completed by 2013.

Conclusions

The monovalent meningococcal serogroup A polysaccharide-tetanus toxoid conjugate vaccine, *MenAfriVac*™, was developed beginning in 2003 to meet the need for a low-cost vaccine to combat the recurrent meningococcal serogroup A epidemics in the sub-Saharan "meningitis belt" of Africa. The vaccine was

developed using a so-called "push strategy" whereby support for vaccine development and testing is provided in exchange for price concessions so that a needed product can be developed and licensed in an efficient manner. The advantages and risks of this approach have been well described in reference 22 and 23. The main benefit is the proof of concept, i.e., when markets are unattractive to major manufacturers there is a way to develop needed vaccines and drugs outside the usual commercial supplier chains.

MenAfriVac[TM] was licensed in 2010 for immunization of populations aged between one and 29 y. Large-scale immunization campaigns began in December 2010. The 2011 impact data from Burkina Faso are excellent; no case of meningococcal A disease has occurred in a vaccine recipient.[41] While it is tempting to argue that the vaccine will completely eliminate Group A meningococcal epidemics and meet the one goal of the project we think it is too early to make that assertion. The Burkina Faso introduction was ideal; a well funded preparation on an infrastructure with strong laboratory based surveillance.[38] Hence, we do not think the Burkina results should be applied prospectively in all belt countries. We think the introductions over the next three years in countries with infrastructures that are not as well developed as those in Burkina Faso will provide for a much sounder evaluation of the overall public health benefit that will be realized from *MenAfriVac*.

Note

Marie-Pierre Preziosi is a staff member of the WHO. The author alone is responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy or views of the WHO.

Disclosure of Potential Conflicts of Interest

The authors have no conflicts-of-interest and none has a financial interest in manufacture of meningococcal conjugate vaccines.

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ORIGINAL ARTICLE

Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans

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ABSTRACT

BACKGROUND

Group A meningococci are the source of major epidemics of meningitis in Africa. An affordable, highly immunogenic meningococcal A conjugate vaccine is needed.

METHODS

We conducted two studies in Africa to evaluate a new MenA conjugate vaccine (PsA-TT). In study A, 601 children, 12 to 23 months of age, were randomly assigned to receive PsA-TT, a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (*Haemophilus influenzae* type b conjugate vaccine [Hib-TT]). Ten months later, these children underwent another round of randomization within each group to receive a full dose of PsA-TT, a one-fifth dose of PsACWY, or a full dose of Hib-TT, with 589 of the original participants receiving a booster dose. In study B, 900 subjects between 2 and 29 years of age were randomly assigned to receive PsA-TT or PsACWY. Safety and reactogenicity were evaluated, and immunogenicity was assessed by measuring the activity of group A serum bactericidal antibody (SBA) with rabbit complement and performing an IgG group A–specific enzyme-linked immunosorbent assay.

RESULTS

In study A, 96.0% of the subjects in the PsA-TT group and 63.7% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline; in study B, 78.2% of the subjects in the PsA-TT group and 46.2% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline. The geometric mean SBA titers in the PsA-TT groups in studies A and B were greater by factors of 16 and 3, respectively, than they were in the PsACWY groups ($P<0.001$). In study A, the PsA-TT group had higher antibody titers at week 40 than the PsACWY group and had obvious immunologic memory after receiving a polysaccharide booster vaccine. Safety profiles were similar across vaccine groups, although PsA-TT recipients were more likely than PsACWY recipients to have tenderness and induration at the vaccination site. Adverse events were consistent with age-specific morbidity in the study areas; no serious vaccine-related adverse events were reported.

CONCLUSIONS

The PsA-TT vaccine elicited a stronger response to group A antibody than the PsACWY vaccine. (Funded by the Meningitis Vaccine Project through a grant from the Bill and Melinda Gates Foundation; Controlled-Trials.com numbers, ISRCTN78147026 and ISRCTN87739946.)

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For more than a century, major meningococcal meningitis epidemics have occurred every 10 to 12 years in what is known as the African meningitis belt, which stretches from Senegal to Ethiopia.[1-3] The majority of these epidemics have been caused by group A *Neisseria meningitidis*, and incidence rates have been as high as 500 cases per 100,000 population, with most cases occurring in persons between 1 and 29 years of age.[4,5] In 2009, more than 50,000 cases of group A meningococcal meningitis were reported in northern Nigeria.[6] Because of the epidemic potential and high disease burden of group A meningococcal disease, controlling it is a public health priority in Africa.[1-3,7]

To address this problem, the World Health Organization (WHO) has emphasized case management and reactive emergency vaccination with polysaccharide vaccines.[8,9] Although group A polysaccharide vaccine induces a solid antibody response in persons between 1 and 29 years of age and has been shown to be effective in African field trials,[10-12] reactive vaccination campaigns are expensive and logistically difficult, and they have not eliminated meningococcal epidemics. In addition, the immunity induced by polysaccharide vaccines is short-lived and has little or no effect on carriage.[13,14]

In response to the need for more effective meningococcal vaccines in Africa, the Meningitis Vaccine Project (MVP), a partnership between the WHO and the Program for Appropriate Technology in Health (PATH), an international nonprofit organization, was established in 2001 with funding from the Bill and Melinda Gates Foundation. The goal of this partnership is to eliminate epidemics of group A meningitis through the development, testing, licensure, and introduction of a group A meningococcal conjugate vaccine that would be affordable in Africa.[15] The new group A meningococcal conjugate vaccine, referred to here as PsA-TT, costs less than 50 cents per dose.[15,16] After the completion of a phase 1 study involving healthy adults in India,[17] two clinical studies were conducted to evaluate the safety and immunogenicity of a single dose of the PsA-TT vaccine as compared with that of a licensed vaccine with activity against meningococcal polysaccharide groups A, C, Y, and W135 in persons between 1 and 29 years of age. We report the results of both studies.

