

Introduction of a group A meningococcal conjugate vaccine in sub-Saharan Africa: Cost/savings analysis

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Abbreviations

A/C	Group A and C <i>Neisseria meningitidis</i>
A/C/Y/W	Quadrivalent meningococcal conjugate vaccine
AFRO	African regional office of the World Health Organization
BCG	Bacillus Calmette and Guerin
CBER	Center for Biologics Evaluation and Research
CHOICE	Choosing Interventions that are Cost-Effective
DTPwHibHepB	Diphtheria, Tetanus, Pertussis(whole-cell), <i>Haemophilus influenzae</i> type b, Hepatitis B
DTP3	Diphtheria, Tetanus, Pertussis (third dose)
EPI	Expanded Program on Immunization
GSK	GlaxoSmithKline
ICC	Interagency Coordinating Committee
IR	Incidence rate
Men A	Group A <i>Neisseria meningitidis</i>
Men A conjugate	Group A meningococcal conjugate vaccine
Men B	Group B <i>Neisseria meningitidis</i>
Men C	Group C <i>Neisseria meningitidis</i>
MOH	Ministry of Health
MVP	Meningitis Vaccine Project
OPV	Oral Poliomyelitis Vaccine
PATH	Program for Appropriate Technology in Health
PCR	Polymerase Chain Reaction
PS	Polysaccharide
SIIL	Serum Institute of India Limited
USAID	United States Agency for International Development
VDP	Vaccine Preventable Disease
WHO	World Health Organization
UK	United Kingdom
US	United States
US\$	United States dollars

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Executive Summary

The Meningitis Vaccine Project (MVP) is developing a group A meningococcal conjugate vaccine, (Men A conjugate) to control group A epidemics. The vaccine will also be available as an Expanded Program on Immunization (EPI) vaccine for infants under one year of age. GlaxoSmithKline (GSK) has suspended development of a combination Expanded Program on Immunization (EPI) vaccine that included meningococcal A/C conjugate vaccine (DTPwHibHepBMenA/C). A quadrivalent (A/C/Y/W) conjugate vaccine has been licensed for toddler to adult use in the US. This polyvalent vaccine will not be included in this analysis because it was not designed for African markets, is in limited supply and is very expensive (US\$ 80-US\$ 100 per dose).

The planned strategy for the introduction of the Men A conjugate vaccine in Africa has been influenced by assessments of meningococcal conjugate vaccines that were tested in Africa and Europe. The results of the Group C meningococcal conjugate (Men C conjugate) vaccine introduction in the United Kingdom (UK) where the powerful role of herd immunity has been well documented have been particularly helpful. These studies showed that comprehensive immunization of 1 to 25 year olds induced a powerful herd immunity that resulted in protection of both vaccinated and unvaccinated persons. Detailed carriage studies showed that introduction of the Men C conjugate vaccine had a major inhibitory effect on colonization. Subsequently, public health officials in the Netherlands used these data to design a Men C control program based on immunizing 1 to 18 year olds in a catch-up campaign followed by a single dose for toddlers at 14 months. This approach has been successful with major decreases in cases in vaccinated and unvaccinated persons, including virtual disappearance of the disease in infants. Therefore, comprehensive vaccination of 1 to 29 year olds with a Men A conjugate vaccine is a cornerstone of a meningococcal conjugate vaccine introduction strategy in Africa.

Nonetheless, an important challenge after the catch-up mass immunizations of 1 to 29 year olds is the protection of birth cohorts, particularly as they age into their toddler years.

After detailed consultations with AFRO/VPD three strategies will be analyzed in this document. The first is based on the current EPI schedule that is used in most African countries with vaccines given at birth, 6, 10 and 14 weeks and 9 months. A second approach for countries with poor DTP3 coverage is to conduct serial “follow up” campaigns every five years aimed at providing a single dose for 1 to 4 year olds. A third approach linked with “EPI plus” is to provide a single dose of Men A conjugate vaccine sometime between 12 and 18 months.

To summarize:

For countries with >80% DTP3 coverage; schedule that fits current African EPI schedule

- either two doses of the Men A conjugate vaccine (14 weeks and 9 months) or a single dose at 9 months (a detailed Phase 2 study that will begin in Ghana in April 2008 will determine the safety and immunogenicity of both schedules);

For countries with <60% DTP3 coverage

- follow-up campaigns (single dose of Men A conjugate vaccine to 1 to 4 year olds every 5 years)

For countries wishing to expand vaccine delivery beyond 12 months, already with a DTP 3 coverage >85%

- single dose of Men A conjugate vaccine between 12 and 18 months (EPI plus)

African Ministries of Health are faced with demands that dramatically outstrip their resources; hence ministries will have to prioritize the introduction of new vaccines. This document presents an analysis of costs and savings with the introduction of a Men A conjugate vaccine. Two epidemiologic settings will be analyzed: (1) the hyperendemic area of the African meningitis belt that includes Chad, Mali, Ethiopia, Sudan, Burkina Faso, Niger and nine northern states of Nigeria; and (2) the other countries in the meningitis belt (Benin, Cameroon, Central African Republic, Cote d'Ivoire, Eritrea, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Mauritania, Senegal, Togo and Uganda).

We developed a Group A *Neisseria meningitidis* disease burden model for a hypothetical country of 12 million located in the meningitis belt using population-based incidence and bacteriologic data from Niger. We then developed costing models for the introduction of Men A conjugate vaccine catch-up campaigns in 1 to 29 year olds and the three proposed strategies to immunize birth cohorts. We then compared these projected costs with the costs of the current reactive strategies using meningococcal A/C polysaccharide (PS) vaccines. We added the potential savings in laboratory costs and health care costs after the introduction of meningococcal conjugate vaccines. We then repeated this process for countries located in the meningitis belt but not considered hyper-endemic.

The analysis shows that there are major cost savings associated with the introduction of a Men A conjugate vaccine. Most of the savings are linked to a switch in vaccines from the A/C PS vaccine that is currently purchased to a less expensive but more potent Men A conjugate vaccine that allows for the implementation of an effective preventive strategy. The least expensive option for immunizing birth cohorts is giving the Men A conjugate vaccine in the EPI schedule either as a single dose at 9 months or as two doses (14 weeks and 9 months). One strategy (single dose of Men A conjugate vaccine at 12 to 18 months) requires a new EPI visit after 12 months that adds new costs.

The potential benefits for the introduction of a Men A conjugate vaccine are enormous. The elimination of epidemic meningitis through a programmed introduction of Men A conjugate vaccine uses many of the lessons learned from polio supplementary immunization activities, yellow fever and measles campaigns. District micro-planning, stock management, vaccination teams, advocacy and communication are all strategies that are well understood by African immunization teams. Linking the Men A conjugate vaccine catch-up campaign with yellow fever or measles campaigns could also decrease costs.

The model used for the computations benefits from the availability of excellent epidemiologic and bacteriologic data from Niger. The model does not include economic benefits from decreased deaths and disability; clearly there are some but they are difficult to quantify. A major strength of the analysis is that the cost of the Men A conjugate vaccine is known: US\$ 0.40 per dose. The analysis strongly suggests that Men A conjugate vaccine introduction strategies are cost effective and should be introduced into hyper-endemic countries as soon as possible. Other countries in the meningitis belt should include the Men A conjugate vaccine as well, but the addition of this vaccine will require new funds.

1 Introduction

1.1 The Meningitis Vaccine Project (MVP)

The Meningitis Vaccine Project (MVP) is a partnership between the World Health Organization (WHO) and PATH that was created in 2001 through a grant from the Bill & Melinda Gates Foundation ⁽¹⁾. The project's goal is to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure and widespread use of conjugate meningococcal vaccines.

Ensuring that this new conjugate vaccine is affordable is one of the core principles of MVP ⁽²⁾. African public health officials have repeatedly emphasized the importance of price as a limiting factor in the sustainable use of vaccines in Africa. This is particularly true in the meningitis belt countries that encompass some of the poorest countries in the world. In order to assure a low-priced, high quality vaccine, MVP has developed a new paradigm for vaccine development; a consortium where the raw materials come from one place, the technology from another, and the manufacturing facility from another. By playing a coordinating role between companies that (a) supply basic materials, (b) provide the technical and scientific know-how, and (c) manufacture the vaccine at an affordable price, the MVP model encourages international partnerships that are focused on addressing a well-defined public health goal within the context of the financial realities of the end user. The low-cost vaccine resulting from this approach will ensure accessibility to countries of the meningitis belt in Africa and sustainable uptake of the vaccine. Broad and sustained uptake is critical for achieving public health impact and meeting the goal of the project. In the long term the MVP strategic plan may be a useful model to develop other orphan vaccines that are currently not available and whose primary markets are low-income countries in the developing world

Clinical lots of the Men A conjugate vaccine were prepared in 2004 and a Phase I clinical study was successfully completed in 2005. Phase II studies began in 2006 in Mali and the Gambia. Immunologic data 4 weeks after 12 to 23 month olds received a single dose of Men A conjugate vaccine showed that the conjugate vaccine was superior to polysaccharide vaccine ⁽⁴⁾. Clinical studies were expanded in 2007 to include 2 to 29 year olds in Senegal, Mali and The Gambia. It is anticipated that the Men A conjugate vaccine will be licensed in India in August 2008. Introduction of the Men A conjugate vaccine into meningitis belt countries will be phased according to disease burden and programmatic strengths.

2 Background

2.1 Need for a cost analysis

Sub-Saharan Africa is burdened with many critical health care problems that include high endemic rates of malaria, HIV/AIDS, epidemic meningitis, malnutrition and cholera to name a few. Ministries of Health are faced with demands that dramatically outstrip their resources; hence ministries have to prioritize the introduction of new vaccines. Epidemic meningitis, as pointed out earlier, is a greatly feared problem and elimination of the threat of epidemic disease would dramatically simplify the public health mission in many meningitis belt countries. Nonetheless, cost analyses must be prepared for all new vaccines that will document the costs and benefits associated with introduction of these new products. The following document presents such an analysis for the Men A conjugate vaccine being developed by MVP. The analysis will not consider a combination vaccine that is no longer

being developed by GSK or a polyvalent conjugate vaccine (Sanofi Pasteur) developed specifically for the US market.

