**Case study: Evaluation of pneumococcal conjugate vaccine impact and safety following introduction into the national immunization program of Cote d'Ivoire**

**Background**

Pneumococcus is a leading cause of morbidity and mortality among children worldwide and particularly in developing countries. The most common forms of serious disease include non-bacteremic and bacteremic pneumonia, bacteremia and sepsis, and meningitis. Peritonitis, septic arthritis, and endocarditis also may occur. Pneumococcus may cause less serious disease such as otitis media and sinusitis.

In most of the world, pneumococcus causes disease primarily among infants, toddlers, and the elderly, with a higher ratio of meningitis to pneumonia among children. In the meningitis belt, including Northern Cote d'Ivoire, pneumococcal disease incidence remains highest among infants but then remains at a high level throughout life, such that approximately two-thirds of disease and death may occur among older children and working age adults.

The capsular polysaccharides (PS) on the surface of *S. pneumoniae* are the basis for the serotyping classification of the bacterium among 40 serogroups comprising 90 serotypes, only 20 of which are responsible for 70% of invasive pneumococcal disease. The most common serogroups worldwide are 6, 14, 19 and 23, but other serogroups such as 1, 5 or 8 contribute substantially to invasive pneumococcal disease in developing countries. Most surveillance and thus most knowledge of serotype distribution comes from children age <5 years. Additionally, few studies have evaluated serotype distribution in non-bacteremic pneumonia cases (e.g., through lung punctures or transtracheal aspirates). Consequently, the true serotype distribution remains unknown. Lastly, serotype distribution varies geographically. In the meningitis belt, after early childhood, serotype 1 causes approximately two-thirds of invasive cases.

A matter of concern is the increasing antibiotic resistance of *S. pneumoniae*, where it has added to the urgency of developing more effective pneumococcal vaccines for this age group.

The true burden of pneumococcal infections is not well documented anywhere, but particularly in developing countries, where persons with serious disease may lack access to care and which have poorly functioning and under-equipped disease surveillance systems and diagnostic facilities. In several surveys done in sub-Saharan Africa, *S. pneumoniae* was found to account for about 25% to >30% of the cases of meningitis among children less than 5 years old. A study from The Gambia conservatively estimated an annual invasive pneumococcal disease incidence of 500 per 100,000 infants and 250 per 100,000 children less than 5 years of age. A recent study from Kenya reported an annual incidence of presentation to the hospital with pneumococcal bacteremia of 597 per 100,000 children younger than 5 years of age. Case fatality ratios for invasive pneumococcal disease across all age groups range from 5% to 20% for bacteremia and from 40% to >50% for meningitis. From 25% to 56% of children who survive meningitis suffer from long-term neurologic sequelae.

Several factors increase the risk of invasive pneumococcal infection. In much of Africa, the most important contributor is HIV infection. For example, a clinical study among HIV-infected young adults in Uganda reported an annual incidence of 1700 cases of invasive pneumococcal disease per 100,000 population. Influenza also increases the risk of secondary pneumococcal infection. Based on evidence from past influenza pandemics, the attack rate for secondary pneumococcal pneumonia in a pandemic setting is anticipated to reach 13%. Lastly, in the meningitis belt pneumococcal disease occurs in a highly seasonal pattern, similar to meningococcal meningitis; reasons for this remain unknown but may include mucosal damage due to the hot, dry Saharan winds and seasonal viral respiratory infections.

The original pneumococcal conjugate vaccine (PCV) included seven serotypes, but was missing serotype 1, making it substantially less useful for Africa and particularly meningitis belt countries. More recent 10-valent and 13-valent formulations include serotype 1 and many countries have applied for GAVI funding for introduction, including several in the meningitis belt.

PCV success may be hampered by the replacement in the nasopharynx of vaccine serotypes by other non-vaccine serotypes. This in turn may lead to an increase in non-vaccine serotype disease. Effects have varied by location. For example, strain replacement has only had relatively modest effects on disease in most U.S. populations, whereas in the U.K. it has almost undone the indirect impact in the adult age group, and among Alaska Native people led to similar disease rates before and several years after PCV-7 introduction. The relative contribution of true serotype replacement, background changes in disease epidemiology unrelated to vaccine, and changes in surveillance methodology remains unknown.

Cote d'Ivoire has not yet elected to introduce PCV. The country has just emerged from civil war and is working on rebuilding public health infrastructure. It has many pressing public health needs, including discussion of other important vaccines such as rotavirus. If a decision is made to introduce vaccine, disease impact will be critical to sustaining support, particularly as GAVI funding declines and country co-pays increase.

**Task**

The MOH asked the Cote d'Ivoire National Immunization Technical Advisory Group (NITAG) – called the National Committee of Independent Experts for Vaccination and Vaccines (CNEIV-CI) – to design a PCV impact plan in anticipation of PCV introduction. The plan could include impact on confirmed pneumococcal disease, pneumococcus-associated disease syndromes such as acute respiratory infection or purulent meningitis, and mortality. It could also include programmatic (e.g., human resources and cold chain) and financial impact, as well as safety evaluation. The goal of this exercise is to develop a reasonable short list of the highest priority studies and assessments for monitoring the usefulness of PCV.

**Composition of the CNEIV-CI**

CNEIV-CI deals with both adult and childhood immunizations. It consists of the following core members:

- Chairman (professor of public health)
- Vice chair (professor of infectious diseases)

Additional expertise:

- Public health and health policy
- Microbiology
- Pediatrics
- Infectious diseases
- Pharmacy/logistics
- Applied vaccinology
- Epidemiology and biostatistics
- Health economics
- Sociology/anthropology
- Gynecology and obstetrics
- Workplace medicine
- Paramedical associations

**Advice on the group work process**

- Choose the chairman. Choose the rapporteur.
- Give each member of the group a role of the different participants at the meeting, and debate the value of the different studies, including cost, feasibility, ease of implementation, existence of background data needed for pre- and post-vaccine introduction comparison, etc…. You will need to make some assumptions. The facilitators of the group will try to provide you with more data should you need it.

The meeting should last no longer than 1 hour 20 minutes, after which the MOH has arranged for the chairman of the expert group to give a summary of their advice to the Ministry of Finance who presently is drafting the 5-year financial plan of the country.

**Infant immunization program of Cote d'Ivoire**

| Vaccine | Full vaccine name | Schedule |
|---|---|---|
| BCG | Bacille Calmette-Guérin vaccine | Birth |
| DTwPHibHep | Diphtheria and tetanus toxoid with whole cell pertussis, Hib and HepB vaccine | 6,10,14 weeks |
| Measles | Measles vaccine | 9 months |
| OPV | Oral polio vaccine | Birth; 6, 10, 14 weeks |
| VitaminA | Vitamin A supplementation | 6, 12, 18, 24, 30, 36 months |
| YF | Yellow fever vaccine | 9 months |

**Cote d'Ivoire country indicators**

| | |
|---|---|
| Under 5 mortality rate | 123/1000 live births |
| Infant mortality rate | 86/1000 live births |
| Life expectancy | 55 years |
| Annual number of births | 673,000 |
| Total population | 19.7 million |
| DPT3 coverage estimate | 85% |
| Adult (age 15-49 years) HIV prevalence | 3.4% |
| GNI per capita | 1070 USD |

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6. Blau J, Faye PC, Senouci, et al. Establishment of a National Immunization Technical Advisory Group in Côte d'Ivoire: process and lessons learned. Vaccine 2012;30:2588-93.


## ABSTRACTS

Lancet. 2009 Sep 12;374(9693):893-902.

**Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates.**

O'Brien KL, Wolfson LJ, Watt JP, et al.
GAVI's PneumoADIP, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA. klobrien@jhsph.edu

### Abstract

**BACKGROUND:**
Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis, and sepsis in children worldwide. However, many countries lack national estimates of disease burden. Effective interventions are available, including pneumococcal conjugate vaccine and case management. To support local and global policy decisions on pneumococcal disease prevention and treatment, we estimated country-specific incidence of serious cases and deaths in children younger than 5 years.