Methods

Study Design and Oversight

Studies A and B were double-blind, randomized, controlled, comparative trials designed to evaluate the immunogenicity and safety of a single injection of PsA-TT vaccine in healthy residents of the study areas; study A was also designed to evaluate the ability of the vaccine to induce immunologic memory. Study A was conducted among healthy children between 12 and 23 months of age at Centre pour le Développement des Vaccins in Bamako, Mali, and the Medical Research Council Laboratories in Basse, Gambia. Study B was conducted among healthy children and adults between 2 and 29 years of age in Mali, in Gambia, and at the Institut de Recherche pour le Développement in Niakhar, Senegal.

The participants in study A were 601 children, 12 to 23 months of age, who were randomly assigned in equal proportions to receive PsA-TT (MenAfriVac, Serum Institute of India); a reference vaccine, PsACWY (Mencevax ACWY, GlaxoSmithKline); or a control vaccine, *Haemophilus influenzae* type b conjugate Hib-TT, (Hiberix, GlaxoSmithKline). Ten months later, 589 of the participants underwent within-group randomization to receive a booster vaccination with a full dose of PsA-TT, one-fifth of a full dose of PsACWY, or a full dose of Hib-TT.[18] In study B, participants between 2 and 29 years of age were recruited and evenly stratified according to age into three groups: 2 to 10 years, 11 to 17 years, and 18 to 29 years. They were then randomly assigned in a ratio of 2:1 to receive the PsA-TT vaccine or the PsACWY vaccine. Immunogenicity, reactogenicity, and short-term safety were assessed 4 weeks after both the primary and booster vaccinations were administered in study A and 4 weeks after the primary vaccination in study B. Immunogenicity was also evaluated 10 months after primary vaccination and 1 week after booster vaccination in study A. Only the staff members at the study sites who were responsible for preparing the vaccines were aware of group assignments; the subjects, other site staff members, investigators, laboratory personnel, and sponsors were unaware of group assignments throughout the study period.

The main criteria for exclusion were a history of vaccination against *N. meningitidis* within the preceding 6 years, known exposure to *N. meningitidis*

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within the preceding 3 months, allergy or known hypersensitivity after any vaccination, and a positive pregnancy test. (Further details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Both studies were conducted in accordance with the study protocols (available at NEJM.org).

The trials were designed and conducted in accordance with the Good Clinical Practice Guidelines established by the International Conference on Harmonization and with the Declaration of Helsinki.

The Serum Institute of India provided all vaccines except the Mencevax vaccine used in study A, which was provided by GlaxoSmithKline; all vaccines were provided free of charge. All authors contributed to the writing of the study and participated in the decision to publish the manuscript. Each participating community provided permission to conduct the study, and written informed consent was obtained before enrollment from all subjects between 18 and 29 years of age and from all parents or guardians of subjects younger than 18 years of age. Information on approval of the study by various committees charged with monitoring research involving human subjects is provided in the Supplementary Appendix.

VACCINES

A reconstituted dose of PsA-TT vaccine (0.5 ml) contained 10 μg of group A polysaccharide conjugated to 10 to 33 μg of tetanus toxoid, 0.3 mg Al^{3+} in $AlPO_4$ (aluminum phosphate) as adjuvant, TRIS buffer, 0.01% thimerosal, and 0.9% sodium chloride. A reconstituted dose of reference vaccine, PsACWY (0.5 ml), contained 50 μg of purified polysaccharide from each of the *N. meningitidis* groups A, C, Y, and W135; lactose; sodium chloride; and water for injection. A reconstituted dose of the control vaccine, Hib-TT (0.5 ml), used in study A contained 10 μg of the polyribosylribitol phosphate capsular polysaccharide of *H. influenzae* type b (Hib) conjugated to 20 to 40 μg of tetanus toxoid, lactose, and sodium chloride. Vaccines were injected intramuscularly in the right deltoid unless participants were younger than 2 years of age, in which case, the right thigh was injected; the one-fifth booster doses of the PsACWY vaccine were administered subcutaneously in the right deltoid.[19]

IMMUNOLOGIC EVALUATION

Blood samples were obtained before vaccination and 4 weeks after the primary vaccination in study A and the single vaccination in study B. In study A, samples were also obtained before the booster vaccination (i.e., 10 months after primary vaccination), 1 week and 4 weeks after the booster vaccination. For each blood sample collected, a thick smear was examined for malaria. The immunogenicity of the PsA-TT vaccine and the group A component of the PsACWY vaccine was assessed by measuring the activity of group A serum bactericidal antibody (SBA) with rabbit complement and performing a group A–specific IgG enzyme-linked immunosorbent assay (ELISA). Measurement of SBA titers was performed at the Health Protection Agency, Manchester, United Kingdom,[20] and the ELISA was performed at the Centers for Disease Control and Prevention (CDC), Atlanta, with the use of the standard reference serum CDC1992.[21] The SBA reference strain was F8238, and titers were expressed as the reciprocal of the final serum dilution, resulting in a colony-count reduction of at least 50% after 60 minutes of incubation.

The primary end point for immunogenicity was seroconversion, defined as an SBA titer that was at least four times as high as that at baseline 28 days after immunization (e.g., baseline titers ≤4 required postimmunization titers ≥16). Other end points included a level of group A–specific IgG that was at least 4 times as high as that at baseline, an SBA titer of 8 or more and 128 or more,[22] percentages of subjects with a group A–specific IgG concentration of 2 μg per milliliter or more, geometric mean titer, and geometric mean concentration.