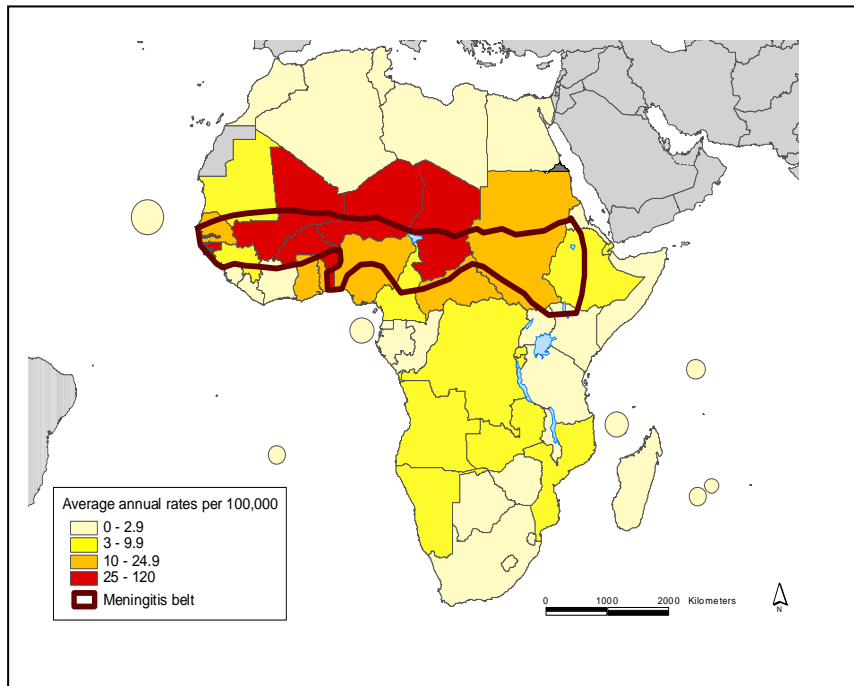
The following analysis studies the problem of epidemic meningitis in two epidemiologic settings; the hyper-endemic area of the meningitis belt that includes Chad, Mali, Ethiopia, Sudan, Burkina Faso, Niger and nine northern states of Nigeria; and the other countries in the meningitis belt with lower incidence rates. Countries located outside the meningitis belt are not discussed. The analysis is more detailed for hyper-endemic countries because of the importance of epidemic meningitis in these areas and the quality of baseline data available from these countries.

2.2 The African meningitis belt

The highest global burden of meningococcal disease occurs in sub-Saharan Africa, in what is known as the “meningitis belt,” a vast area stretching from Senegal in the west to Ethiopia in the east (Figure 1), with an estimated 2003 population of 430 million people in 21 countries. This area is characterized by a particular climate thought to favor the occurrence of epidemic meningitis. During the dry season, between December and June, the area is hot, windy and dusty when meningitis becomes epidemic. The reasons are unclear but are probably related to environmental damage of the upper respiratory tract with enhanced propensity for meningococci to become invasive ⁽³⁾. At the same time, the transmission of *N. meningitidis* is favored by overcrowding and large population displacements due to pilgrimages and traditional markets. This conjunction of factors is thought to explain the large epidemics which occur during this season.

Meningococcal meningitis in sub-Saharan Africa is largely a disease of 5 to 14 year olds. The most comprehensive population-based review of bacterial meningitis in the African meningitis belt was done in Niger after the Group A epidemic in 1995-1996. Investigators summarized clinical and bacteriologic data from 1981 to 1996 ⁽⁹⁻¹⁰⁾. They identified 1 481 infants (less than 12 months) with bacterial meningitis: the principal pathogens were *H. influenzae* (35%), *S. pneumoniae* (26%) and *N. meningitidis* (18%). While *N. meningitidis* accounted for 18 % of cases of meningitis in infants, this represented only 6 % of all cases of meningococcal meningitis, 1 to 29 year olds accounted for over 90 % of isolates.

Figure 1 African meningitis belt showing hyperendemic countries



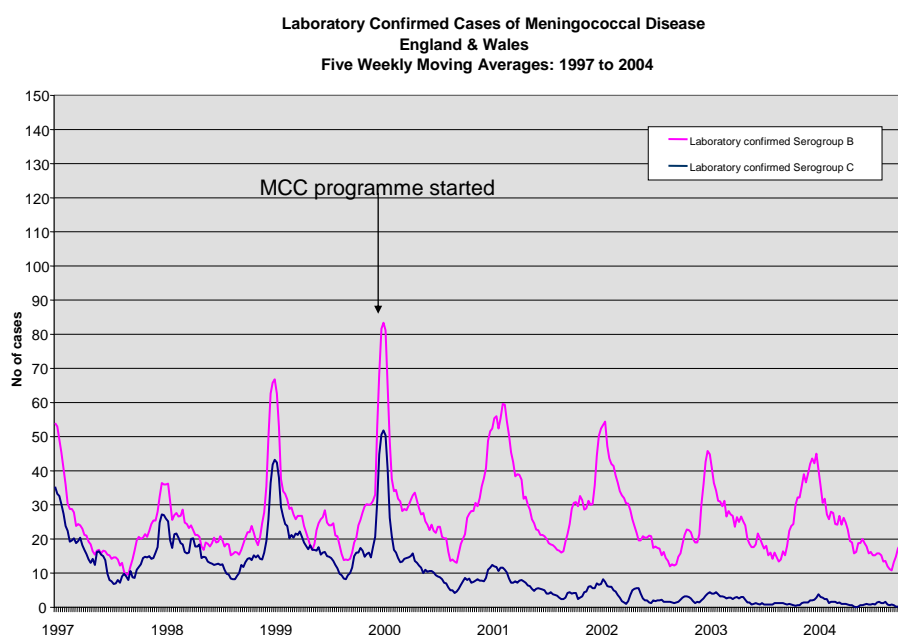
2.3 Vaccination strategies to introduce Men A conjugate vaccines

Conjugate polysaccharide vaccines have had a powerful impact on disease incidence when they have been widely used⁽¹¹⁻¹³⁾. High Hib vaccine coverage has eliminated meningitis due to *H. influenzae*; pneumococcal conjugate vaccine use in US infants has resulted in a major decrease in invasive pneumococcal disease not only in vaccine recipients but in the elderly as well. This effect has been attributed to the ability of the pneumococcal conjugate vaccine to block carriage of vaccine strains, hence impeding circulation of the organism in the general population. A similar effect was noted in the UK after the introduction of a meningococcal conjugate C vaccine.

Up to 1999 the UK was faced with increased number of cases of Men C *N. meningitidis*. In response to this threat the UK asked vaccine manufacturers to develop a monovalent Men C conjugate vaccine. This was successfully accomplished and three products were introduced into the UK in 1999. The UK chose to do a catch-up campaign with a single dose of vaccine in 1 to 18 year olds (later extended to age 25) as well as introducing the vaccine in the UK infant immunization program as a three dose vaccine (3, 4 and 5 months).

The results were dramatically positive⁽¹³⁾, Figure 2). There was a major fall in cases of Men C meningitis that has continued through 2007. Detailed follow-up studies on efficacy in various age groups yielded interesting results. Infants immunized at 3, 4 and 5 months lost their protection as measured serologically by one year; nonetheless, there was little disease in this cohort over time⁽¹⁰⁾. The reason for the continued protection of this at-risk group became clear as evidence mounted in favor of a powerful herd immunity that had been induced by the 1 to 25 year old catch-up campaign. In short, the 1 to 25 year old immunizations led to a major decrease in the circulation of Group C meningococci with protection of the unvaccinated (herd immunity)⁽⁹⁾. An extensive carriage study showed a significant decrease (67%) in the circulation of the epidemic strain in vaccinated teenagers⁽¹¹⁾.

Figure 2 Cases of meningococcal C and B disease in the UK 1997-2004



Extensive modeling studies tested various hypotheses and the most persuasive interpretation of the UK data was that the catch-up campaign in less than 25 year olds resulted in a major protection against colonization such that circulation of the organism in the population was severely restricted⁽¹²⁾. In fact, the UK data was consistent with the hypothesis that control of meningococcal disease in infants in the UK was achieved as a result of the herd immunity induced after a single dose of vaccine in 1 to 25 year olds. These data were used by public health officials in The Netherlands when they decided to introduce a Men C conjugate vaccine⁽¹³⁾. They chose not to offer infant immunizations and instead did a catch-up campaign in 1 to 18 year olds and gave a single dose to toddlers at 14 months. The results are summarized in Table 1. Vaccinating 1 to 18 year olds plus a single dose of Men C conjugate vaccine in toddlers resulted in a striking protection in all age groups whether vaccinated or not vaccinated. Two years after the campaign there was but a single case of Men C meningitis in an infant.

Table 1 Cases of meningococcal C disease in The Netherlands by age and year⁽¹³⁾

Age (yr)	2000	2001	2002*	2003	2004	
0	2	20	13	11	1	Vaccinated cohorts
1	5	16	4	6	1	
2-18	60	164	131	1	1	
19-24	10	19	25	6	1	
25-44	7	18	17	7	6	
>45	21	39	31	11	7	
Total	105	276	221	42	17	

*Introduction of Men C conjugate vaccine in 2002 using strategy of a catch-up campaign in 1-18 year olds and a one-dose schedule at 14 months (no infant doses given)

These data from the UK and The Netherlands are of great interest to MVP. If a Men A conjugate vaccine blocks colonization like the Men C conjugate vaccine the chances for a major public health success are excellent, particularly if the coverage in the catch-up campaign in 1 to 29 year olds is better than 80%, the coverage reached in the UK. In addition, the UK and the data from the Netherlands clearly point to herd immunity extending to infants and suggest that use of a Men A conjugate vaccine could be delayed to 14 months at an age where the conjugate vaccine is more likely to engender long term protection. The above assumption is based on the premise that Group A *N. meningitidis* circulates in much the same way that Men C circulates, i.e., predominantly in socially active teenagers. Men A carriage studies are being planned in several countries from 2008-2010 to research this assumption.