**METHODS:**
We measured the burden of pneumococcal pneumonia by applying the proportion of pneumonia cases caused by S pneumoniae derived from efficacy estimates from vaccine trials to WHO country-specific estimates of all-cause pneumonia cases and deaths. We also estimated burden of meningitis and non-pneumonia, non-meningitis invasive disease using disease incidence and case-fatality data from a systematic literature review. When high-quality data were available from a country, these were used for national estimates. Otherwise, estimates were based on data from neighbouring countries with similar child mortality. Estimates were adjusted for HIV prevalence and access to care and, when applicable, use of vaccine against Haemophilus influenzae type b.

**FINDINGS:**
In 2000, about 14.5 million episodes of serious pneumococcal disease (uncertainty range 11.1-18.0 million) were estimated to occur. Pneumococcal disease caused about 826,000 deaths (582,000-926,000) in children aged 1-59 months, of which 91,000 (63,000-102,000) were in HIV-positive and 735,000 (519,000-825,000) in HIV-negative children. Of the deaths in HIV-negative children, over 61% (449,000 [316,000-501,000]) occurred in ten African and Asian countries.

**INTERPRETATION:**
S pneumoniae causes around 11% (8-12%) of all deaths in children aged 1-59 months (excluding pneumococcal deaths in HIV-positive children). Achievement of the UN Millennium Development Goal 4

for child mortality reduction can be accelerated by prevention and treatment of pneumococcal disease, especially in regions of the world with the greatest burden.

Lancet. 2005 Mar 26-Apr 1;365(9465):1139-46.
**Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial.**

Cutts FT, Zaman SM, Enwere G, et al.
Medical Research Council Laboratories, Banjul, The Gambia.

**Erratum in**
Lancet. 2005 Jul 2-8;366(9479):28.

**Abstract**
**BACKGROUND:**
Pneumonia is estimated to cause 2 million deaths every year in children. Streptococcus pneumoniae is the most important cause of severe pneumonia. We aimed to assess the efficacy of a nine-valent pneumococcal conjugate vaccine in children.

**METHODS:**
We undertook a randomised, placebo-controlled, double-blind trial in eastern Gambia. Children age 6-51 weeks were randomly allocated three doses of either pneumococcal conjugate vaccine (n=8718) or placebo (8719), with intervals of at least 25 days between doses. Our primary outcome was first episode of radiological pneumonia. Secondary endpoints were clinical or severe clinical pneumonia, invasive pneumococcal disease, and all-cause admissions. Analyses were per protocol and intention to treat.

**FINDINGS:**
529 children assigned vaccine and 568 allocated placebo were not included in the per-protocol analysis. Results of per-protocol and intention-to-treat analyses were similar. By per-protocol analysis, 333 of 8189 children given vaccine had an episode of radiological pneumonia compared with 513 of 8151 who received placebo. Pneumococcal vaccine efficacy was 37% (95% CI 27-45) against first episode of radiological pneumonia. First episodes of clinical pneumonia were reduced overall by 7% (95% CI 1-12). Efficacy of the conjugate vaccine was 77% (51-90) against invasive pneumococcal disease caused by vaccine serotypes, 50% (21-69) against disease caused by all serotypes, and 15% (7-21) against all-cause admissions. We also found an efficacy of 16% (3-28) against mortality. 110 serious adverse events arose in children given the pneumococcal vaccine compared with 131 in those who received placebo.

**INTERPRETATION:**
In this rural African setting, pneumococcal conjugate vaccine has high efficacy against radiological pneumonia and invasive pneumococcal disease, and can substantially reduce admissions and improve child survival. Pneumococcal conjugate vaccines should be made available to African infants.

BMC Infect Dis. 2010 Feb 10;10:22.
**African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults.**

Gessner BD, Mueller JE, Yaro S.
Agence de Médecine Préventive, 25-28 Rue du Dr, Roux, Paris 75728, France. bgessner@aamp.org

**Abstract**
**BACKGROUND:**
Pneumococcal conjugate vaccine strategies in GAVI-eligible countries are focusing on infant immunization but this strategy may not be optimal in all settings. We aimed to collect all available population based data on pneumococcal meningitis throughout life in the African meningitis belt and then to model overall meningitis risk to help inform vaccine policy.

**METHODS:**
After a systematic review of literature published from 1970 through the present, we found robust population-based Streptococcus pneumoniae (Sp) meningitis data across age strata for four African meningitis belt

countries that included 35 surveillance years spanning from 1970 to 2005. Using these data we modeled disease risk for a hypothetical cohort of 100,000 persons followed throughout life.

**RESULTS:**
Similar to meningococcal meningitis, laboratory-confirmed pneumococcal meningitis was seasonal, occurring primarily in the dry season. The mean annual Sp meningitis incidence rates were 98, 7.8 to 14, and 5.8 to 12 per 100,000 among persons <1, 1 through 19, and 20 to 99 years of age, respectively, which (in the absence of major epidemics) were higher than meningococcal meningitis incidences for persons less than 1 and over 20 years of age. Mean Sp meningitis case fatality ratios (CFR) among hospitalized patients ranged from 36-66% depending on the age group, with CFR exceeding 60% for all age groups beyond 40 years; depending on the age group, Sp meningitis mortality incidences were 2 to 12-fold greater than those for meningococcal meningitis. The lifetime risks of pneumococcal meningitis disease and death were 0.6% (1 in 170) and 0.3% (1 in 304), respectively. The incidences of these outcomes were highest among children age <1 year. However, the cumulative risk was highest among persons age 5 to 59 years who experienced 59% of pneumococcal meningitis outcomes. After age 5 years and depending on the country, 59-79% of meningitis cases were caused by serotype 1.

**CONCLUSIONS:**

In the African meningitis belt, Sp is as important a cause of meningitis as Neisseria meningitidis, particularly among older children and working age adults. The meningitis belt population needs an effective serotype 1 containing vaccine and policy discussions should consider vaccine use outside of early childhood.

Clin Infect Dis. 2009 Mar 1;48 Suppl 2:S181-9.

**Incidence, seasonality, age distribution, and mortality of pneumococcal meningitis in Burkina Faso and Togo.**

Traore Y, Tameklo TA, Njanpop-Lafourcade BM, et al.
Université de Ouagadougou, Ouagadougou, Burkina Faso.

**Abstract**
Streptococcus pneumoniae causes a substantial proportion of meningitis cases in the African meningitis belt; however, few reports exist to quantify its burden and characteristics. We conducted population-based and sentinel hospital surveillance of acute bacterial meningitis among persons of all ages in Burkina Faso and Togo in 2002-2006. S. pneumoniae and other organisms were identified by culture, polymerase chain reaction, or detection of antigen in cerebrospinal fluid (CSF). Information was collected on 2843 patients with suspected acute bacterial meningitis. CSF specimens were collected from 2689 (95%) of the patients; of these 2689, 463 (17%) had S. pneumoniae identified, 234 (9%) had Haemophilus influenzae type b identified, and 400 (15%) had Neisseria meningitidis identified. Of the 463 cases of S. pneumoniae meningitis, 99 (21%) were aged <1 year, 71 (15%) were aged 1-4 years, 95 (21%) were aged 5-14 years, and 189 (41%) were aged >or=15 years (age was unknown for 9 [2%]). In Burkina Faso, the annual incidence rate of pneumococcal meningitis was 14 cases per 100,000 persons, with annual incidence rates of 77, 33, 10, and 11 cases per 100,000 persons aged <1 year, <5 years, 5-14 years, and >or=15 years, respectively. The case-fatality ratio for S. pneumoniae meningitis was 47% (range for age groups, 44%-52%), and 53% of deaths occurred among those aged >5 years. S. pneumoniae meningitis had an epidemic pattern similar to that of N. meningitidis meningitis. Of 48 isolates tested for serotype, 18 were from children aged <5 years; of these 18, 3 isolates (17%) each were serotypes 1, 2, and 5, and 5 isolates (28%) were serotype 6A. The 7-, 10-, and 13-valent pneumococcal conjugate vaccines would cover 6%, 39%, and 67% of serotypes identified among children aged <5 years, respectively. Of the 30 serotypes identified for patients aged >or=5 years, 18 (60%) were serotype 1, whereas no other serotype constituted >10%. The 7-, 10-, and 13-valent vaccines would cover 7%, 70%, and 77% of serotypes. Epidemic pneumococcal meningitis in the African meningitis belt countries of Burkina Faso and Togo is common, affects all age groups, and is highly lethal. On the basis of a modest number of isolates from a limited area that includes only meningitis cases, 7-valent pneumococcal conjugate vaccine might have only a limited and short-term role. By contrast, the proposed 10- and 13-valent vaccines would cover most of the identified serotypes. To better inform vaccine policy,