SAFETY EVALUATION

Subjects were observed for 30 minutes after vaccination to record and treat immediate reactions. Subjects were monitored for local and systemic postimmunization reactions during daily home visits for 4 days; adverse events were assessed for 1 month, and serious adverse events were assessed throughout the course of each study. Subjects (or their parents or guardians) were asked about tenderness and induration at the vaccination site; fever, vomiting, and diarrhea (for all subjects) as well as lethargy, irritability, and loss of appetite (for subjects between 1 and 10 years of age) and

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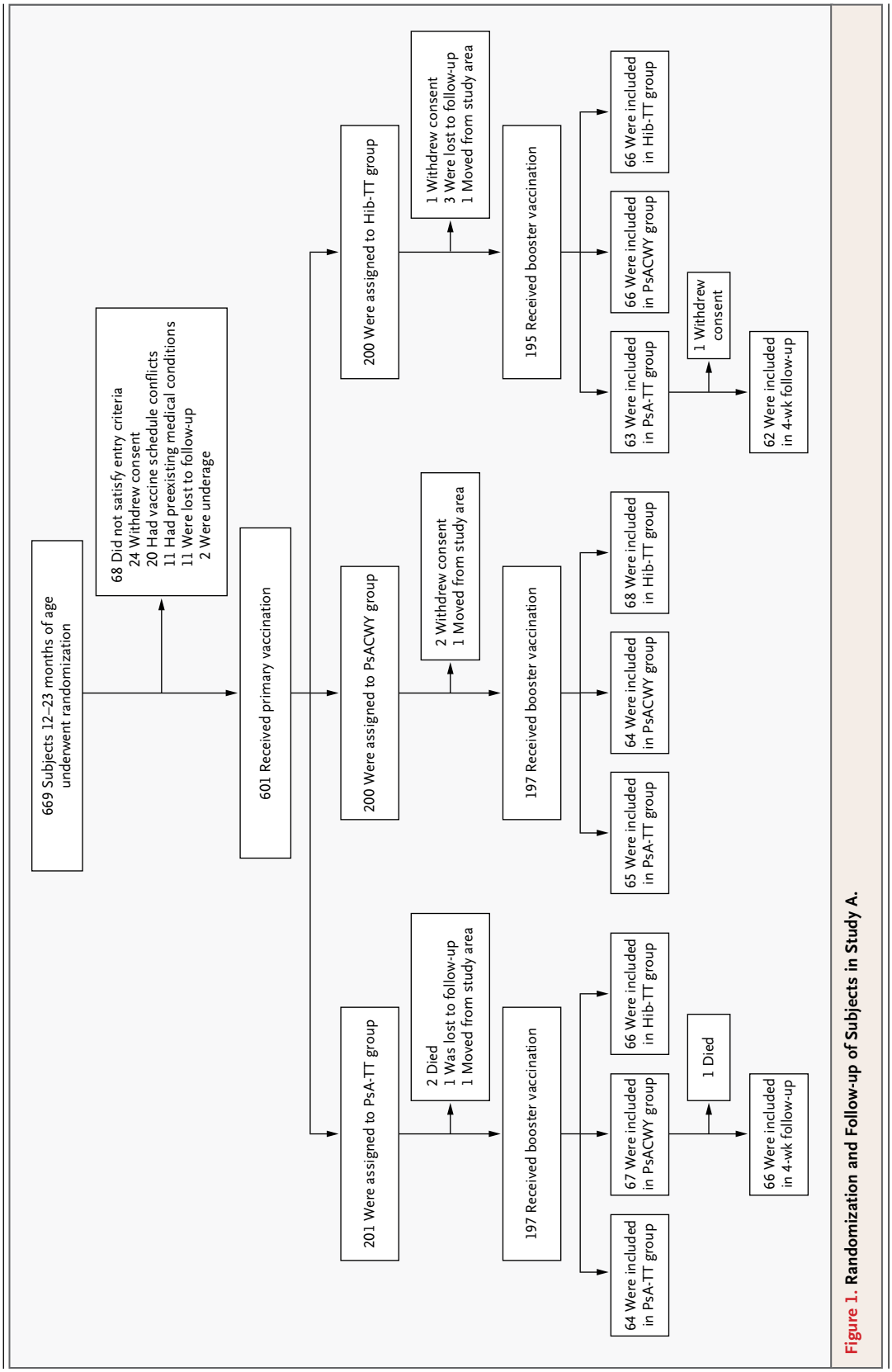

Figure 1. Randomization and Follow-up of Subjects in Study A.