2.4 Men A conjugate vaccines being developed for Africa

2.4.1 MVP Men A conjugate vaccine

MVP is working with three partners to develop a Men A conjugate vaccine: SynCo BioPartners B.V. in Amsterdam for supply of meningococcal polysaccharide A; Serum Institute of India Limited (SII) for supply of tetanus toxoid and vaccine manufacturing; and the Center for Biologics Evaluation and Research of the United States Food and Drug Administration (CBER) for development of a conjugation technology that chemically links the two main components of the vaccine to produce a conjugate product. CBER transferred its conjugation technology to SII, and SII scaled up the process for commercial manufacturing. SII agreed to manufacture a Men A conjugate vaccine at a target price of US\$ 0.40 per dose. Clinical lots of the Men A conjugate vaccine were prepared in 2004 and a Phase I clinical study was successfully completed in 2005⁽¹⁴⁾. The Men A conjugate vaccine will be manufactured at SII and will be available in amounts ranging from 25 million to 40 million doses annually according to vaccine introduction plans. The first 25 million doses will cost US\$ 0.40 per dose and future price increases are linked to a global inflation index.

2.4.2 Men A/C combination vaccine (DTPwHibHepBMenA/C)

GSK has developed a combination vaccine that adds a Men A/C conjugate to its pentavalent (DTPwHibHepB) vaccine. The vaccine is given as an EPI vaccine with doses at 6, 10 and 14 weeks. The vaccine was tested in Phase II trials in the Philippines and Ghana. While the vaccine induced immunity to Group A meningococci the antibody titers fell to low levels by one year. In 2007 GSK withdrew its European Medicines Agency application to license the vaccine under article 57.

2.5 Proposed schedules for the use of Men A conjugate vaccine

2.5.1 Catch-up campaign (single dose to 1 to 29 year olds)

The catch up campaign is an essential step to prevent epidemic meningitis because the strategy is highly likely to create herd immunity.

2.5.2 Protecting birth cohorts

After detailed consultations with AFRO/VPD staff three strategies were chosen for analysis. The first is based on the current EPI schedule that is used in most African countries with vaccines given at birth, 6, 10 and 14 weeks and 9 months. A second approach for countries with poor DTP3 coverage is to conduct serial “follow up” campaigns every five years aimed at providing a single dose for 1 to 4 year olds. A third approach linked with “EPI plus” is to provide a single dose of Men A conjugate vaccine sometime between 12 and 18 months.

Schedule that fits current African EPI schedule for countries with >80% DTP3 coverage

- either two doses of the Men A conjugate vaccine (14 weeks and 9 months) or a single dose at 9 months (a detailed Phase 2 study that will begin in Ghana in April 2008 will determine the safety and immunogenicity of both schedules)

For countries with low, <60%, DTP3 coverage

- follow-up campaigns (single dose of Men A conjugate vaccine to 1 to 4 year olds every 5 years)

For countries wishing to expand vaccine delivery beyond 12 months, already with DTP3 coverage >85%

- single dose of Men A conjugate vaccine between 12 and 18 months (EPI plus)

3 Methods

3.1 Description of the model and assumptions

A model of meningococcal A disease in a population of 12 million over a ten year period was constructed using population-based epidemiologic data from Niger ⁽⁶⁾.

- Country example

The model describes meningitis in a hyperendemic country with a 2005 population of 12 million. (1 to 29 population is 70% of total population; under one population is 4% of total population; yearly population increase 3%). Because age cut offs are not precisely followed during mass immunizations, a figure of 75% was used for the 1 to 29 “target” population.

- Crude meningitis incidence rate and *N. meningitidis* incidence rate ⁽¹¹⁾

The crude incidence rate for meningitis is 100.8 per 100 000 per year; *N. meningitidis* incidence at 55.3 cases per 100 000 per year; 85% of cases group A; case fatality rate 12%; residual morbidity after meningitis (deafness, etc...) 24% ⁽⁶⁾.

- Rates of meningitis for other organisms ⁽⁶⁾

Table 2 shows the average annual incidence (per 100 000) according to pathogen, in Niger, during inter-epidemic years (1981-1994).

Table 2 Rates of meningitis by organism: Niger ⁽⁶⁾

Pathogen	Incidence rate per 100 000	Correction for indeterminate etiology*	Corrected incidence rate per 100 000*
<i>N. meningitidis</i>	25.8	6.8	32.6
<i>S. pneumoniae</i>	14.9	4.0	18.9
<i>H. influenzae</i>	12.3	3.3	15.6
Other	2.6	0.8	3.4
Total “non-<i>N. meningitidis</i>” rate of 37.9 per 100 000			

*reassigns 14.9/100 000 rate of “indeterminate etiology” according to % distribution of known pathogens.

- Rates of *N. meningitidis* during an epidemic year

Table 3 Rates for epidemic meningitis: Niger, single year ⁽⁶⁾

Crude meningitis rate	347.6 per 100 000
<i>N. meningitidis</i> rate (crude IR less non- <i>N. meningitidis</i> IR)	309.7 per 100 000

- Laboratory costs for case investigation ⁽¹⁵⁾

Lumbar puncture is done in 50 % of endemic cases and 10 % of epidemic cases: (Lumbar puncture kit US\$ 2.00; Gram stain \$0.60; Latex agglutination US\$ 15.60, PCR US\$ 6.0 for a negative sample; US\$ 12.00 for a positive sample).

- Effectiveness of Men A conjugate vaccine

Because herd immunity is induced after the catch-up campaign in 1 to 29 year olds all interventions are estimated to have an effectiveness of 95% against Group A *N. meningitidis* that will last at least ten years.

- Vaccination costs (interventions)

Mass vaccination of 1 to 29 year olds with Men A conjugate vaccine:

Vaccine cost US\$ 0.40/dose years 1-5; US\$ 0.43/dose years 6-8; US\$ 0.45/dose years 9-10; 15% handling cost (rounded to US\$ 0.46/dose); administration and operational costs US\$ 0.74/vaccinee (includes auto-destruct syringes at US\$ 0.06/syringe with 10% wastage and disposal boxes at US\$ 1/box with 50% wastage); total cost per vaccinee of US\$ 1.20; vaccine wastage 25%).

- Single dose of Men A conjugate vaccine at 12-18 months; vaccine costs as above; vaccine wastage of 40%; new EPI visit at 14 months was cost at US\$ 1.50 per visit.
- Two doses of Men A conjugate vaccine (14 weeks and 9 months) or a single dose at 9 months; vaccine costs as above; vaccine wastage of 40 % (rest of costs covered by EPI).

- Acute health care costs

Two methods were used to estimate acute health care costs for a case of meningitis:

- Burkina Faso MOH data ⁽¹⁶⁾: US\$ 80 per episode (includes antibiotics, hospital, and transport and clinic costs); sensitivity analysis at US\$ 50 and US\$ 110 were done.
- WHO CHOICE model ⁽¹⁷⁾: 25% population urban; one outpatient visit US\$ 10.42; all cases seen. For hospitalized persons five inpatient days at US\$ 32.08/day; all urban cases hospitalized. 75% population rural; one outpatient visit US\$ 6.14; one third of cases hospitalized; five inpatient days at US\$ 18.85/day (mean of first and second level hospital rate); US\$ 10 antibiotic cost for the non-hospitalized.

- Chronic care costs

Chronic care costs could not be quantified and were not included.

- Vaccine expenditures associated with A/C polysaccharide vaccine

From 1999 to 2003, 109 075 684 doses of A/C PS vaccine were purchased by countries in the hyperendemic area (21 815 137 doses per year). A/C PS vaccine cost in the model calculation

was set at US\$ 0.44 per dose for years 1-4, US\$ 0.50 per dose for years 5-8 and US\$ 0.56 per dose in years 9-10. A 15% surcharge for shipping was included. Administration and operational costs of US \$0.74 per vaccinee were used for either preventive or reactive campaigns. Vaccine wastage was estimated at 25%. The purchases of A/C PS vaccine from 1999 to 2003 for all African countries that purchased vaccine are summarized in Table 5. The five year totals were arbitrarily doubled to provide cost estimates in the ten year model.

Table 4 A/C meningococcal polysaccharide vaccine purchases 1999-2003*

Countries	Average total population 99-03	Average population 1-29 years 99-03	Total doses of A/C purchased 99-03	Average annual A/C purchased 99-03	A/C doses vaccine/ population	A/C doses vaccine/ population 1-29
Burkina Faso	12 270 000	8 908 436	13 139 967	2 627 993	1.071	1.475
Chad	8 106 000	5 570 283	5 637 830	1 127 566	0.696	1.012
Ethiopia	67 286 292	46 184 170	14 146 399	2 829 280	0.210	0.306
Mali	12 271 000	8 869 557	11 744 228	2 348 846	0.957	1.324
Niger	11 152 000	7 983 668	5 863 100	1 172 620	0.526	0.734
Nigeria 9 States	58 603 000	40 172 356	42 746 250	8 549 250	0.729	1.064
Sudan	32 163 310	20 782 538	15 797 910	3 159 582	0.491	0.760
Totals	201 851 603	138 471 008	109 075 684	21 815 137	0.540	0.788
Other meningitis belt countries						
Benin	6 393 839	4 440 411	8 209 086	1 641 817	1.284	1.849
Cameroon	15 417 068	15 417 068	1 621 250	324 250	0.105	0.105
Central African Republic.	3 764 274	2 522 698	747 580	149 516	0.199	0.296
Cote d'Ivoire	16 094 736	10 958 297	1 646 249	329 250	0.102	0.150
Eritrea	3 855 119	2 676 317	887 510	177 502	0.230	0.332
Gambia	1 349 994	859 428	1 390 750	278 150	1.030	1.618
Ghana	20 036 984	13 450 093	9 997 600	1 999 520	0.499	0.743
Guinea	8 236 521	5 575 774	1 932 100	386 420	0.235	0.347
Guinea Bissau	1 408 795	964 816	612 500	122 500	0.435	0.635
Kenya	31 026 377	21 955 967	944 250	188 850	0.030	0.043
Mauritania	2 727 465	1 816 720	71 480	14 296	0.026	0.039
Senegal	9 626 837	6 594 139	6 283 631	1 256 726	0.653	0.953
Togo	4 676 514	3 188 976	936 183	187 237	0.200	0.294
Uganda	24 265 910	17 697 748	1 820 000	364 000	0.075	0.103
Totals	148 880 434	108 118 452	37 100 169	7 420 034	0.249	0.343
Countries with meningitis epidemics outside the belt						
Burundi	6 454 927	4 617 050	2 174 000	434 800	0.337	0.471
Democratic Republic of Congo	49 984 928	35 068 389	103 005	20 601	0.002	0.003
Rwanda	7 931 774	5 571 691	4 895 200	979 040	0.617	0.879
Somalia	9 110 193	6 352 068	300 000	60 000	0.033	0.047
Angola	12 801 181	8 851 583	779 605	155 921	0.061	0.088
Totals	86 283 004	60 460 781	8 251 810	1 650 362	0.096	0.136