continued and expanded surveillance is essential to document serotypes associated with pneumonia, changes in serotype distribution across time, and the impact of vaccine after vaccine introduction.

Lancet. 2011 Dec 3;378(9807):1962-73. Epub 2011 Apr 12.
**Serotype replacement in disease after pneumococcal vaccination.**

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Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, USA. weinbergerdm@mail.nih.gov

**Abstract**
Vaccination with heptavalent pneumococcal conjugate vaccine (PCV7) has significantly reduced the burden of pneumococcal disease and has had an important public health benefit. Because this vaccine targets only seven of the more than 92 pneumococcal serotypes, concerns have been raised that non-vaccine serotypes (NVTs) could increase in prevalence and reduce the benefits of vaccination. Indeed, among asymptomatic carriers, the prevalence of NVTs has increased substantially, and consequently, there has been little or no net change in the bacterial carriage prevalence. In many populations, pneumococcal disease caused by NVT has increased, but in most cases this increase has been less than the increase in NVT carriage. We review the evidence for serotype replacement in carriage and disease, and address the surveillance biases that might affect these findings. We then discuss possible reasons for the discrepancy between near-complete replacement in carriage and partial replacement for disease, including differences in invasiveness between vaccine serotypes. We contend that the magnitude of serotype replacement in disease can be attributed, in part, to a combination of lower invasiveness of the replacing serotypes, biases in the pre-vaccine carriage data (unmasking), and biases in the disease surveillance systems that could underestimate the true amount of replacement. We conclude by discussing the future potential for serotype replacement in disease and the need for continuing surveillance.

Vaccine. 2012 Mar 28;30(15):2588-93. Epub 2012 Feb 11.
**Establishment of a National Immunization Technical Advisory Group in Côte d'Ivoire: process and lessons learned.**

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**Abstract**
In January 2010, Côte d'Ivoire became the first GAVI-eligible country in sub-Saharan Africa to establish a National Immunization Technical Advisory Group (NITAG). The Côte d'Ivoire "National Committee of Independent Experts for Vaccination and Vaccines" (CNEIV-CI) was created to strengthen national capacity for evidence-based policy decisions with regard to immunization and vaccines. The primary reasons for success in Côte d'Ivoire were a strong political will, the availability of sufficient national expertise, a step-by-step country-driven process, and the provision of technical assistance to the Ministry of Health. The challenges included operating within the socio-political crisis, and initial reluctance from some stakeholders due to the potential overlap with other existing committees. The latter rapidly dissolved over the course of numerous meetings held with the SIVAC Initiative to clarify the mandate of a NITAG.

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# Establishment of a National Immunization Technical Advisory Group in Côte d'Ivoire: Process and lessons learned

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ABSTRACT

In January 2010, Côte d'Ivoire became the first GAVI-eligible country in sub-Saharan Africa to establish a National Immunization Technical Advisory Group (NITAG). The Côte d'Ivoire "National Committee of Independent Experts for Vaccination and Vaccines" (CNEIV-CI) was created to strengthen national capacity for evidence-based policy decisions with regard to immunization and vaccines. The primary reasons for success in Côte d'Ivoire were a strong political will, the availability of sufficient national expertise, a step-by-step country-driven process, and the provision of technical assistance to the Ministry of Health. The challenges included operating within the socio-political crisis, and initial reluctance from some stakeholders due to the potential overlap with other existing committees. The latter rapidly dissolved over the course of numerous meetings held with the SIVAC Initiative to clarify the mandate of a NITAG.


## 1. Introduction

Immunization is an important, cost-effective and successful public health intervention [1]. With the increase in resources allocated to immunization through the GAVI Alliance [2], there have been important changes in vaccination programs and policies. Multiple health priorities, limited human resources and logistical capacities [3], and the high cost of vaccines relative to limited public funds have increased the need for evidence-based decision making in immunization programs. Evidence-based decision-making processes can provide more support for immunization programs than other health interventions. Meanwhile, within immunization programs such processes can inform decisions related to new vaccine introduction, prioritization, schedules, target groups and other issues linked to immunization and vaccines.

An important step that countries can take is to establish a national expert group to advise the Ministry of Health (MOH). To date, most industrialized countries and some developing countries have already constituted National Immunization Technical Advisory Groups (NITAGs) to guide immunization policies [4]. These multidisciplinary national committees include expertise in various areas (epidemiology, economics, public health, anthropology, pediatrics, pharmacology, vaccinology, and infectious diseases) and are responsible for providing recommendations on immunization and vaccines to the minister of health. The World Health Organization (WHO) now recommends that all countries establish national immunization and vaccination committees [5].

To help low- and middle-income countries achieve this goal, the Bill & Melinda Gates Foundation provided funding to the Agence de Médecine Préventive (AMP), in partnership with the International Vaccine Institute (IVI) to develop the Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative [6]. This article describes the methodology used by the national authorities in Côte d'Ivoire with the support of the SIVAC Initiative to establish the first sub-Saharan African NITAG in a GAVI-eligible country.

## 2. Context

### 2.1. Immunization policies and programs

Côte d'Ivoire is a French-speaking West African country with a 2010 birth cohort of 649,477. Expanded Program on Immunization

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**Table 1**
Vaccination schedule in Côte d'Ivoire, 2009.

| Ages | Vaccine[a] |
|---|---|
| At birth | BCG + OPV 0 |
| 6 weeks | DTP-HepB-Hib1 + OPV 1 |
| 10 weeks | DTP-HepB-Hib2 + OPV 2 |
| 14 weeks | DTP-HepB-Hib3 + OPV 3 |
| 9 months | Measles + yellow fever |
| 18 months | 4th dose DTP-HepB-Hib + OPV |
| Pregnant women | Tetanus toxoid<br>1st Dose: at the first contact<br>2nd Dose: one month after first dose<br>3rd Dose: 6 months after second dose<br>4th Dose: one year after the third dose<br>5th Dose: one year after the fourth dose |

[a] BCG: Bacillus Calmette-Guérin (for tuberculosis); OPV: oral polio vaccine; DTP: diphtheria-tetanus-pertussis; HepB: hepatitis B; Hib: *Haemophilus influenzae* type b.

(EPI) services were launched in 1978 and are now delivered through approximately 1500 vaccination centers and involve all levels of the health system structure. Since March 2009, the immunization schedule has included nine vaccine preventable diseases: tuberculosis, diphtheria, pertussis, tetanus, poliomyelitis, measles, yellow fever, hepatitis B and *Haemophilus influenzae* type b (Table 1).