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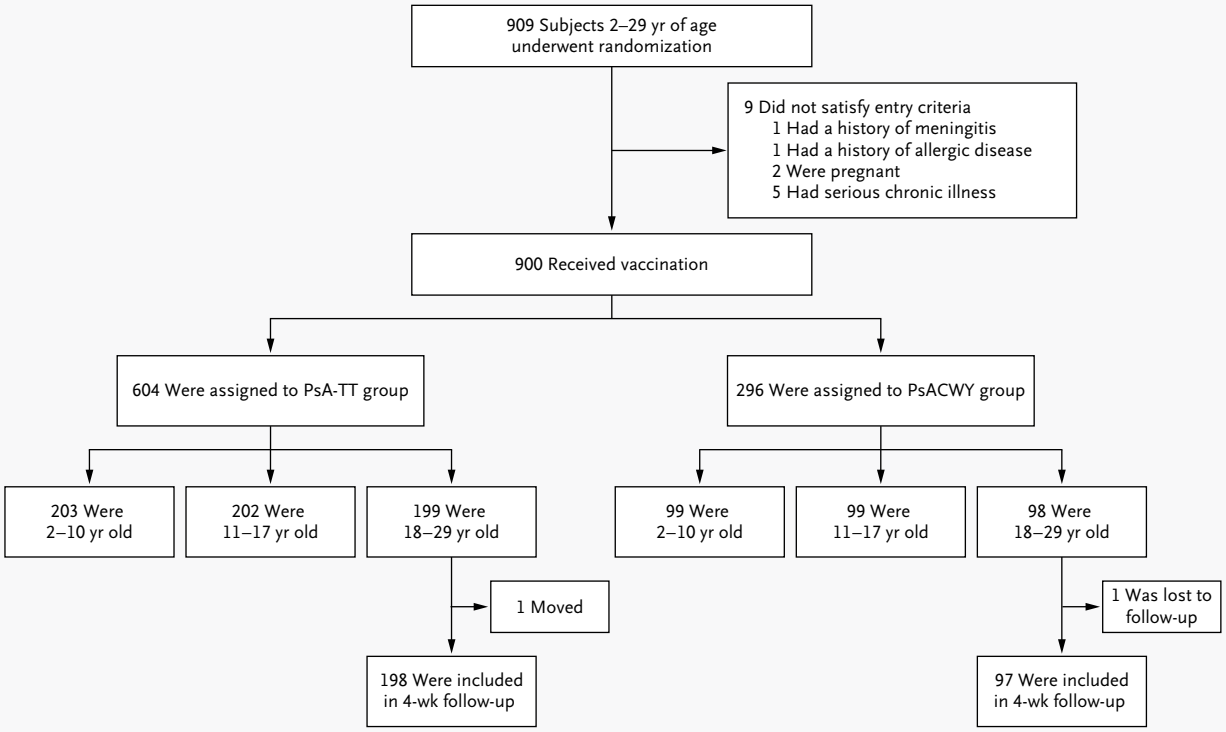

Figure 2. Randomization and Follow-up of Subjects in Study B.

headache, fatigue, myalgia, and arthralgia (for subjects older than 10 years of age). Solicited reactions within 4 days were presumed to be vaccine-related. Assessment of causality in the case of unsolicited adverse events was performed by the study investigators at each site. A data and safety monitoring board was established for studies A and B.

STATISTICAL ANALYSIS

The primary objective of each study was to demonstrate that the PsA-TT vaccine was not inferior to the PsACYW vaccine, as determined by the achievement of an SBA titer that was at least four times as high as that at baseline (noninferiority margin for the titer increase, 0.10). The 95% confidence interval for the difference in the proportions of subjects with this response in the PsACWY and PsA-TT groups was calculated with the use of the Miettinen–Nurminen method.[23] If the upper limit of the confidence interval was less than 0.10, the PsA-TT vaccine was considered to be noninferior to the PsACWY vaccine. The exact 95% confidence intervals for the binomial proportions were calculated for all applicable secondary end points in each vaccine group. The Cochran–Mantel–Haenszel test was used to compare the proportions between vaccine groups with adjustment for age in study B. Student's t-test and Fisher's exact test were used to compare the groups as appropriate. Reverse cumulative distribution curves were generated 4 weeks after primary immunization. All immunogenicity and safety analyses were conducted in the intention-to-treat population. Missing values were treated as missing at random. Data were analyzed with SAS software, version 9.1.3. Calculations of the sample size required for the noninferiority assessment were based on formulas derived by Farrington and Manning[24] (see the Supplementary Appendix for details).

RESULTS

STUDY POPULATION

In study A, among the 669 subjects who underwent randomization, 601 (300 in Mali and 301 in the Gambia) received the primary vaccination between September 18 and November 6, 2006; and 589 received a booster vaccination 10 months later (Fig. 1). In study B, among the 909 subjects who underwent randomization, 900 were vacci-

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Table 1. Immunogenicity Results in the Two Studies.*

Vaccine	Week 0, Preprimary	Week 4, Postprimary	Week 40, Prebooster	Week 41, 7 Days after Booster	Week 44, 28 Days after Booster
Study A — 12–23 mo of age					
			Serum Bactericidal Antibody GMT (95% CI)		
Primary					
PsA-TT	14.3 (9.9–20.7)	6234.5 (4947.9–7855.7)†	1167.9 (873.7–1561.3)†		
Booster					
PsA-TT			1130.6 (666.0–1919.2)	21,720.7 (17,706.0–26,645.6)‡	10,037.4 (7884.5–12,778.2)‡
PsACWY			1735.6 (1136.3–2650.8)	8679.1 (7135.4–10,556.8)‡	5048.3 (4144.0–6149.9)‡
Hib-TT			801.3 (457.6–1403.1)	1448.2 (918.3–2283.7)‡	1649.1 (1022.7–2659.3)‡
Primary					
PsACWY	16.2 (10.9–24.1)	365.3 (248.7–536.5)†	47.2 (31.1–71.6)†		
Booster					
PsA-TT			42.9 (20.8–88.3)	12,214.2 (9435.7–15,810.8)	6708.9 (5097.6–8829.5)
PsACWY			61.3 (28.2–133.0)	2294.5 (1799.6–2925.4)‡	692.4 (379.9–1261.9)‡
Hib-TT			40.5 (20.1–81.5)	103.4 (51.1–209.1)‡	190.8 (91.1–399.4)‡
Primary					
Hib-TT	12.6 (8.7–18.2)	60.9 (39.8–93.2)	52.6 (34.1–81.0)		
Booster					
PsA-TT			42.6 (20.3–89.4)	14,063.4 (10,939.9–18,078.9)‡	9342.9 (7043.8–12,392.4)‡
PsACWY			66.0 (30.8–141.5)	4418.6 (3281.0–5950.7)‡	1562.2 (957.7–2548.4)‡
Hib-TT			51.2 (23.5–111.5)	76.3 (35.2–165.4)	268.1 (128.0–561.5)
			Group A–Specific IgG GMC (95% CI) *μg/ml*		
Primary					
PsA-TT	0.1 (0.1–0.1)	18.2 (16.0–20.7)†	1.0 (0.9–1.3)†		
Booster					
PsA-TT			1.0 (0.8–1.4)	69.2 (49.6–96.5)‡	38.1 (25.5–57.2)‡
PsACWY			1.1 (0.8–1.5)	18.3 (13.9–24.2)‡	15.0 (11.6–19.3)‡
Hib-TT			1.0 (0.7–1.4)	1.1 (0.8–1.5)‡	1.1 (0.7–1.6)‡
Primary					
PsACWY	0.1 (0.1–0.1)	1.5 (1.2–1.9)†	0.4 (0.4–0.5)†		
Booster					
PsA-TT			0.4 (0.3–0.5)	34.0 (24.9–46.3)	38.1 (29.7–48.9)
PsACWY			0.5 (0.3–0.7)	3.3 (2.1–5.1)‡	3.2 (2.0–5.1)‡
Hib-TT			0.5 (0.3–0.6)	0.5 (0.4–0.7)‡	0.5 (0.3–0.6)‡