**data kindly furnished by Sanofi-Pasteur and GlaxoSmithKline*

4 Disease burden calculations: A ten-year model for a hyperendemic country with a population of 12 million

The following model (Figure 3; Table 5) was constructed using data from the population-based study of meningitis in Niamey, Niger⁽⁵⁾. Meningitis is a common clinical problem in sub-Saharan Africa; a crude incidence rate of 100.8 cases per 100 000 per year predicts that between 12 000 and 15 000 cases will occur annually or a total of over 130 000 cases over a ten-year period. About 80 % of these cases are attributed to three agents, *S. pneumoniae*, *H. influenzae* and *N. meningitidis*. About 20 % of cases are indeterminate and likely to represent disease from one of these three agents but where spinal fluid cultures are not diagnostic. The disease burden due to group A *N. meningitidis* varies from year to year but on average accounts for about one half of the endemic bacterial meningitis disease burden. During meningitis epidemics the vast majority of isolates are group A and during outbreaks attack rates can soar to 500-1 000 per 100 000. Year 5 in the following table and figure represents such an epidemic year with an incidence rate of 309.7 per 100 000

Figure 3 Meningitis in a hyperendemic country with population of 12 million: comparison with reported data (see Table 6)

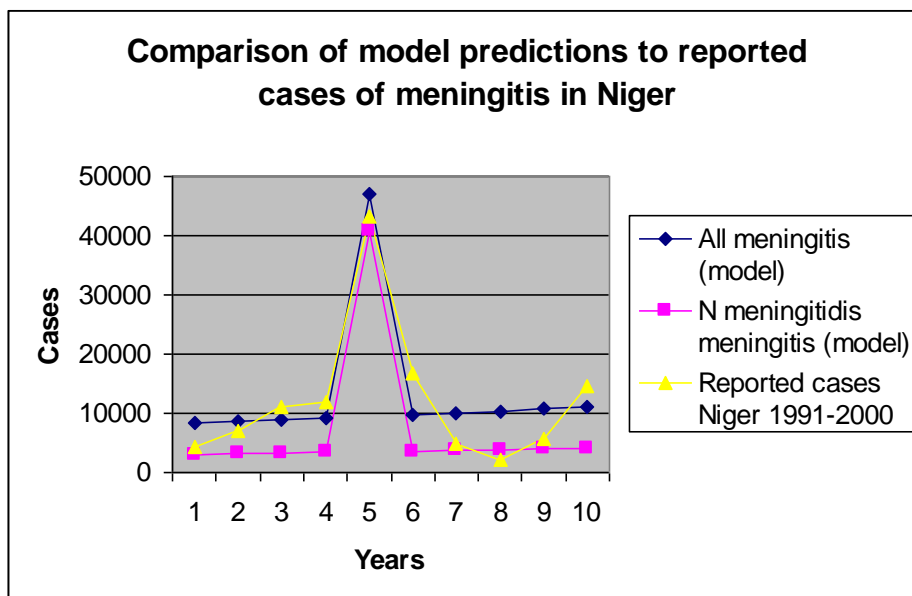


Table 5 Cases and deaths due to *N. meningitidis* group A in a sub-Saharan country over a 10-year cycle; nine years were "endemic" years and a single "epidemic" year ⁽⁵⁾

Year	Population	Total meningitis cases	Cases of Nm	Deaths Nm	Cases of Men A	Deaths due to Men A	Disability due to Men A
Endemic 1	12 000 000	8 460	3 096	372	2 632	316	556
Endemic 2	12 360 000	8 714	3 189	383	2 711	325	572
Endemic 3	12 730 800	8 975	3 285	394	2 792	335	590
Endemic 4	13 112 724	9 244	3 383	406	2 876	345	607
Epidemic 5	13 506 106	46 947	40 802	4 896	34 682	4 162	7 325
Endemic 6	13 911 289	9 807	3 589	431	3 051	366	644
Endemic 7	14 328 628	10 102	3 697	444	3 142	377	664
Endemic 8	14 758 486	10 405	3 808	457	3 237	388	684
Endemic 9	15 201 241	10 717	3 922	471	3 334	400	704
Endemic 10	15 657 278	11 038	4 040	485	3 434	412	725
Total		134 410	72 810	8737	61 888	7 427	13 071

In a single hyperendemic country with a population of about 12 million like Mali, Burkina Faso and Niger, about 62 000 cases of meningococcal A disease and over 7 600 deaths would be expected to occur over a decade in the absence of control measures. During an epidemic year over 35 000 cases would occur. The model should be viewed as illustrative but useful to quantify disease burden and to project potential cost savings. As shown in Figure 2 the real situation is more complex with major meningococcal epidemics spanning at least two years followed by a significant drop in cases. Smaller micro epidemics occur in most years in a background of yearly reactive and preventive immunizations with Men A/C PS vaccine. However, as previously mentioned the effect of PS vaccines is transient and an important motivation for the development of a Men A conjugate vaccine is the ability to create a durable single dose preventive strategy for 1 to 29 year olds that induces herd immunity.

5 Intervention with Men A conjugate vaccine

Conjugate vaccines have had a powerful impact on disease incidence when they have been used widely. For example, when Hib vaccine is comprehensively used meningitis due to *H. influenzae* has been eliminated ⁽⁷⁾. Pneumococcal conjugate vaccine use in infants in the US has gratifyingly resulted in a major decrease in invasive pneumococcal disease in the elderly ⁽⁸⁾. This effect has been attributed to the ability of pneumococcal conjugate vaccine to block carriage of vaccine strains, hence impeding circulation of the organism in the general population. A similar effect has been noted in the UK following the introduction of a meningococcal conjugate C vaccine, where vaccination of 1 to 25 year olds has resulted in a profound decrease in incidence of Men C disease in vaccinees as well as non vaccinees ⁽⁹⁾. While no carriage data after use of a conjugate Men A vaccine are currently available it would

seem likely that introduction of a Men A conjugate vaccine will also result in herd immunity. Table 6 summarizes the potential public health benefit after the introduction of a Men A conjugate vaccine.

Table 6 Ten year public health benefit in a population of 12 million after the introduction of a Men A conjugate vaccine (95% effective)

Men A cases prevented	58 794
Men A deaths prevented	7 055
Morbidity prevented	14 110

6 Costs associated with introduction of a Men A conjugate vaccine

Costing models were developed for the three proposed strategies (Tables 7, 8, 9). All strategies included a catch-up campaign whereby at least 85% of all 1 to 29 year olds would receive a single dose of Men A conjugate vaccine. Strategies to protect birth cohorts differed: one strategy used a single dose of Men A conjugate at 12-18 months; a second used the Men A conjugate as a two or one-dose EPI antigen (14 weeks and 9 months or single dose at 9 months); while the third was a follow-up campaign strategy (campaigns targeting 1 to 4 year olds 6 and 11 years after the initial catch-up campaign in 1 to 29 year olds). This approach is similar to the one developed for measles control in African countries and may be of value to countries with DTP3 coverage less than 60 %.

6.1 Catch-up campaign

Table 7 Catch-up campaign costs, (1 to 29 year olds); country population 12 million

Target population (75%)	9 000 000
Target with 85% coverage	7 650 000
Vaccine doses (25% wastage)	9 562 500 doses
Vaccine costs (US\$ 0.46/dose; shipping & wastage included)	US\$ 4 398 750
Administration costs (US\$ 0.74/vaccinee)	US\$ 5 661 000
Total	US\$ 10 059 750

Meningitis vaccine campaign costs could be significantly reduced if the costs are shared with other initiatives such as measles and yellow fever campaigns. No allowances were made for these potential savings.

6.2 Protection of newborn cohorts over ten years

Table 8 Summary costs for introduction of Men A conjugate vaccine: initial catch-up campaign for 1 to 29 year olds and immunization of birth cohorts over 10 years

Vaccination strategy: Cost US\$			
	One dose Men A conjugate vaccine at 12-18 months	Two doses Men A conjugate vaccine at 14 weeks and 9 months	Single dose of Men A conjugate vaccine at 9 months
Catch-up 1-29 year olds	US\$ 10 059 750	US\$ 10 059 750	US\$ 10 059 750
Vaccine costs	US\$ 2 065 768	US\$ 4 131 536	US\$ 2 065 768
Costs for new EPI month visit	US\$ 4 650 000	0	0
Training, cold chain, logistics	US\$ 500 000	US\$ 500 000	US\$ 500 000
Total	US\$ 17 275 518	US\$ 14 691 286	US\$ 12 625 518

There are differences in costs across the three strategies. The least expensive strategy is a single dose of Men A conjugate vaccine at 9 months, i.e., as part of the EPI schedule. The most expensive strategy is giving a single dose of Men A conjugate vaccine at 12-18 months because it requires a new EPI visit beyond the nine month scheduled visit for measles vaccine. Adding a new visit to the EPI calendar is not a simple matter. In general, EPI has not encouraged the inclusion of booster doses of vaccine until the coverage level for fully immunized infants is at 80 % or better⁽¹⁸⁾. In any case, the single dose Men A conjugate vaccine strategy at 12-18 months calls for a new EPI visit. This change in the EPI calendar will entail new costs. To estimate these costs we used data from the “Diseases Control Priorities Project” to estimate the cost of a new EPI visit at 14 months⁽¹⁹⁾. The cost per fully immunized child for sub-Saharan Africa, in 2001 US dollars, was US\$ 14.21. That figure included five visits and completion of the 6-antigen (DTP, BCG, OPV, measles) schedule with the last visit at nine months. Labor accounted for about 40 % of the costs while facility and vaccine costs took up 35% and 25 % of the costs, respectively.