Between 2005 and 2007, administrative coverage rates reported by the MOH steadily improved while a decline in coverage (except for Bacillus Calmette-Guérin [BCG]) was reported for 2008 (Table 2). This can be explained partly by the internal political and military strife experienced by the country since 2000. With the decrease in vaccine coverage, some vaccine-preventable diseases have reoccurred, including 183 measles, 26 wild poliovirus, 22 yellow fever, and 6 neonatal tetanus cases in 2009. The drop in coverage rates which led to outbreaks in polio, yellow fever, measles and tetanus motivated the MOH to increase the number of supplementary immunization activities (SIAs). Despite the increase in SIAs which added to the financial and human cost of routine immunization in the country, no significant improvement was seen in coverage rates. In 2009, the minister of health asked the Inter-Agency Coordination Committee (ICC) to provide him with data on the impact of the SIAs on the coverage rates in the country. However, ICCs address primarily financial and operational issues; consequently, the ICC members created an ad hoc committee to work on the topic. This experience convinced the minister of the benefit of a standing technical consultative organ such as a NITAG to address scientific issues related to immunization policy, including the observed drop in immunization coverage.

### 2.2. National immunization expertise

Côte d'Ivoire has two medical schools. Additionally, the University of Cocody-Abidjan is one of the primary sponsors of the EPIVAC training course (www.epivac.org) and health professionals also have access to the International Course on Epidemiology and Applied Information Technology [7,8]. The EPIVAC and ICEAIT programs operate in Africa. EPIVAC provides master's level training in public immunization program management while ICEAIT provides training in epidemiology with a focus on disease surveillance and outbreak investigation and response. Both courses support NITAG creation by creating a critical mass of local professionals trained in vaccinology and developing a culture of evidenced-based decision making in immunization and disease surveillance. Finally, Côte d'Ivoire has a Pasteur Institute and research facilities. All these structures provide an ample supply of professionals with expertise in immunization issues.

**Table 2**
EPI vaccination coverage rates in Côte d'Ivoire between 2005 and 2008 (Côte d'Ivoire Ministry of Health, administrative sources).

| Vaccine[a] | 2005 | 2006 | 2007 | 2008 |
|---|---|---|---|---|
| BCG | 61% | 77% | 85% | 91% |
| Penta 3 | 56% | 77% | 80% | 74% |
| OPV3 | 56% | 76% | 80% | 58% |
| Measles vaccine | 50% | 73% | 78% | 63% |
| Yellow Fever vaccine | 52% | 67% | 78% | 50% |

[a] BCG: Bacillus Calmette-Guérin (for tuberculosis); OPV: oral polio vaccine.

## 3. Creation of the NITAG in Côte d'Ivoire: a step-by-step country-driven process

### 3.1. The methodology proposed by the SIVAC Initiative

The SIVAC approach for the creation of NITAGs is based on a country-driven, step-by-step process aimed at ensuring country ownership and sustainability. The specific criteria for country selection include geographic representativeness, routine immunization coverage rates, availability of expertise, and political stability. Information comes from literature reviews, a review of the WHO and UNICEF immunization data, and consultations with WHO regional offices [6]. Once a country is selected, the SIVAC Initiative visits the country to meet with national health authorities and partners to explain the advantages of establishing a NITAG and evaluate the willingness of the country to implement a NITAG. If national authorities express interest, SIVAC makes a second country visit to initiate the development of a concept paper. The first visit allows the country to better understand the concept of a NITAG and the SIVAC approach, while simultaneously allowing SIVAC staff to assess the motivation of the country to create a NITAG. The second visit allows for in-depth work on the creation of the NITAG, based on a concept paper approach. The concept paper, developed by the country, describes the current situation of immunization policies and programs, lists potential partners, describes the envisioned NITAG composition and terms of reference, and proposes priority topics to be put on the agenda. When finalized, the concept paper is then submitted to a large number of experts for discussion and consensus during a national workshop. Based on the final version of the concept paper endorsed by the national authorities, the MOH develops the legal documents related to the establishment of the NITAG. Once the NITAG is legally established in the country, the next steps are to appoint the committee members, identify specific agenda topics, organize formal committee meetings, develop recommendations, and disseminate recommendations to the MOH. After the establishment of the NITAG, the SIVAC Initiative provides support to the country mainly by reinforcing the scientific and technical capacities of the NITAG executive secretariat. Detailed support activities provided by SIVAC are tailored to the country, and are established annually in consultation with the NITAG itself.

### 3.2. The process in Côte d'Ivoire

SIVAC visited Côte d'Ivoire in January 2009 (Fig. 1) to present the initiative and the concept of establishing a NITAG to the national health authorities, influential national experts, and staff from partner institutions (WHO and UNICEF). The aim of this initial visit was to evaluate the feasibility of establishing a NITAG in the country by assessing the support of the national authorities and the availability of national expertise. SIVAC first met with the director and deputy director of the Cabinet of the MOH, who expressed interest in creating a NITAG. This was followed by a meeting with other senior MOH staff, and staff from the National Institute for Public Hygiene (INHP). Intensive discussion took place on the concept of NITAG independence, the relationships between the NITAG and the

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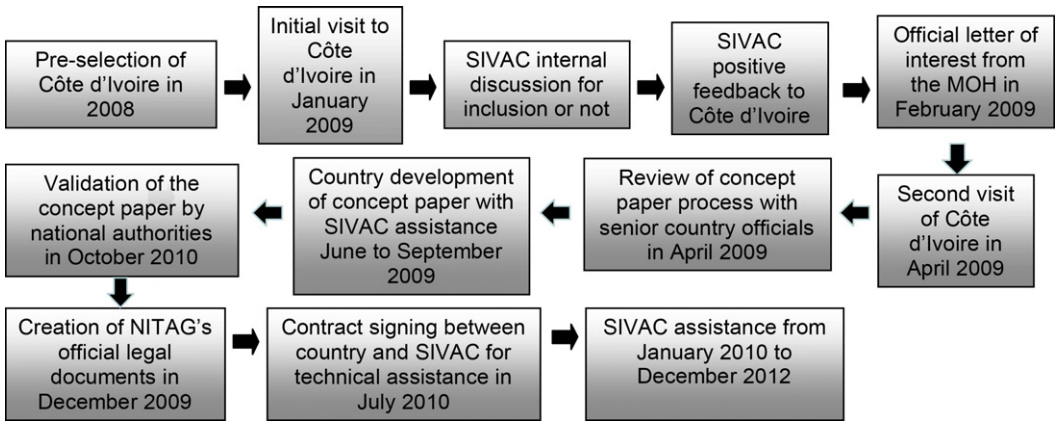


**Fig. 1.** The process in Côte d'Ivoire.

ICC, the NITAG and the Expanded Program on Immunization (EPI), and potential overlap in the terms of reference between the NITAG and other existing immunization committees in Côte d'Ivoire. This discussion helped clarify the role of a NITAG. Shortly after this visit, in February 2009 the SIVAC Initiative received an official letter of interest from the minister of health.

A second visit to Côte d'Ivoire was organized in April 2009. SIVAC held discussions with national authorities and potential local partners regarding the implementation of a NITAG in Côte d'Ivoire including the WHO, UNICEF, the INHP, the MOH, the Pasteur Institute, and representatives and professors from the main universities in the country. The minister of health designated the deputy director for immunization and vaccines at the INHP to be the focal point for coordinating the development of the future NITAG.

From June to October 2009, the MOH focal point and his team coordinated the development of a concept paper by a working group of national experts. The working group was composed of ten members from INHP, the MOH and the universities (Table 3). The MOH NITAG focal point organized a national expert consensus meeting attended by the members of the working group to finalize the concept paper before submission to the minister of health [9]. Once finalized, the MOH focal point presented the concept paper to the deputy director of the MOH Cabinet, to acquire a final endorsement from the minister of health. In November 2009, the MOH focal point met with the legal department of the MOH to draft the legal documents establishing the NITAG, including a list of members and the ministerial decree. This was followed by a presentation to the coordination committee of the MOH, which included the directors and the Cabinet of the MOH. The committee emphasized that the NITAG's role would be limited to recommendations and would therefore exclude any implementation role; stressed that the NITAG members rather than the NITAG as an institution would be independent; requested a more narrow and targeted role for the NITAG; and asked that some high level members be represented by deputies. Once these modifications were made, the documents were delivered to the MOH for finalization.