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Primary					
Hib-TT	0.1 (0.1–0.2)	0.1 (0.1–0.1)	0.1 (0.1–0.2)		
Booster					
PsA-TT			0.1 (0.1–0.2)	15.8 (10.7–23.2)‡	15.4 (11.7–20.2)‡
PsACWY			0.1 (0.1–0.2)	1.9 (1.3–2.8)‡	1.8 (1.2–2.6)‡
Hib-TT			0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.2 (0.1–0.2)
Study B — 2–29 yr of age§					
			Serum Bactericidal Antibody GMTs (95% CI)		
Primary					
PsA-TT	223.3 (181.3–274.9)	4712.6 (4336.0–5122.0)†			
PsACWY	316.0 (240.4–415.3)	1191.4 (969.1–1464.6)†			
			Group A–Specific IgG GMC (95% CI) *μg/ml*		
Primary					
PsA-TT	2.1 (1.9–2.5)	65.6 (60.0–71.6)†			
PsACWY	1.9 (1.5–2.3)	12.9 (10.9–15.3)†			

* Values for serum bactericidal antibody with rabbit complement are geometric mean titers (GMTs); IgG values are geometric mean concentrations (GMCs).
† For serum bactericidal antibody titers and IgG levels, P<0.001 by Student's t-test for the comparison of PsA-TT with PsACWY at week 4 in both studies and at week 40 in study A.
‡ For serum bactericidal antibody titers and IgG levels in study A, P<0.001 by Student's t-test for the following comparisons: PsACWY/PsACWY versus PsA-TT/PsA-TT, PsACWY/Hib-TT versus PsA-TT/Hib-TT, PsACWY/PsACWY versus PsA-TT/PsACWY, and Hib-TT/PsACWY versus Hib/PsA-TT at week 41 and week 44, except that P=0.002 for IgG levels at week 41 for PsACWY/Hib-TT versus PsA-TT/Hib-TT. (Slash marks separate the primary and booster vaccines.)
§ The results for the age groups from 2 to 10 years of age, 11 to 17 years of age, and 18 to 29 years of age are available in the Supplementary Appendix.

nated (300 subjects each in Mali, the Gambia, and Senegal) (Fig. 2). All vaccinated subjects were included in the analyses. Immunogenicity data on SBA titers were available for at least 93% of the subjects at each time point in both studies. Demographic and clinical characteristics of the subjects are summarized in the Supplementary Appendix.

IMMUNOGENICITY

Immunogenicity was measured 4 weeks after primary vaccination. In study A, 96.0% of the subjects in the PsA-TT group (95% confidence interval [CI], 92.2 to 98.2) had SBA titers that were at least four times as high as those at baseline, as compared with 63.7% of subjects in the PsACWY group (95% CI, 56.5 to 70.5) and 35.6% of those in the Hib-TT group (95% CI, 28.8 to 42.7). In study B, 78.2% of the subjects in the PsA-TT group (95% CI, 74.7 to 81.5) and 46.2% of those in the PsACWY group (95% CI, 40.4 to 52.1) had titers that were at least four times as high as those at baseline. Similar changes in titer were noted across all age groups. On the basis of guidelines from the European Medicines Agency, the differences between the PsACWY and PsA-TT groups of –32.2 percentage points (95% CI, –39.6 to –25.0%) in study A and –32.0 percentage points (95% CI, –38.5% to –25.4%) in study B support a claim of superiority for the PsA-TT vaccine (P<0.001 for both comparisons).[25]

In studies A and B, the geometric mean SBA titers (Table 1) and the proportions of subjects with SBA titers of 128 or more after vaccination were significantly higher in the PsA-TT group than in the other vaccine groups (for details, see the Supplementary Appendix). Postimmunization levels of group A–specific IgG were significantly higher in the PsA-TT vaccine group than in the other vaccine groups in both studies and across all age groups. (See Table 1 for geometric mean concentrations according to vaccine type, and see the Supplementary Appendix for titers that were at least four times as high as those at baseline and for percentages of subjects with an IgG level of 2 μg per milliliter or more.) Reverse cumulative distribution curves for SBA titers according to study and age group are shown in Figure 3; postimmunization results were consistently better with the PsA-TT vaccine.