Estimates were made for the average cost per person with several “scale ups” for immunization coverage. The example that was most pertinent for our analysis was the estimate that a “second opportunity for measles vaccine at a fixed facility” would add US\$ 1 per vaccinee. In order to make allowances for inflation since 2001 that will continue through the planned ten years of immunizations, we used the figure of US\$ 1.50 (not including vaccine costs) as the incremental cost for the addition of an EPI visit at 12-18 months. This per visit cost is lower than the “average visit cost” of US\$ 2.84 because of the savings that are possible when adding visits. For example, detailed costing studies from Peru suggest that the marginal cost of adding a new vaccine is lower than the average cost until volume increases to about 30 %⁽²⁰⁾. A new EPI visit at 12-18 months would add about 12 % in volume unless the public response for a meningitis vaccine was overwhelming. If this were the case, the 12-18 month visit might well attract “zero dose” or partially immunized infants. Lastly, the modeling exercise we present does not take into account the opportunity for other immunizations or needed health interventions that could be given after 12 months, such as booster dose of EPI antigens, second dose measles, vitamin A, impregnated bed nets, etc...

Continuing with our model of a hyper-endemic country in the meningitis belt with a population of 12 million and an annual growth rate of 3% we calculated the number of potential 12-18 month visits over a 10 year span assuming 75% coverage of the cohort. Over the ten years there would be almost 3.1 million new visits that would occur at 14 months; at an average of US\$ 1.50 per visit the additional cost would be about US\$ 4.6 million. Table 9 includes these data in a summary table that compares the three EPI strategies.

The additional costs associated with a new visit at 12-18 months makes a two or one dose strategy within the EPI schedule (14 weeks/9 months or 9 months) more attractive. In addition, the use of a two-dose strategy with an initial dose of a meningitis vaccine at 14 weeks may serve to increase DTP3 coverage because of the interest shown by African mothers to obtain in meningitis vaccines for their children.

6.3 Catch-up campaign of 1 to 29 year olds plus follow-up campaign of 1 to 4 year olds every 5th year (years 6 and 11)

This strategy is similar to that being used to control measles in countries with poorly functioning EPI programs. The initial campaign in 1-29 year olds is identical to that described above but instead of introducing the conjugate into the EPI, follow-up campaigns target 1 to 5 year olds in years 6 and 11. Such a strategy is attractive in countries where DTP3 coverage is less than 60% and if the follow-up campaigns could be linked with measles control activities.

Table 9 Costs to introduce a Men A conjugate vaccine in an initial catch-up for 1 to 29 year olds plus follow-up campaigns in years 6 and 11 for 1 to 4 year olds

	Costs US\$
*Catch-up campaign (initial 1-29 year old)	\$10 059 750
*Follow-up campaign (year 6 1-4 year olds)	\$2 136 343
*Follow-up campaign (year 11 1-4 year olds)	\$2 476 607
Training, cold chain, logistics	\$500 000
Total	\$15 172 700

**Includes vaccine, shipping costs, syringes, safety boxes with wastage.*

7 Potential savings with introduction of a Men A conjugate vaccine

7.1 A/C polysaccharide vaccine purchases and administration costs

Substantial amounts of Men A/C PS vaccine are purchased annually by meningitis belt countries (Table 4). From 1999 to 2003 the 21 countries that are part of the meningitis belt purchased over 150 million doses of A/C PS vaccine, i.e., over 30 million doses annually. These vaccines are used both to respond to epidemics as well as a significant fraction being given as preventive immunizations. For example, Mali in 2002 purchased and administered over 2 million Men A/C PS inoculations in major cities as a precautionary step when Mali was a host country for the Africa football cup.

The model is based on a hyper-endemic country with a population of 12 million. We used an annual vaccine purchase of 2.5 million doses of Men A/C PS vaccine or 25 million doses over the ten years of the exercise. The projected costs for implementing an A/C PS vaccine policy over ten years is about US\$ 30 million. Sensitivity analyses for average annual purchases

from 1.5 million to 3.5 million doses gave a range of ten-year expenses from US\$ 16.7 to US\$ 39 million, (Table 10)

Table 10 Projected A/C PS vaccine and administration costs over 10 years in a hyper-endemic country with a population of 12 million

	Cost (US\$)
Vaccine cost: 25 000 000doses; (US\$ 0.44 years1-4; US\$ 0.50 years 5-8; US\$ 0.56 years 9-10)	US\$ 14 030 000
Vaccine shipping (15%)	US\$ 1 830 000
Administration costs: 18 750 000 doses; (US\$ 0.74/ vaccine; includes syringes and disposal boxes)	US\$ 13 875 000
Vaccine and Administration costs	US\$ 29 735 000

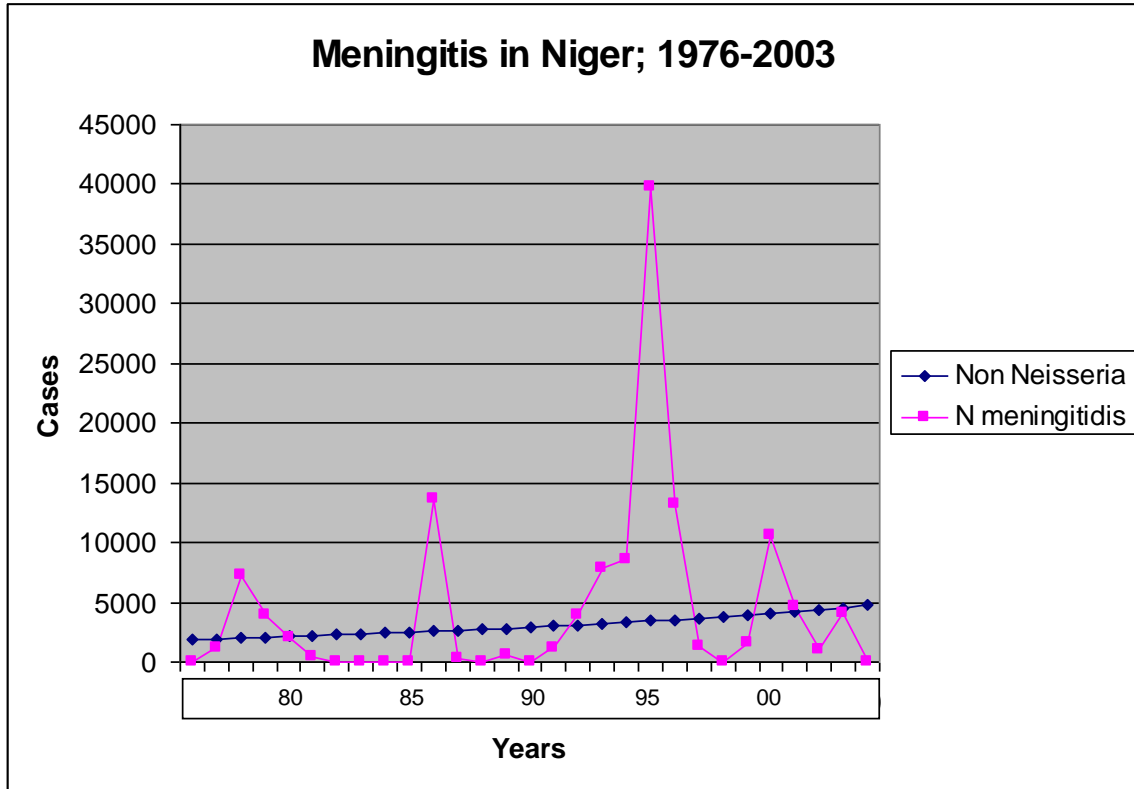
(Sensitivity analysis: Vaccine and administrative costs for 1.5 million doses annually or 15 million doses over ten years is US\$ 16 743 000; vaccine and administration costs for 3.5 million doses annually, 35 million doses over ten years, is US\$ 39 067 000.)

7.2 Impact of A/C PS vaccine

The impact of the use of PS vaccine in meningitis belt countries is difficult to estimate. PS vaccine has been used in response to epidemics where effectiveness is closely related to speed with which reactive vaccination programs are implemented. There is ample documentation that reactive immunizations are often done too late to have a significant impact on epidemics. In addition, meningococcal PS vaccine is given as a preventive strategy as was the case in Mali in 2002 in preparation for the African football cup games. There have been no large population based studies that have measured the impact of the Men A/C PS immunization programs in Africa. What is clear is that meningitis belt countries continue to have epidemics of group A disease despite major purchases and use of PS vaccine; all countries are considered at risk for major epidemics. These data suggest that A/C PS vaccine is having, at best, a modest effect on disease incidence. For example, Niger (Figure 4), a country that purchased over 17 million doses of A/C PS vaccine from 1998 to 2003, (about 2.8 million doses per year), the incidence rate for non-*N. meningitidis* meningitis was calculated to be 37.9 cases per 100 000 using population-based data from Campagne ⁽⁵⁾.