**Table 3**
Composition of the National Immunization Technical Advisory Group (NITAG) working group in Côte d'Ivoire.

| Institution | Number of representatives | Title of representatives |
|---|---|---|
| Public Health National Institute | 2 | Head of Vaccinology department<br>Epidemiological surveillance department |
| Expanded Program on Immunization Coordination Directorate | 4 | Coordination director<br>Coordinating deputy director<br>Health economist<br>Medical doctor |
| Infectious Disease Department, Treichville Hospital | 2 | Professor<br>Medical doctor |
| Public Health Department, Research and Training Unit, Abidjan Hospital | 2 | Assistant<br>Deputy assistant |

## 4. The NITAG of Côte d'Ivoire: the CNEIV-CI

### 4.1. Organization, responsibilities and functioning mode

In December 2009, the ministerial decree establishing the Comité National d'Experts Indépendants pour la Vaccination de Côte d'Ivoire *(CNEIV-CI)* or "National Committee of Independent Experts for Vaccination and Vaccines" CNEIV-CI within the MOH was signed followed in January 2010 by the designation of core members of the NITAG. The legally defined role of the CNEIV-CI is to advise the minister of health on all topics related to vaccines and immunizations. This includes, for example, vaccination policies and strategies, introduction of vaccines, prioritization of new vaccines, revision of vaccine schedules, and immunization coverage. The committee is composed of three types of members: independent national experts from a wide range of disciplines (core members), representatives from the MOH and other related ministries (ex-officio members), and representatives from partner institutions (liaison members such as WHO, UNICEF, AMP) (Table 4). Only the first group is allowed to vote.

As reflected by the NITAG name, the core members of the CNEIV-CI are independent as is the institution as a whole. This is also specified in the 2009 ministerial decree that describes the conflict of interest procedure for NITAG members, and which follows WHO recommendations on independence. The objective of CNEIV-CI's work is to advise the MOH through a consultative role.

The committee is chaired by a professor of public health, assisted by a vice chair, who is a professor of infectious diseases. The National Institute for Public Hygiene (Institut National d'Hygiène Publique, INHP) acts as the scientific and technical secretariat of the committee. The deputy director in charge of immunization and vaccines at the INHP is in charge of the secretariat work for the NITAG, and is assisted by a deputy executive secretary and a team.

The budget for the CNEIV-CI is limited and includes funding mainly for costs associated with meeting organization. During the

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**Table 4**
Committee members of the Côte d'Ivoire National Immunization Technical Advisory Group.

| Core member representation | Non core members (ex officio and liaison) representation |
|---|---|
| Public health and health policy (1) | Health General Directorate |
| Microbiology (Bacteriology/Virology) (1) | Public Hygiene National Institute |
| Pediatrics (2) | Pharmacy and Drugs Directorate |
| Infectious diseases (2) | Equipment Infrastructure and Maintenance Directorate |
| Pharmacy/logistics (2) | National Institute of Health Professionals Training |
| Applied vaccinology (1) | Public Health National Institute |
| Epidemiology and biostatistics (2) | Expanded Program on Immunization Coordination Directorate |
| Health economics (1) | National Program of school and university health |
| Sociology/anthropology (1) | Economics and Finance Ministry |
| Gynecology and obstetrics (1) | Domestic affairs and Emergency Preparedness Ministry |
| Workplace medicine (1) | Workplace Medicine Ministry |
| Paramedical associations (2) | Armed forces Health Ministry |
| | World Health Organization |
| | United Nations International Children's Emergency Fund |
| | Agence de Médecine Préventive |

first year of activity, the SIVAC Initiative supported most of the costs followed by a gradual handover of budget items to the INHP which should be complete by the third year. The terms of SIVAC assistance are specified in an official document signed by the INHP and AMP.

In general, the establishment of the Côte d'Ivoire NITAG followed the guidelines established by WHO, such as having an official document authorizing the NITAG's existence and having written standard operating procedures (SOPs). In some cases, however, the process was adapted for the local context, such as the number of members and their rotation (Table 5).

### 4.2. First activities

In January 2010, the Côte d'Ivoire's minister of health presided over a ceremony to mark the launch of the CNEIV-CI. The first technical meeting occurred during March 2010 at the INHP offices. Discussion topics at this initial meeting included the attendance of ministries other than the MOH, the nomination of the new minister of health, the strengths and weaknesses of the current immunization services; training of the committee members and secretariat; new vaccines; immunization logistic issues; and target groups for vaccination. The committee members decided upon an agenda for 2010, including the functioning of the committee, determinants and barriers to immunization demand, new vaccine introduction, and vaccination outside of routine EPI activities. To better address the second ordinary session of the committee, the scientific and technical secretariat of the CNEIV-CI relied upon two working groups, which dealt with procedural rules for the functioning of the Committee recommendations to address the low EPI immunization coverage in Côte d'Ivoire.

Since March 2010, there have been in total four NITAG meetings. Three other meetings should have taken place but were cancelled

**Table 5**
Processes developed by the Côte d'Ivoire National Immunization Technical Advisory Group (NITAG).

| Topic | Côte d'Ivoire National Immunization Technical Advisory Group process | Comment |
|---|---|---|
| Establishment | • Ministerial order establishing the committee<br>• Ministerial decree nominating the President and members of the committee<br>•Documents signed by minister of health | Conforms to World Health Organization recommendations |
| Size | • 17 core members<br>• 12 ex officio members<br>• 3 liaison members | World Health Organization-recommended number of core members: between 10 and 15<br>A greater number was selected to duplicate some areas of expertise and broaden committee expertise |
| Composition | • 11 specialities in the field of immunization and vaccines | Conforms to World Health Organization recommendations |
| Appointment | Using criteria developed by the National Immunization Technical Advisory Group working group, the General Director of Health proposed the National Immunization Technical Advisory Group creation to the minister of health | Conforms to World Health Organization recommendations |
| Rotation of core members | Renewable every four years indefinitely | World Health Organization recommends limitations on duration of committee membership |
| Standard operating procedures | The committee has standard operating procedures that define its operating rules | Conforms to World Health Organization recommendations |
| Agenda setting | • Agenda is defined by the core members of the committee and the secretariat<br>• Extraordinary sessions for unexpected topics | Conforms to World Health Organization recommendations |
| Meeting frequency | Four ordinary sessions per year | Conforms to World Health Organization recommendations |
| Institution in charge of the scientific and technical secretariat | Public Hygiene National Institute vaccinology department | Conforms to World Health Organization recommandations<br>Public Hygiene National Institute acts as the central coordinating structure for National Immunization Program activities |
| Financial operating resources | • Resources planned to be allocated in the general operating budget of the Public Hygiene National Institute<br>• Financial support for transportation and food | Conforms to World Health Organization recommendations |
| Communication/reports | • Advice and recommendations directly transmitted to the minister of health<br>• Other forms of transmission possible according to the committee | Conforms to World Health Organization recommendations |

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because of the political crisis. Topics discussed during those meetings included the SOPs of the NITAG, the drivers and obstacles for the functioning of the EPI program, and the burden of disease of vaccine preventable diseases after the political crisis. The most recent meeting of the NITAG was held in September 2011. During this meeting, the NITAG adopted a recommendation aimed at improving vaccination coverage and performances of the EPI in Côte d'Ivoire. One of the challenges is linked to the fact that the high frequency of polio eradication campaigns (six in 2011) drives away resources from routine immunization. The recommendation has been submitted to the MOH for approval.