PERSISTENCE OF IMMUNOLOGIC RESPONSE

Forty weeks after the primary vaccination in study A, the proportions of subjects who still had an

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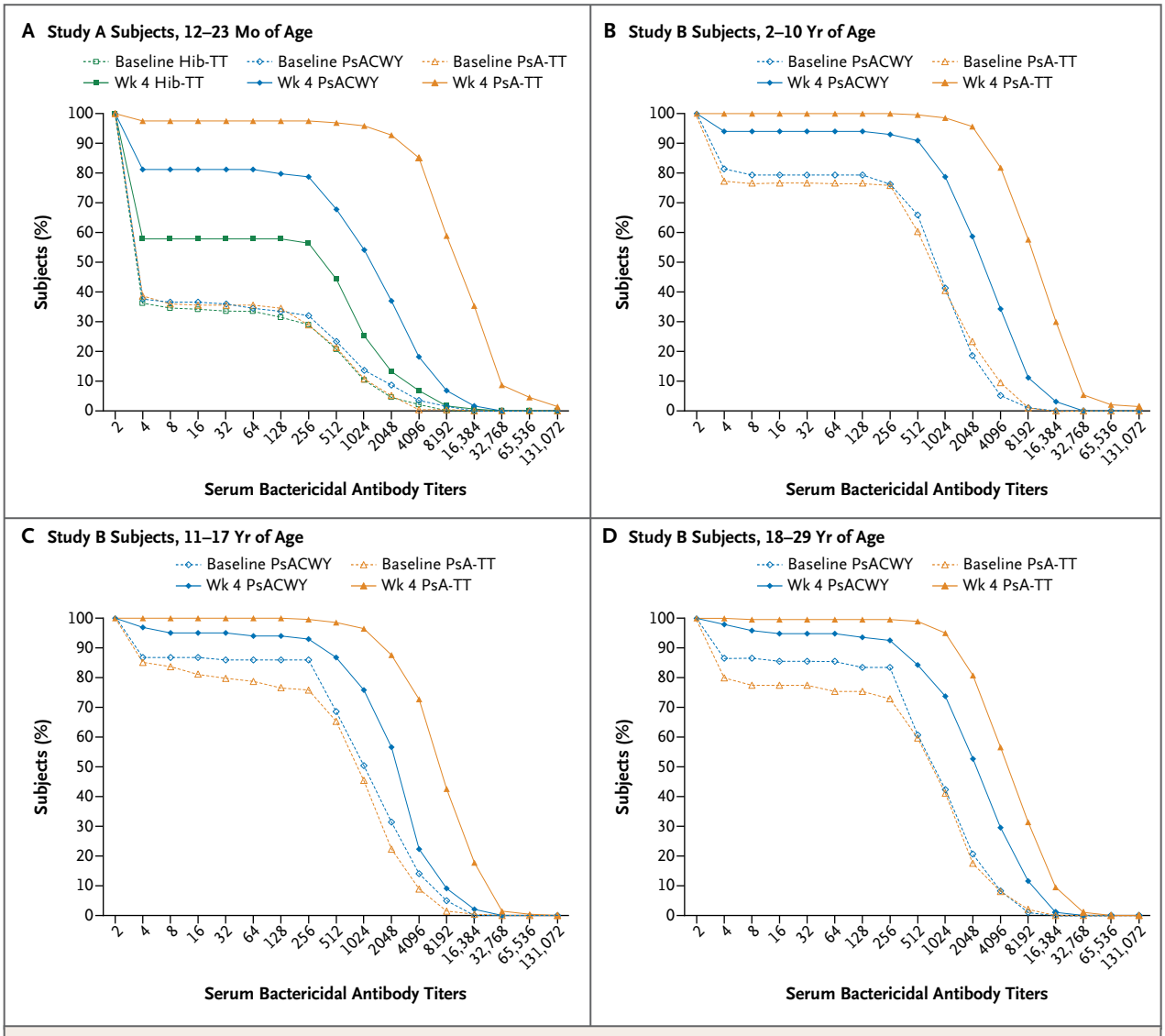

Figure 3. Reverse Cumulative Distribution Curves for Antibody Titers in Studies A and B, According to the Vaccine Group and the Age of the Subjects.

Subjects in study A were randomly assigned to the MenA conjugate vaccine (PsA-TT), a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (*Haemophilus influenzae* type b conjugate vaccine [Hib-TT]); subjects in study B were randomly assigned to PsA-TT or PsACWY. Serum bactericidal antibody activity with rabbit complement was measured at baseline and 4 weeks after primary vaccination. Results are shown for subjects in study A, who were 12 to 23 months old (Panel A), and subjects in Study B, who were assigned by age to one of three groups: those 2 to 10 years old (Panel B), those 11 to 17 years old (Panel C), and those 18 to 29 years old (Panel D). All x-axis values are titers expressed as reciprocals of serum dilutions.

increase by a factor of 4 or more in the SBA titer, as compared with the preimmunization titer, were 82.1% (95% CI, 75.9 to 87.2) in the PsA-TT group, 38.3% (95% CI, 31.4 to 45.5) in the PsACWY group, and 38.3% (95% CI, 31.5 to 45.6) in the Hib-TT group. The geometric mean SBA titers in the three groups were 1167.9 (95% CI, 873.7 to 1561.3), 47.2 (95% CI, 31.1 to 1.6), and 52.6 (95% CI, 34.1 to 81.0), respectively, and the proportions of subjects with SBA titers of 128 or more were 92.3% (95% CI, 87.6 to 95.6), 54.6% (95% CI, 47.3 to 61.7), and 54.1% (95% CI, 46.8 to 61.3), respectively.