Cases of *N. meningitidis* meningitis were estimated by subtracting non-*Neisseria* cases from total cases reported from Niger. When there were more non-*Neisseria* cases than reported cases the number of *Neisseria* cases was set at 0. This type of analysis highlights the impact of *N. meningitidis* epidemics. During this 30-year period, the Niger population increased from 4.2 to 11.5 million. The number of expected cases of *H. influenzae* and pneumococcal meningitis was at about 5 000 cases in 2003. The number of reported meningitis cases in non-epidemic years is about 3 500 and probably reflects under reporting. Nonetheless, there were clear epidemics in 1978, 1979, 1986, 1993, 1994, 1995, 1996 and 2000, all due to Group A *N. meningitidis*.

Figure 4 Meningitis in Niger 1976-2003



Successful reactive approaches require a functioning surveillance system, the laboratory capability to identify the epidemic strain, an available vaccine supply and a logistic system capable of quickly mounting an immunization campaign. A failure in any one of these steps results in delays and puts the public health goal at risk. In addition, once a PS vaccine is given another two weeks is necessary for the immune response to generate sufficient protective antibody. Since most meningitis epidemics last 6-8 weeks program immunizations must be given no later than 4 to 5 weeks after the onset of the epidemic if the intervention is to be effective. Reactive campaigns that are mounted from vaccine stocks that are locally available are likely to be much more effective because, all things being equal, vaccine delivery is likely to be done more swiftly than when asking for vaccine from the International Coordination Committee. Nonetheless, because meningococcal epidemics are difficult to predict, polysaccharide vaccines are sometimes used preventively in districts considered to be at increased risk (no epidemics for longer than three years). Such interventions are frequently done because a certain quantity of PS vaccine that is in country risks being outdated and discarded. Rather than throwing the vaccine away it is usually given to school aged children or as community immunizations in districts considered to be at high risk. These efforts are often done somewhat arbitrary and their impact has not been well measured.

For the sake of this analysis we have ascribed two possible benefits to the use of polysaccharide vaccine. The first benefit is an increase in community immunity against Group A *N meningitidis*. To estimate this improved immunity we created a ten year model for hyperendemic countries using the PS vaccine data from 1999 to 2003 that has been described (Table 4). We used the following assumptions about length and degree of protection for two age groups: less than three years of age protection at 95% for year 1, 50% for year 2 and no

protection in year three; persons above age three years at 95% year 1, 75% year 2, 50% year 3 and 0% at year 4. In addition in the model we assumed that PS vaccine use was evenly distributed across the 6 month-29 year age group; that there were no repeat vaccinations and that there was no vaccine wastage, i.e., all purchased vaccine was correctly given to 6 month-29 year olds.

Using a static spread sheet analysis that used the country-specific annual doses of vaccine purchased from Table 5, we estimated the % population that would be protected each year for 10 years. We then averaged out the fraction of the population that would have been protected. On average, we estimated that the use of about 220 million doses of PS vaccine over 10 years would have decreased susceptibility of the population by about 22 % given the assumptions presented above.

A second possible impact with reactive use of the PS vaccine is to shorten meningococcal epidemics. Estimating this impact is very difficult because effectiveness depends heavily on the time of introduction of the PS vaccine in relation to the epidemic. All too frequently the vaccine response acquires a political dimension and often PS vaccine is given when an epidemic is ending or has finished. This variability in response time means that the impact of A/C PS vaccine in reactive campaigns in meningitis belt countries is difficult to measure but it is generally conceded to be low. In one study where PS vaccine was available locally and surveillance teams were ready to respond about 23% of cases were prevented⁽⁶⁾. In 2005-2007 the ICC under WHO leadership assessed the time it takes from receiving a request for PS vaccine at WHO/HQ to the initiation of vaccinations in country and has shown that in the best of circumstances it takes at least one month. When one adds the necessary time to mount an immune response the time from declaration of an epidemic to acceptable immunologic protection in a population ranges from 7 to 12 weeks, hence when the epidemic is waning. In the absence of solid data we chose to present data at two levels, zero benefit when vaccinations are begun late and 25% percent reduction (optimal benefit) when vaccine is available locally, surveillance is of a high quality and vaccine is given within 2 weeks of the onset of an epidemic.

In summary, the maximum benefit from the current purchase of about 20 million doses of meningococcal PS vaccine is to decrease the number of cases by about 50%; however, given all of the problems described the likely figure is probably between 10% and 25%. Nonetheless, we chose to analyze the possible benefit from PS vaccine at two levels; a 25% and 50% reduction in cases.

7.3 Savings in laboratory costs

The standard of care in meningitis belt countries is to perform a lumbar puncture in all cases of suspected meningitis in endemic years. Lumbar puncture kits are provided and there has been an increased emphasis on Gram stain and Pastorex testing of spinal fluid specimens. Testing costs have been recently studied by CERMES and their data are used⁽¹⁵⁾. We assumed that about 50% of endemic cases of meningitis undergo lumbar puncture. During epidemics only the first 20-30 cases are studied bacteriologically. Later cases are evaluated clinically. To predict potential savings in laboratory costs we arbitrarily assumed that half of all endemic cases are tested and that 10 % of epidemic cases undergo lumbar puncture. Not all tests are done and for the sake of simplicity a cost of US\$ 15 per test was used to calculate potential savings. The savings in laboratory costs was estimated at US\$ 243 000; Table 12.

Table 11 Potential savings (US\$) in laboratory diagnostic tests after introduction of a Men A conjugate vaccine program

Cases prevented		Laboratory tests not done		Potential savings (US\$ 15/case)		Potential total savings (US\$)
endemic	epidemic	endemic	epidemic	endemic	epidemic	
25 846	32 948	12 923	3 295	US\$ 193 845	US\$ 49 425	US\$ 243 270

7.4 Savings in acute health care costs

There is a paucity of data on costs incurred to manage a case of meningitis in sub-Saharan Africa. We used data from a study of treatment costs that was done in relation to the 2002 W135 *N. meningitidis* epidemic. The Burkina Faso Ministry of Health instituted a policy of being responsible for acute care costs of cases of meningitis. They also convened a task force to study the impact of this policy as well as obtaining better information on the costs incurred by families when meningitis strikes ⁽¹⁶⁾. The study was done in districts that had reached incidence rates of at least 5 per 100 000. The study focused on the initial consultation visit, the hospitalization and costs of supporting the hospitalized family member, laboratory costs and transportation costs. The results of their study are presented in Table 12 and potential health care cost savings are summarized in Table 13.

Table 12 Average costs (US\$) for treatment of a case of meningitis during the 2002 meningitis epidemic in Burkina Faso ⁽¹⁶⁾

Treatment	District health facility		Urban hospitalization	
	CFA	US\$	CFA	US\$
Consultation	100	0.18	1 050	1.91
Hospitalization	1 000	1.82	12 500	22.72
Treatment (antibiotic)	26 000	47.27	26 000	47.27
Follow-up	10 000	18.18	10 000	18.18
Total	37 100	US\$ 67.45	49 550	US\$ 90.08

The total costs per case ranged from US\$ 67 to US\$ 90. We chose to calculate acute health care costs at US\$ 80 per case but included a sensitivity analysis at US\$ 50 and US\$ 110 per case.

Table 13 Potential savings in acute health care costs (MOH data, Burkina Faso 2003)

Men A cases prevented	Costs saved US\$ 80/case	Costs saved US\$ 50/case	Costs saved US\$ 110/case
58 794	US\$ 4 703 520	US\$ 2 939 700	US\$ 6 467 340

In addition, we also used the WHO CHOICE model (Table 14) to calculate health care costs for meningitis using the assumptions that were previously described in section 3.1 ⁽¹⁷⁾. Results using this approach are summarized in Table 14 and yielded an average cost of US\$ 77.68 per

case. In short, the per-case costs were quite comparable using both methods. No attempt was made to factor the dollar value of a death prevented.

Table 14 Acute care costs using WHO CHOICE model

Urban population (25%)		Costs US\$
Health center visit (100%)		161 218
Five day hospitalization (100%)		2 481 709
Total urban		2 642 927
Rural population (75%)		
Health center visit (90%)		256 495
Five day hospitalization (33%)		1 443 653
Antibiotics (outpatient (66%))		464 160
Total rural		2 164 308
Grand total		US\$ 4 807 235 (average US\$ 77.68 per case)

We felt it inappropriate to assign these totals as potential savings with the introduction of a Men A conjugate vaccine because there was some preventive benefit that was accruing to countries with the use of A/C PS vaccine. As previously discussed this benefit, in terms of cases prevented, cannot be accurately estimated and we chose to propose potential savings in acute health care costs using the following assumptions. During a ten-year period comprehensive use of a Men A conjugate vaccine as described would result in more effective prevention of meningitis cases of group A *N. meningitidis* over that realized with the A/C PS vaccine. Two levels of improvement (25% and 50%) were studied, (Table 15).

Table 15 Savings in health care costs (US\$) with Men A conjugate vaccine at 25% and 50% levels of effectiveness of PS vaccine

PS vaccine efficacy	Cases prevented with PS vaccine	Cases prevented with Men A conjugate vaccine	Potential added benefit of Men A conjugate (new disease prevented)	Potential savings in acute health care costs US\$ 80 per case	Potential savings in acute health care costs WHO CHOICE model (US\$)
25%	12 005	58 794	46 789	US\$ 3,743 120	US\$ 3 634 569
50%	24 001	58 794	34 973	US\$ 2,783 440	US\$ 2 716 702

The two methods gave essentially the same results: Introduction of a Men A conjugate vaccine could yield savings in health care costs ranging from US\$ 2.7 to US\$ 3.7 million over a ten-year period.

7.5 Chronic health care costs

About a quarter of acute meningitis survivors are left with some disability. For example, the commonest cause of acquired deafness in Burkina Faso is meningitis. While there are some schools that address the rehabilitation of the chronically ill they are not numerous. For

example, Burkina Faso has four schools that help rehabilitate deaf children. About 2 000 children participate in the program at a cost of about US\$ 80 per year plus room and board. Because of the difficulty in assigning costs due to meningitis no dollar sum was used to compute this cost. Nonetheless, these are real costs to society but they cannot be accurately quantified at the present time.