Several months after NITAG implementation and after holding the first ordinary session, the president and general secretary of the CNEIV-CI attended a meeting of the French NITAG, the Technical Committee on Vaccinations (CTV), an advisory body located at the French High Council of Public Health. This visit was arranged so that the representatives of the Côte d'Ivoire Committee could better understand the functioning mode of a NITAG based on a long-standing model in a French-speaking country. This visit also provided an opportunity for the two NITAGs to initiate regular exchanges between their members.

## 5. Lessons learned

Côte d'Ivoire piloted many of the SIVAC Initiative processes; however, no systematic evaluation tool has yet been developed. Therefore the lessons learned presented here are primarily qualitative. The SIVAC Initiative, in collaboration with WHO, is in the process of defining a list of process, output and outcome indicators to support self-evaluation of NITAGs. This in turn will allow for the establishment of criteria to assess the drivers and limitations of success. The CNEIV-CI and the SIVAC Initiative are planning to evaluate the NITAG after three years of activity.

### 5.1. Drivers for success

The CNEIV-CI represents the first NITAG to have emerged in French-speaking sub-Saharan Africa. The two main drivers for success were a strong political will, mainly from the minister of health himself through his Cabinet, and the availability of sufficient national expertise. Other drivers included the step-by-step country-driven process and collaboration between the MOH and SIVAC. The strong political will was influenced by the presence of two champions who facilitated the process of creation of the NITAG: the deputy director of the Cabinet of the MOH and the deputy director for immunization and vaccines at INHP. They both had extensive professional experience in immunization, and attended the EPIVAC and Cocody University training programs. The deputy director of the Cabinet of the MOH had the role of facilitator and informant to the minister of health; the deputy director for immunization and vaccines, in his role of focal point for the MOH, acted as the facilitator for all the stakeholders involved.

The organization of the committee and recruitment of core members was facilitated by a long-standing commitment in Côte d'Ivoire toward higher education, which resulted in the availability of many experts in the field of immunization. Since the committee was based on a ministerial order, it had the authority it needed to recruit members and have a direct liaison to the implementing institution, namely the MOH.

The concept of a NITAG was new to all stakeholders at the beginning of the collaboration. To overcome this limitation, the SIVAC Initiative played an educational role by explaining the mandate of NITAGs, i.e. to act as a technical advisory committee to the MOH. This was contrasted with the activities of various existing committees (such as the ICC), and WHO recommendations, and supported by examples from other countries with functioning NITAGs. The meetings organized with all stakeholders served to remove barriers so that once the minister of health decided to create the committee, all stakeholders agreed as well.

### 5.2. Challenges

The socio-political crisis which occurred in 2002 had a negative impact on vaccination services. With the progressive return to a more stable socio-political situation in 2009, the national health authorities were confronted with multiple challenges in an environment characterized by scarce resources. Thus, the implementation of routine EPI follow-up activities and numerous supplementary vaccination activities by the minister of health mobilized most of the departments involved in the drafting of the NITAG concept paper during 2009.

Creation of the NITAG was facilitated by the relative political stability that existed during the creation period. During 2010, upheavals related to a disputed national election led CNEIV-CI to cancel its meetings and postpone its work for a year. However, the crisis did not affect the composition of the NITAG and since the new Government has been in place, the NITAG has been meeting and is functioning well. A NITAG meeting will take place in the first quarter of 2012 to plan for the 2012 agenda. Topics to be discussed include the development of a framework for managing AEFI, the assessment of immunization and surveillance activities in 2011, and the introduction of new vaccines.

Some NITAG members had extensive other priorities. This led to delays in the finalization of the concept paper and subsequent delays in NITAG creation. It is likely that this challenge will exist in all developing countries, given the great needs in the field of immunization, limited technical expertise, and the consequent great demands placed on in-country professionals.

Finally, several MOH members did not recognize the usefulness and relevance of a NITAG at first, arguing that many immunization advisory committees already existed. Moreover, some MOH members also initially objected to NITAG committee member independence, which was eventually clarified to mean member independence, with the committee itself serving the MOH.

## 6. The future

For many years, decision making in Côte d'Ivoire was mainly influenced by regional and international rather than national recommendations. A significant milestone was achieved in December 2009 when Côte d'Ivoire's MOH created the CNEIV-CI, the first NITAG in a GAVI-eligible African country. The example of Côte d'Ivoire can set the stage for other countries in the region to establish their own NITAG.

Looking forward, some risks can be foreseen. Although the recent political crisis temporarily suspended the work of the CNEIV-CI, the NITAG resumed its meetings. The challenge is now to ensure that the committee meets regularly a year and that all members attend, as it is likely that many pressing health priorities will exist. In this context, it will be important that members advocate the NITAG to the members of government. This is particularly pertinent given that the implementation of NITAG recommendations requires endorsement by the minister of health. Finally, NITAG functioning requires substantial preparatory work by the NITAG executive secretariat; however, it remains in doubt whether Côte d'Ivoire will be able to provide staff with sufficient availability and technical expertise to serve on the secretariat. For example, in the United States, the US Centers for Disease Control and Prevention serves this function for the American Committee on Immunization Practices; however, no equivalent structure exists in Côte d'Ivoire.

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RESEARCH ARTICLE Open Access

# African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults

Bradford D Gessner[1*], Judith E Mueller[1], Seydou Yaro[2]

## Abstract

**Background:** Pneumococcal conjugate vaccine strategies in GAVI-eligible countries are focusing on infant immunization but this strategy may not be optimal in all settings. We aimed to collect all available population based data on pneumococcal meningitis throughout life in the African meningitis belt and then to model overall meningitis risk to help inform vaccine policy.

**Methods:** After a systematic review of literature published from 1970 through the present, we found robust population-based *Streptococcus pneumoniae* (Sp) meningitis data across age strata for four African meningitis belt countries that included 35 surveillance years spanning from 1970 to 2005. Using these data we modeled disease risk for a hypothetical cohort of 100,000 persons followed throughout life.

**Results:** Similar to meningococcal meningitis, laboratory-confirmed pneumococcal meningitis was seasonal, occurring primarily in the dry season. The mean annual Sp meningitis incidence rates were 98, 7.8 to 14, and 5.8 to 12 per 100,000 among persons <1, 1 through 19, and 20 to 99 years of age, respectively, which (in the absence of major epidemics) were higher than meningococcal meningitis incidences for persons less than 1 and over 20 years of age. Mean Sp meningitis case fatality ratios (CFR) among hospitalized patients ranged from 36-66% depending on the age group, with CFR exceeding 60% for all age groups beyond 40 years; depending on the age group, Sp meningitis mortality incidences were 2 to 12-fold greater than those for meningococcal meningitis. The lifetime risks of pneumococcal meningitis disease and death were 0.6% (1 in 170) and 0.3% (1 in 304), respectively. The incidences of these outcomes were highest among children age <1 year. However, the cumulative risk was highest among persons age 5 to 59 years who experienced 59% of pneumococcal meningitis outcomes. After age 5 years and depending on the country, 59-79% of meningitis cases were caused by serotype 1.

**Conclusions:** In the African meningitis belt, Sp is as important a cause of meningitis as *Neisseria meningitidis*, particularly among older children and working age adults. The meningitis belt population needs an effective serotype 1 containing vaccine and policy discussions should consider vaccine use outside of early childhood.