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A similar pattern characterized the between-group differences in geometric mean concentrations of group A–specific IgG, which were as follows: 1.0 μg per milliliter (95% CI, 0.9 to 1.3) in the PsA-TT group, 0.4 μg per milliliter (95% CI, 0.4 to 0.5) in the PsACWY group, and 0.1 μg per milliliter (95% CI, 0.1 to 0.2) in the Hib-TT group. Significant differences were also found between the PsA-TT vaccine group and the PsACWY and Hib-TT groups for the other end points based on group A–specific IgG values (a level that was at least four times as high as that at baseline and percentages of subjects with a concentration of 2 μg or more per milliliter); these data are provided in the Supplementary Appendix.

IMMUNOLOGIC MEMORY

To evaluate the ability of the study vaccines to induce immunologic memory, we measured geometric mean SBA titers and geometric mean concentrations of group A–specific IgG 7 days after the booster vaccination in study A. Among the subjects who received one fifth of the full dose of the PsACWY vaccine, geometric mean SBA titers were 8679.1 in the group primed with the PsA-TT, 2294.5 in the group primed with PsACWY, and 4418.6 in the group primed with Hib-TT. Among subjects who received PsA-TT as the booster dose, the geometric mean SBA titers were 21720.7 in the group primed with PsA-TT, 12214.2 in the group primed with PsACWY, and 14063.4 in the group primed with Hib-TT (Table 1). Serologic data recorded 28 days after the administration of boosters, summarized in Table 1, showed similar trends.

SAFETY

Postimmunization reactions and adverse events are shown in Table 2. No reactions occurred immediately after immunization. Rates of injection-site and systemic reactions during the first 4 days after immunization and rates of adverse events during the first 28 days after immunization were similar among vaccine groups. However, induration in study A and tenderness in study B were reported more frequently after primary vaccination in the PsA-TT group, whereas vomiting in study A and fatigue in study B were reported more frequently in the PsACWY group. Diarrhea (in study A), headache (in study B, among subjects 11 to 29 years of age), and fever (in study B, among subjects in all age groups — 2 to 29 years of age) were the most frequently reported systemic postimmunization reactions after primary vaccination. Local and systemic postimmunization reactions were transient and mild and resolved without sequelae.

Commonly reported adverse events included malaria, respiratory infections, gastroenteritis, and conjunctivitis. All adverse events resolved without sequelae, and no vaccine-related adverse events were recorded. In study A, 16 serious adverse events were reported within 2 years after primary vaccination, and in study B, 5 serious adverse events in 5 subjects were recorded within 1 year. In study A, 5 of the 16 serious adverse events were fatal; no deaths were reported in study B. In both studies there were no significant differences among vaccine groups with respect to serious adverse events after vaccination (Table 2). For detailed data on solicited local and systemic reactions, adverse events, and serious adverse events, see the Supplementary Appendix.

DISCUSSION

The level of SBA activity correlates with the degree of protection against meningococcal disease.[26,27] An SBA titer at least four times as high as that at baseline is accepted as a criterion for seroconversion and has been used to support the licensing of the meningococcal conjugate vaccines Menactra (Sanofi Pasteur) and Menveo (Novartis) in the United States.[28,29] This criterion can be particularly difficult to meet in a population with high baseline titers of antibodies against *N. meningitidis*. Among the subjects in study B who were older than 2 years of age, 75% had baseline functional antibody titers of 128 or higher. Nonetheless, we found that the criterion of an SBA titer at least four times as high as that at baseline worked well across all age groups in comparing the immunogenicity of the PsA-TT conjugate vaccine with that of the reference polysaccharide vaccine, PsACWY. The higher proportion of responses in the PsA-TT group than in the polysaccharide group indicated that the conjugate vaccine was superior.[25]

The maintenance of antibody levels over time is a key determinant of immunologic protection; when antibody levels decline, protection wanes, even if vaccinees are primed for the development of immunologic memory.[30] The proportion of subjects with persistent antibody responses at 40 weeks was significantly higher with PsA-TT

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Table 2. Reactions and Adverse Events in the Two Studies.

Immunization and Vaccine Group	Total No. of Subjects	Local Reactions, ≤4 Days after Immunization		Systemic Reactions, ≤4 Days after Immunization		Adverse Events, ≤28 Days after Immunization		Serious Adverse Events, ≤280 Days after Immunization or 450 Days after Booster*	
		no.	% (95% CI)	no.	% (95% CI)	no.	% (95% CI)	no.	% (95% CI)
Study A, 12–23 mo of age									
Primary									
PsA-TT	201	27	13.4 (9.0–18.9)†	33	16.4 (11.6–22.3)	69	34.3 (27.8–41.3)	3‡	1.5 (0.3–4.3)
PsACWY	200	10	5.0 (2.4–9.0)†	31	15.5 (10.8–21.3)	62	31.0 (24.7–37.9)	5	2.5 (0.8–5.7)
Hib-TT	200	19	9.5 (5.8–14.4)	31	15.5 (10.8–21.3)	53	26.5 (20.5–33.2)	1	0.5 (0.0–2.8)
Booster									
PsA-TT/PsA-TT	64	2	3.1 (0.4–10.8)	8	12.5 (5.6–23.2)	3	4.7 (1.0–13.1)	0	0 (0.0–5.6)
PsA-TT/PsACWY	67	0	0 (0.0–5.4)	8	11.9 (5.3–22.2)	5	7.5 (2.5–16.6)	1§	1.5 (0.0–8.0)
PsA-TT/Hib-TT	66	0	0 (0.0–5.4)	4	6.1 (1.7–14.8)	4	6.1 (1.7–14.8)	0	0 (0.0–5.4)
PsACWY/PsA-TT	65	1	1.5 (0.0–8.3)	6	9.2 (3.5–19.0)	7	10.8 (4.4–20.9)	2§	3.1 (0.4–10.7)
PsACWY/PsACWY	64	0	0 (0.0–5.6)	11	17.2 (8.9–28.7)	6	9.4 (3.5–19.3)	1¶	1.6 (0.0–8.4)
PsACWY/Hib-TT	68	1	1.5 (0.0–7.9)	4	5.9 (1.6–14.4)	7	10.3 (4.2–20.1)	1	1.5 (0.0–7.9)
Hib-TT/PsA-TT	63	1	1.6 (0.0–8.5)	12	19.0 (10.2–30.9)	5	7.9 (2.6–17.6)	0	0 (0.0–5.7)
Hib-TT/PsACWY	66	0	0 (0.0–5.4)	5	7.6 (2.5–16.8)	12	18.2 (9.8–29.6)	0	0 (0.0–5.4)
Hib-TT /Hib-TT	66	1	1.5 (0.0–8.2)	9	13.6 (6.4–24.3)	6	9.1 (3.4–18.7)	1	1.5 (0.0–8.2)
Study B, 2–29 yr of age‖									
Primary									
PsA-TT	604	34	5.6 (3.9–7.8)**	18	3.0 (1.8–4.7)	56	9.3 (7.1–11.9)	2	0.3 (0.0–1.2)
PsACWY	296	5	1.7 (0.6–3.9)**	5	1.7 (0.6–3.9)	28	9.5 (6.4–13.4)	3	1.0 (0.2–2.9)