8 Cost/savings analysis

A comparison of costs and savings associated with the introduction of a Men A conjugate vaccine is presented in Tables 16 and 17. In all instances the introduction of a Men A conjugate vaccine results in significant cost savings.

Table 16 Potential cost savings (US\$) after introduction of a Men A conjugate vaccine

		Potential cost savings US\$
Elimination of purchases of A/C PS vaccine		US\$ 15 860 000
Elimination of reactive and preventive campaigns with A/C PS vaccine		US\$ 13 875 000
Savings in laboratory costs (scenario 2)		US\$ 243 270
Savings in acute health care costs over those realized with A/C PS vaccine	25% reduction in cases	US\$ 3 743 120
	(50% reduction in cases)	(US\$ 2 783 440)
Total potential savings		US\$ 33 721 390

Table 17 Projected cost/savings (US\$) over 10 years by type of intervention

Newborn cohort strategy	Cost to implement US\$	1-29 Catch-up US\$	Total cost US\$	Savings over 10 years* US\$	Average annual savings
Single dose Men A conjugate at 12-18 months	7 215 768	10 059 750	17 275 518	15 485 752	US\$ 1.5 million
Two doses Men A conjugate at 14 weeks and 9 months	4 631 536	10 059 750	14 691 286	18 069 984	US\$ 1.8 million
Single dose of Men A conjugate at 9 months	2 065 768	10 059 750	12 125 518	20 635 762	US\$ 2.1 million
Follow-up campaigns 1 to 4 year olds	5 112 940	10 059 750	15 172 690	17 588 580	US\$ 1.8 million

*Estimated current costs of US\$ 32 761 270 using A/C PS vaccine minus total cost of Men A conjugate vaccine strategy.

The four strategies save between 1.5 million to 2.1 million dollars US. The single dose (9 months) and two-dose (14 weeks and 9 months) EPI strategy are attractive because they do

not require a change in the current EPI schedule. If a country chose to introduce a new EPI visit (12-18 months) the costs for any other services being given would, of course, decrease the attributable costs for delivering a Men A conjugate vaccine.

Most of the savings are linked to a switch from the A/C PS vaccine to a Men A conjugate vaccine that is less expensive but more potent and allows for the implementation of an effective preventive strategy. In addition, there are significant potential savings in health care costs. Nonetheless, there is an important caveat about the “savings” that would accrue from no longer having to purchase A/C PS vaccine. Over the last 20 years A/C PS vaccine purchases in hyper-endemic countries usually took place after the onset of a meningitis epidemic. Donations or purchases of vaccine occurred under urgent or semi-urgent conditions. The introduction of a Men A conjugate vaccine should occur as a planned public health initiative and hopefully in the absence of an epidemic. Under such conditions accessing donor funds would occur outside of the context of fighting an acute epidemic, i.e., it may be more difficult to identify donor support for a Men A conjugate vaccine to be given preventively. Country Interagency Coordinating Committees (ICC) is expected to play a key role in the advocacy for a true preventive strategy aimed at eliminating epidemic meningococcal meningitis.

The potential benefits are considerable. Establishment of herd immunity through the catch-up campaign will eliminate epidemic meningitis due to Group A *N. meningitidis*. District micro-planning, stock management, vaccination teams, advocacy and communication are all strategies that are well understood by African immunization teams and the proposed strategies fit well with these competencies. The ability to link the introduction of a Men A conjugate vaccine with yellow fever or measles campaigns could decrease Men A conjugate vaccine administration costs.

The model used for the disease burden predictions is based on reliable epidemiologic and bacteriologic data from Niger. A major strong point is the knowledge that the Men A conjugate vaccine will cost less than US\$ 0.50 per dose. There are uncertainties in the model, for example, there are no good population-based data on the effect of the A/C PS vaccine on disease reduction. Nonetheless, if the Men A conjugate vaccine eliminates epidemic meningitis while reducing only 25 % of endemic cases; the intervention is still hugely cost saving. In addition, the model as it is presented adds no economic benefit from reductions in death and disability; any benefit will only increase the savings with the Men A conjugate vaccine introduction.

8.1 Cost/savings estimate for entire hyperendemic area

The estimated 2009 population in the hyperendemic area is about 240 million, or about 20 times the size of the model that was developed. Since the epidemiology of bacterial meningitis is similar across these countries the cost/savings estimates can be applied to the entire region (Tables 18-19). These projections are based on the following assumptions: Estimated 2009 population 240 million; annual growth of 3%; ten-year cost of US\$ 15 million to introduce a Men A conjugate either as a “catch-up/EPI” or “catch-up/follow-up” in a population of 12 million. The projected savings for a population of 12 million include a decrease in health care costs (US\$ 2.8 million), laboratory costs (US\$ 0.24 million); elimination of A/C PS vaccine purchases (US\$ 16 million) and A/C PS vaccine administration costs (US\$ 14 million).

Table 18 Costs for the introduction of Men A conjugate vaccines in Chad, Niger, Mali, Burkina Faso, Sudan, Ethiopia and the nine Northern states of Nigeria from 2010-2019, (US\$).

Strategy	Cost for 12 million country model	Projected cost 240 million region
Men A conjugate vaccine catch-up (1-29 yrs plus 1 dose Men A conjugate vaccine at 14 months)	US\$ 17.2 million	US\$ 344 million
Men A conjugate vaccine catch-up (1-29 yrs plus 2 doses Men A conjugate at 14 weeks and 9 months)	US\$ 14.7 million	US\$ 294 million
Men A conjugate vaccine catch-up (1-29 yrs plus a single dose of Men A conjugate at 9 months)	US\$ 12.1 million	US\$ 242 million
Men A conjugate vaccine catch-up (1-29 yrs plus 2 follow-up campaigns (1-4 year olds) in years 6 and 11)	US\$ 15.1 million	US\$ 302 million

Table 19 Potential savings (US\$) after the introduction of Men A conjugate vaccines in all countries

Category	Projected savings for 12 million country model	Projected savings in the 240 million hyperendemic region*
Health care	US\$ 2.8 million	US\$ 56 million
Laboratory	US\$ 0.24 million	US\$ 4.8 million
A/C PS vaccine purchases	US\$ 15.9 million	US\$ 318 million
A/C PS vaccine administration	US\$ 13.9 million	US\$ 278 million
Total potential savings	US\$ 32.84 million	US\$ 656.8 million

* region includes Mali, Burkina Faso, Niger, Chad, Sudan, Ethiopia and the nine Northern states of Nigeria.

The results are impressive. There are potential savings of about US\$ 650 million with the introduction of a less expensive and more effective Men A conjugate vaccines. Admittedly, the “savings” in health care costs as they apply to hospitals and health centers may be more difficult to identify in real terms. However, the out-of-pocket expenses that a family must bear when a child or adolescent develops meningitis are real and these costs would certainly be reduced with fewer cases of Men A meningitis.

8.2 Other meningitis belt countries

Cost/savings calculations after the introduction of Men A conjugate vaccines in other meningitis belt countries are more uncertain. In general, meningitis surveillance is more comprehensive in countries and the excellent population-based incidence and bacteriologic data from Niamey, Niger provided a reliable source of information that we could use to create our model. Such is not the case for other meningitis belt countries. Hence, the ten-year model that was useful for assessing costs and savings in hyper-endemic countries is not as useful for some of these countries. There are countries like Benin and Ghana (Figure 5), with good surveillance systems that show incidence curves not unlike those in the model previously described. However, the majority of other countries do not have well-functioning surveillance systems and calculating accurate disease burden estimates is difficult given the incomplete reporting.

Figure 5 Meningitis in Benin and Ghana: 1993-2003

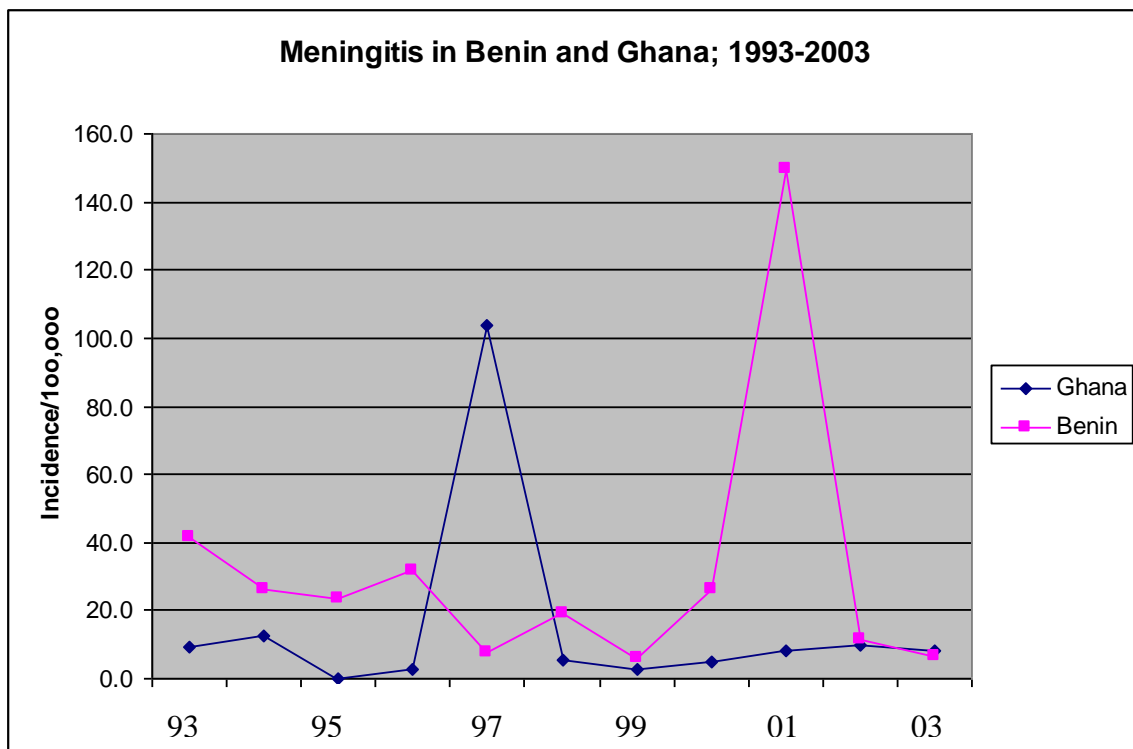


Table 21 lists the reported meningitis cases from 1993 to 2003 for countries in the meningitis belt that are not generally considered to be hyper-endemic. For several countries the number of reported cases is low but they often have isolated years where there are a burst of cases. These years are highly likely to represent group A meningococcal outbreaks. Examples include Benin in 1993 and 2001, Cameroon in 1993, 1998-2001, Central African Republic in 2000-2001, Gambia in 1997, Ghana in 1994, 1997 and 2002, Guinea in 1994, Guinea-Bissau in 1999, Senegal in 1998-1999, Togo in 1997 and 2001 and Uganda in 2003. In short, most if not all meningitis belt countries had at least one or more epidemic years of meningitis, however, the endemic and true epidemic disease burden is not known because of incomplete reporting in many of these countries.