## Background

Pneumococcal vaccine policy discussions for Africa have focused almost exclusively on developing a pneumococcal conjugate vaccine for use in infancy or early childhood [1,2]. The Global Alliance for Vaccines and Immunization (GAVI)-sponsored PneumoADIP has a mission statement limited to accelerating "access to new, lifesaving pneumococcal vaccines for the world's children." (website: http://www.preventpneumo.org/mission.cfm, last accessed June 24, 2008). Fewer discussions have occurred regarding pneumococcal vaccine use among older children and adults and no vaccine strategies have been formulated. This focus on pediatric disease may be misplaced in the African meningitis belt [3], a region of sub-Saharan Africa that is characterized

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by particularly high and seasonal incidences of bacterial meningitis and annual rainfall between 300 and 1100 mm. For example, data we collected from an exhaustive polymerase chain reaction-based surveillance system in and around Bobo-Dioulasso, Burkina Faso, during 2002-7 suggest that high pneumococcal meningitis burden extends throughout life and is associated with a high case fatality ratio [4-6]. The current report aims to summarize and model data on pneumococcal meningitis burden in the African meningitis belt and to discuss implications for vaccine policy.

## Methods

### Search criteria

We searched PubMed, CINAHL Plus, and the ISI Web of Knowledge (containing SCI-Expanded, SSCI, and A&HCI) databases and the references of retrieved articles. English and French language articles from 1970 to the present were included. A single author (BDG) performed all data abstraction and entered data into an Excel spreadsheet. No validity assessment of retrieved articles was performed.

### Article retrieval

The primary meningitis outcome was the Sp meningitis incidence by age group throughout life in the African meningitis belt. Step one of the search was designed to be sensitive in identifying potential articles. Consequently, search terms were non-specific and included "meningitis" in combination with one of the meningitis belt countries including (alphabetically) Burkina Faso, Chad, Ethiopia, The Gambia, Guinea, Guinea Bissau, Mali, Niger, Senegal, and Sudan plus the northern half of the Central African Republic, Cote d'Ivoire (and Ivory Coast), Ghana, Kenya, Nigeria, Togo, and Uganda. Articles that reported only meningococcal, *Haemophilus influenzae* type b (Hib), or epidemic meningitis in their title had their abstracts reviewed but then uniformly excluded as having no information on pneumococcal disease. This led to identification of 45 articles, including 12 from The Gambia, eight from Ethiopia, five each from Northern Nigeria and Senegal, three each from Mali, Niger and Burkina Faso, two from Cote d'Ivoire, and one each from Chad, northern Ghana, northern Togo, and northern Uganda.

Step two involved reviewing the retrieved articles to identify those that reported age-specific pneumococcal meningitis incidence throughout life. Only five articles were identified that provided this information and thus that were included in the evaluation [4,5,7-9]. Four of these articles [4,5,8,9] were of approximately the same quality in that they determined incidence by conducting hospital and health center surveillance for cases and then divided by the estimated population of the area from which cases derived. In many settings in Africa, though, population estimates may not be accurate. Consequently, for these studies incidence rates should be considered rough approximations. The fifth article from Ghana [7] followed a defined population over time. All of the studies were used to estimate meningitis burden; the two studies from Burkina Faso [4,5] reported overlapping data from the same surveillance site and some of the same time periods and thus data were combined. Each of the articles reported surveillance that spanned all months of the year. However, we could not exclude the possibility that persons with meningitis symptoms were more likely to present or receive an evaluation (i.e., lumbar puncture and laboratory evaluation) during the epidemic meningitis season months.

Each of the articles reported surveillance that spanned all months of the year. However, we could not exclude the possibility that persons with meningitis symptoms were more likely to present to a health care facility and receive an evaluation during the epidemic meningitis season. This could have led to an underestimation of pneumococcal meningitis incidence, including by serotype if some serotypes occurred preferentially during particular seasons. This could have been assessed in part by evaluating seasonality by age and serotype but none of the studies reported this information. The similar magnitude of increase of meningococcal and pneumococcal meningitis during the meningitis season and the known seasonality of meningococcal meningitis suggest that this issue did not affect results to a large degree.

### Model structure

Besides reporting the results from individual studies, we estimated the lifetime risk of pneumococcal disease outcomes. First, an average age-specific annual meningitis incidence rate - weighted for the size of the population under surveillance - was calculated for the four included meningitis belt countries. Annual meningitis mortality incidence rates were calculated as the weighted average of the case fatality ratios multiplied by the annual meningitis incidence rates within each age category. To calculate lifetime meningitis risk, age-specific pneumococcal meningitis and meningitis mortality incidence rates were applied to a hypothetical population of 100,000 persons followed from birth until the $100^{th}$ birthday (by which point all persons were assumed to have died). Data are presented by age group through age 99 years. Not all studies reported age groups at the same level of detail; where data were missing, the incidence rate for the closest available older age group was used. Because data were sparse particularly for older ages, for all outcomes identical values were used from age 60 through 99 years. Ghana did not report age-specific case fatality ratios and thus was not included in

estimation of pneumococcal meningitis mortality incidence rates. All estimates were adjusted for all-cause mortality from all causes based on life tables for the four study countries (website: http://www.who.int/whosis/database/life_tables/life_tables.cfm, last accessed July 2, 2008). This adjustment thus accounts for the relatively low life expectancies found in the analyzed countries.

The four study countries reported meningitis incidence rates only among persons who presented to a hospital or health center and who had a diagnostic workup that led to documentation of meningitis. However, an unknown number of persons have undocumented meningitis because of failure to present, pretreatment with antibiotics, lack of lumbar puncture, or problems with specimen transport or storage. Anecdotal reports from our surveillance site in Burkina Faso and our experience in Senegal, Mali, Togo, and Niger suggest awareness of meningitis and care seeking are relatively high, but the contribution of other factors remains unknown. For example, during the dry epidemic meningitis season months, treatment may be presumptive based on clinical symptoms or documentation of purulent cerebrospinal fluid without confirmation of etiology. Manuscripts included in the current analysis do not indicate any attempts by the study teams to increase access to care or increase the percent of cases with etiological confirmation (indeed, the Niger and Senegal studies were retrospective). However, because data from the meningitis belt on the effect of the factors discussed above do not exist, we did not make an attempt to model the burden of undocumented cases.

The African meningitis belt traditionally has been considered to have abnormally high meningococcal - but not necessarily pneumococcal - disease burden [3]. As a point of comparison, we present data on meningococcal meningitis disease incidence and mortality rates. Niger [8] and Senegal [9] reported these data in the same manuscript while Burkina Faso reported data from the same time period and surveillance site in a separate manuscript [10]. Comparison data were not available for Ghana.

## Results

The four countries reporting meningitis incidence rates throughout life included two major metropolitan areas plus rural areas, involved in aggregate 36 years of follow-up, spanned from 1970 to 2005, and identified 2,242 persons with pneumococcal meningitis (Table 1). At all four sites, pneumococcal meningitis was seasonal with the highest number of cases during the dry season (i.e., the epidemic meningitis season). For three sites, pneumococcal meningitis was highly seasonal with case identification decreasing to near zero during other months. Three studies reported serotype results and among those at least 5 years of age (or 2 years for Senegal) serotype 1 contributed at least 60% of cases for all three sites (Table 2).

**Table 1 Characteristics of evaluated countries**

| Characteristic | Burkina Faso* | Senegal* | Niger* | Ghana* |
|---|---|---|---|---|
| Surveillance design | Prospective | Retrospective | Retrospective | Prospective |
| Geographic extent | Three districts | Dakar | Niamey | Northern area |
| Surveillance population | 880,000 | 950,000 | 550,000 | 140,000 |
| Rural/Urban | Both | Urban | Urban | Rural |
| Study years | 2002-2005 | 1970-1979 | 1981-1996 | 1998-2003 |
| Microbiological methods | Culture, antigen detection, PCR | Culture | Culture, antigen detection | Culture, antigen detection |
| Number of confirmed pneumococcal meningitis cases | 249 | 983 | 934 | 76 |
| Percent of cases occurring during dry/epidemic season months of Dec-Apr† | 75% | 49% | 63% | 69% |
| Two months with peak number of cases (percent of total)† | Jan-Feb (38%) | Feb-Mar (21%) | Feb-Mar (31%) | Dec-Jan (35%) |
| Relation of pneumococcal to meningococcal seasonal peak | Similar | 2 months in advance | 1 month in advance | 1 to 2 months in advance |
| 13-valent conjugate vaccine coverage of isolated serotypes | | | | |
| Age <5 years | 67% | 78% (age<2 yrs) | No serotype data | 100% |
| Age 5+ years | 77% | 94% (age 2+ yrs) | No serotype data | 98% |
| Reference | 4,5 | 9 | 8 | 7 |

* Human immunodeficiency virus prevalence in pregnant women age 15-24 years in capital city: Burkina Faso 2.3% (2002), Ghana 3.9% (2003), Senegal 1.1% (2003). Adult HIV prevalence in Niger was 1.2% (2003). Website: http://www.unicef.org/publications/files/SOWC_2005_(English).pdf, last accessed October 2, 2008.