* For study B, data apply to serious adverse events 392 days after immunization.

† P=0.005 by Fisher's exact test for the comparison of PsACWY with PsA-TT. The difference was mainly due to an excess of indurations reported at one site (Mali).

‡ A total of 10 serious adverse events were reported after primary immunization, 2 of which occurred in one subject in the Hib-TT group: 2 cases of bronchopneumonia 106 and 272 days after immunization. Two cases of serious adverse events resulted in death: protein energy malnutrition and acute gastroenteritis 226 and 250 days after immunization in the PsA-TT group.

§ After the booster immunization, a total of 6 serious adverse events were reported in 6 subjects. Three cases of serious adverse events resulted in death: one from complication of marasmus 42 days after immunization in the PsA-TT/PsACWY group, one from cerebral malaria 356 days after immunization in the PsACWY/PsA-TT group, and one from hemorrhage caused by internal injuries resulting from a car accident 398 days after immunization in the PsACWY/PsA-TT group.

¶ One serious adverse event was a case of meningococcal A meningitis in the PsACWY/PsACWY group, which occurred in Mali at the end of the 2008 dry season in a 2-year-old boy. He was promptly treated and recovered without sequelae. Serologic results subsequently revealed that he had a response to primary vaccination with the PsACWY vaccine, but the immunologic response subsided rapidly to preimmunization antibody levels. The subject had a response to a booster of PsACWY vaccine (one fifth of a dose), but the immunologic response again subsided rapidly to preimmunization antibody levels, with no evidence of an anamnestic response.

‖ The results for the age groups from 2 to 10 years of age, 11 to 17 years of age, and 18 to 29 years of age, are available in the Supplementary Appendix. Systemic reaction reported for Study B includes fever, vomiting and diarrhea. See the Supplementary Appendix for details.

** P=0.01 by the Cochran–Mantel–Haenszel test for the comparison of PsACWY with PsA-TT after adjustment for age group; the difference was due to more reports of tenderness in the PsA-TT group than in the PsACWY group.

than with PsACWY, which suggests that recipients of the PsA-TT vaccine would have the benefit of a longer period of protection.

Conjugate vaccines, by recruiting T-helper cells, induce immunologic memory,[31] whereas T-cell–independent polysaccharide vaccines are characterized by hyporesponsiveness after repeated administration.[32] In study A, 7 and 28 days after a booster vaccination with PsACWY at one fifth of the full dose (10 μg), subjects who had been primed with the PsA-TT vaccine had significantly higher geometric mean SBA titers than those who had been primed with the PsACWY or Hib-TT vaccine. The decline in SBA from day 7 to day 28 may be attributable to the early rapid expansion of antibody-secreting cells, and thus increased antibody production, followed by a contraction or down-regulation of antibody-secreting cells as antigen becomes less available. Similar findings have been reported in other studies.[33,34]

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A study conducted in the United States compared the effectiveness of a meningococcal quadrivalent polysaccharide–diphtheria conjugate vaccine with that of a variant of the PsACWY vaccine in children 2 to 10 years of age. Twenty-eight days after immunization, the geometric mean group A SBA titer was greater by a factor of only 0.9 as compared with the PsACWY vaccine (1700 [95% CI, 1512 to 1912], vs. 893 [95% CI, 791 to 1009] with the PsACWY vaccine),[35] whereas in our two studies, titers were greater by factors of 16 (study A) and 3 (study B). Two other meningococcal quadrivalent conjugate vaccines have been shown to be immunogenic in toddlers and young children.[36,37]

Our data show that the new group A meningococcal conjugate vaccine, when tested in Africans between 1 and 29 years of age, had a safety profile similar to that of a licensed polysaccharide vaccine but elicited a significantly stronger and more persistent response from functional antibodies against group A meningococcus. The new vaccine also had the ability to induce immunologic memory. If widespread use of this new vaccine induces herd immunity, as was the case in the United Kingdom with a group C conjugate vaccine, it could potentially decrease epidemics of group A meningococcal infection in the African meningitis belt.

The views expressed in this article are those of the authors and do not necessarily represent the decisions, policies, or views of the WHO.

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