Table 20 **Reported cases of meningitis; other meningitis belt countries: 1993-2003***

Country	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Benin	2 146	1 377	1 294	1 775	442	1 135	380	1624	9 545	764	451
Cameroon	5 372	578	...	178	572	2 887	2 272	1 432	1 822	899	539
Cen. Afr. Rep.	472	155	10	245	757	3 069	2 192	496	179
Cote d'Ivoire	5	3	94	366	220	543	453
Eritrea	7	1	3	0	6	3	2
Gambia	1 390	252	130	63	18
Ghana	1 564	2 173	26	479	19 055	1 049	527	1 003	1 615	2 033	1 666
Guinea	1 578	2 130	238	89	51	58	507	500	579	371	27
Guinea-Bissau	...	30	114	2 836	0	3	0	...
Kenya	146	0	0	25	...
Mauritania	34	32	18	264	294	54	66	14
Senegal	41	11	13	2 709	4 939	454	1 106	132	45
Togo	339	228	619	693	3 262	343	249	425	1 339	868	397
Uganda	1 230	15	301	266	1 840

* Years likely to represent meningococcal A epidemics are shown in **bold**.

8.3 Costs and potential savings from introducing a conjugate Men A vaccine in meningitis belt countries not considered to be hyperendemic.

8.3.1 Assumptions

- *Crude incidence rate of meningitis.* 16.52 per 100 000 (ten-year average [1994-2003] of reported WHO data from Togo, Guinea, Ghana, Senegal and Benin)
- *Costs to introduce Men A conjugate vaccine.* US\$ 16 million to introduce Men A conjugate for ten years in a population of 12 million (catch-up plus one dose of Men A conjugate vaccine at 14 months; or catch-up plus two doses at 14 weeks and 9 months; or catch-up with follow-up campaigns in 1 to 4 year olds); population in “other” meningitis belt countries in 2009 estimated to be about 150 million; total cost to introduce Men A conjugate US\$ 200 million.
- *Savings on A/C PS vaccine.* Non meningitis belt countries purchased about 7.4 million doses of A/C PS vaccine per year or 74 million doses over ten years. A/C PS vaccine cost in the model calculation was set at US\$ 0.44 per dose for years 1-4, US\$ 0.50 per dose for years 5-8 and US\$ 0.56 per dose in years 9-10. A 15% surcharge for shipping was included.
- *Administration costs.* US\$ 0.74 per vaccinee was used for either preventive or reactive campaigns. Vaccine wastage was estimated at 25%. Total savings from A/C PS purchases and administration costs at US\$ 82 598 000
- *Acute care costs.* Introduction of a Men A conjugate vaccine will eliminate epidemics and decrease total number of meningitis cases by 50%; overall crude incidence rate to decrease by 50%, from 16.5 to 8.25 per 100 000; reported meningitis cases to decrease from 300 000 to 150 000 over ten years.

8.3.2 Costs and savings summary

Table 21 Summary of ten year costs and savings (US\$) after introducing a Men A conjugate vaccine in non hyper-endemic countries in the meningitis belt: estimated 2009 population of 150 million

Costs to introduce Men A conjugate vaccine	US\$ 200 000 000
Costs to introduce an A/C combination vaccine (includes catch-up with Men A)	US\$ 425 000 000
Potential savings	
Vaccine cost: 74 million doses; (US\$ 0.44 years 1-4; US\$ 0.50 years 5-8; US\$ 0.56 years 9-10)	US\$ 36 112 000
Vaccine shipping (15%)	US\$ 5 416 800
Administration costs: Doses administered 55 800 000 (US\$ 0.74/ vaccine; includes syringes and disposal boxes)	US\$ 41 070 000
Potential savings in acute health care costs* (from 300,000 cases to 150,000 cases; at a savings of US\$ 80/ per case)	US\$ 12 000 000
Total potential savings	US\$ 94 598 800

*Chronic health care costs not included in computations.

The estimated total savings after the induction of herd immunity is about 95 million dollars for these countries. However, introducing a Men A conjugate vaccine either as a Men A conjugate or a combination vaccine in these countries will cost between US\$ 200 million to US\$ 425 million depending on the strategy that is chosen. The important point is that major new funding will have to be identified to introduce conjugate meningococcal vaccines in these countries. Because of the incomplete surveillance data there may be considerably more savings in acute health care costs. Nonetheless, it is clear that each country in the meningitis belt will have to assess the financial implications associated with the introduction of meningococcal conjugate vaccines. In countries like Ghana and Benin introduction of the conjugate vaccine will clearly save money. Finally, because of the importance of high coverage in the catch-up vaccinations of 1 to 29 year olds it is important that financial sustainability be an important component of planning for introduction.

8.4 Countries outside the meningitis belt

No cost/savings computations were made for countries located outside the meningitis belt. Introducing meningococcal conjugate vaccines will require new funds. As emphasized several times in this presentation – to maximize the public health impact requires a well-planned, comprehensive and well-funded mass vaccination of 1 to 29 year olds plus a commitment to immunize new birth cohorts through follow-up campaigns or routine EPI immunizations. Whatever strategy is planned it must be solidly funded. However, when compared to other “new” vaccines, the Men A conjugate vaccine is not expensive and the funding requirements fall easily within those costs usually associated with African EPI programs.

9 Conclusions

Introducing a Men A conjugate vaccine with a catch-up campaign in 1 to 29 year olds and any one of several strategies to immunize newborn cohorts will save money. The principal savings

accrue from the substitution of a more immunogenic conjugate vaccine for the A/C PS vaccine that is now being purchased and used widely in so-called hyper-endemic countries.

References

1. LaForce FM, Konde K, Viviani S, Preziosi M-P. The Meningitis Vaccine Project. Vaccine reference.
2. Jodar L, LaForce FM, Ceccarini C, Aguado T, Granoff DM. Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries. *Lancet* 2003; 361:1902-1904.
3. Greenwood B. Manson Lecture. Meningococcal meningitis in Africa [published version & manuscript version in file]. *Trans R Soc Trop Med Hyg* 1999; 93(4):341-353.
4. Campagne G, Chippaux JP, Djibo S, Issa O, and Garba A. Epidemiology and control of bacterial meningitis in children less than 1 year in Niamey (Niger). *Bull Soc Pathol Exot* 1999; 92:118-22.
5. Campagne G, Schuchat A, Djibo S, Ousseini A, Cisse L, and Chippaux JP. Epidemiology of bacterial meningitis in Niamey, Niger, 1981-96. *Bull World Health Org* 1999; 77:499-508.
6. Disease Surveillance Unit, Ministry of Health, Niger, 2006
7. Watt JP, Levine OS, Santosham M. Global reduction of Hib disease: what are the next steps? *J Pediatr* 2003; 143(6 Suppl):S163-S187.
8. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003; 348(18):1737-1746.
9. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, and Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet* 2004; 364:365-7.
10. Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *BMJ* 2003; 326(7385):365-366.
11. Maiden MC. Dynamics of bacterial carriage and disease: lessons from the meningococcus. *Adv Exp Med Biol* 2004; 549:23-9.
12. Trotter CL, Gay NJ, and Edmunds WJ. Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. *Am J Epidemiol* 2005; 162:89-100.
13. de Greeff SC, de Melker HE, Spanjaard L, Schouls LM, and van Derende A. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. *Pediatr Infect Dis J* 2006; 25:79-80.
14. Viviani S, Prezios MP, Kshirsagar N, Thatte U, Mur N, Kulkarni P, Carlone G, Borrow R, LaForce FM. A Phase I, Double Blind, Randomized Study to Evaluate a New Meningococcal Group A Conjugate Vaccine in Healthy Indian Adults. Manuscript in preparation.
15. Chanteaux S. Cost of laboratory studies relating to acute meningitis, Challenges in the African Meningitis Belt, Niamey, November 2005.
16. Recherche opérationnelle sur la gratuite de la prise en charge des patients atteints de meningite cérébro-spinale au Burkina Faso, Janvier 2003, Ministère de la Santé, Burkina Faso.
17. WHO Statistical Information System (WHOSIS), 2002 (Africa D Total population, births and mortality rates); Unit costs for base case analysis: WHO African Region – D, Country specific hospital costs, WHO CHOICE, 2002.
18. Global Programme for Vaccines and Immunization, Expanded Programme on Immunization, Immunization Policy. WHO/EPI/GEN/95.03.REV.1, 1996.

19. Brenzel L, Wolfson LJ, Fox-Rushby J, Miller M, Halsey NA. Vaccine-Preventable Diseases in Disease Control Priorities in Developing Countries, 2nd Ed. Edited by DT Jamison, JG Breman, AR Measham, G Alleyne, M Claeson, DB Evans, P Jha, A Mills, P Musgrove. Oxford University Press and the World Bank, 2006.
20. Walker D, Mosqueira NR, Penny ME, et al. Variation in the costs of delivering routine immunization services in Peru. Bull WHO, 2004, 82:676-682.