† In all studies cases per month were estimated from Figures as specific data were not presented.

**Table 2 Serogroup/type distribution by age group and country**

| Serotype | Burkina Faso | | Senegal | | Ghana | |
|---|---|---|---|---|---|---|
| | Age < 5 years | Age 5+ years | Age < 2 years | Age 2+ years | Age < 5 years | Age 5+ years |
| 1 | 3 (17%) | 18 (60%) | 10 (9%) | 90 (63%) | 2 (33%) | 51 (80%) |
| 2 | 3 (17%) | | 15 (14%) | 3 (2%) | | |
| 3 | | | 6 (5%) | 8 (6%) | 2 (33%) | 2 (3%) |
| 5 | 3 (17%) | | 23 (21%) | 8 (6%) | | |
| 6A | 5 (28%) | | 14 (13%)* | 13 (9%)* | | 1 (2%) |
| 6B | 1 (6%) | | | | | |
| 7/7F | | 1 (3%) | | | | 1 (2%) |
| 8 | | | | | | 4 (6%) |
| 9 | | | 6 (5%) | 2 (1%) | | |
| 10/10F | 1 (6%) | | | | | 1 (2%) |
| 12A | | 1 (3%) | 9 (8%)* | 6 (4%)* | | |
| 12B | | 1 (3%) | | | | |
| 12F | | | | | | 2 (3%) |
| 14 | | 2 (7%) | 5 (5%) | 2 (1%) | 2 (33%) | 1 (2%) |
| 18 | | | 4 (4%) | 2 (1%) | | |
| 19A | | 1 (3%) | 4 (4%)* | 4 (3%)* | | |
| 19F | | 1 (3%) | | | | |
| 21 | 1 (6%) | | | | | |
| 23 | | | 14 (13%) | 5 (3%) | | |
| 24A | 1 (6%) | | | | | |
| 25A | | 2 (7%) | | | | |
| 25F | | 2 (7%) | | | | |
| 38 | | | | | | 1 (2%) |
| NT | | 1 (3%) | | | | |
| Total | 18 (100%) | 30 (100%) | 110 (100%) | 143 | 6 (100%) | 64 (100%) |

* These cells present summary data on serogroups 6, 12, and 19 as serotype specific data were not available

Age-specific annual laboratory-confirmed pneumococcal meningitis incidence rates were highest among infants (Table 3). Children age 12 to 23 months also may have been at increased risk but only one study reported results specifically for this age group. Following the first two years of life, and at all four study sites, age-specific annual pneumococcal meningitis incidence were consistent and high for all age groups, with weighted means ranging from 6 to 14 per 100,000 per year. Niger, Burkina Faso, and Senegal also reported - from the same study site and period - data for meningitis due to *Neisseria meningitidis*, the etiology typically associated with the African meningitis belt; however, none of the studies included data from years during which major meningococcal meningitis epidemics occurred. Compared to endemic meningococcal meningitis, pneumococcal meningitis incidence rates were higher in infancy, similar in early childhood, lower in later childhood, similar in young adulthood and then substantially higher from age 30 years on. Pneumococcal case fatality ratios were reported by age group for three sites and were uniformly high, ranging from 36% to 66% (Table 4); the fourth country (Ghana) reported an overall pneumococcal meningitis case fatality ratio of 44%. Compared to meningococcal meningitis, pneumococcal case fatality ratios were higher for all age groups and annual mortality incidence rates were higher by a factor of 2 to 18.

The overall estimated lifetime risk of laboratory-confirmed pneumococcal meningitis was 0.6% (1 in 170 persons) and for laboratory-confirmed pneumococcal meningitis death was 0.3% (1 in 304 persons). Infants age <1 year (i.e., the age group targeted by pneumococcal conjugate vaccine childhood immunization programs) experienced 17% of cases and 16% of deaths, while children age less than 5 years experienced 25% of cases and 24% of deaths. Persons age 60 years or more (i.e., one target age group for pneumococcal polysaccharide vaccine) experienced 16% of cases and 19% of deaths. By contrast, persons age 5 to 59 years of age,

**Table 3 *Streptococcus pneumoniae* (Sp) meningitis incidence rates (per 100,000 per year) by age group and country [4,5,7-9]; *Neisseria meningitidis* meningitis incidences were available from Burkina Faso, Senegal, and Niger and summary means are presented for comparison**

| Age (yrs) | Burkina Faso | Senegal | Ghana* | Niger* | Mean† for Sp | Mean† for Nm‡ |
|---|---|---|---|---|---|---|
| <1 | 77 | 95 | 42 | 150 | 98 | 24 |
| 1 to 4 | 14 | 17 | 19 | 10 | 14 | 20 |
| 5 to 9 | 13 | 4.5 | 25 | 6.4 | 9.1 | 19 |
| 10 to 14 | 10 | 3.7 | | 6.9 | 7.8 | 17 |
| 15 to 19 | 11 | 2.4 | 20 | 9 | 7.8 | 11 |
| 20 to 29 | 6.1 | 4.0 | | 4.7 | 5.8 | 5.0 |
| 30 to 39 | 14.1 | 5.2 | 18 | 3.2 | 8.6 | 3.3 |
| 40 to 49 | 19.1 | 7.8 | | 7.9 | 12 | 2.8 |
| 50 to 59 | 8.0 | 11 | | | 9.7 | 3.3 |
| 60+ | 8.1 | 15 | 25 | | 10 | 2.8 |

*Not all studies reported age groups at the detail shown in column 1. The incidences in Ghana for persons age 5 to 19, 15 to 29, and 30 to 59 years and in Niger for persons 40+ years were 25, 20, 18, and 7.9 per 100,000 persons per year, respectively.

†Weighted mean based on population under surveillance. Where data were not available from a study site for a specific age group, the next oldest age group was used in the calculation of the weighted mean.

‡ Nm = *Neisseria meningitidis*. For comparison, data on Nm are presented for the same surveillance periods and sites except for Ghana, which did not report these data.

**Table 4 *Streptococcus pneumoniae* (Sp) meningitis case fatality ratios by age group and country [4,5,7-9]; *Neisseria meningitidis* meningitis case fatality ratios were available from Burkina Faso, Senegal, and Niger and summary means are presented for comparison**

| Age (yrs) | Burkina Faso* | Senegal | Niger* | Ghana* | Mean† Sp CFR (mortality)‡ | Mean† Nm‡ CFR (mortality§) |
|---|---|---|---|---|---|---|
| <1 | 52% | 55% | 58% | 44% | 53% (53) | 12% (2.9) |
| 1 to 4 | 50% | 50% | 57% | | 52% (7.4) | 17% (3.3) |
| 5 to 9 | 45% | 48% | 16% | | 36% (3.6) | 10% (1.8) |
| 10 to 14 | | 50% | 35% | | 43% (3.5) | 10% (1.7) |
| 15 to 19 | 44% | 35% | 62% | | 47% (3.5) | 9% (1.0) |
| 20 to 29 | | 60% | 58% | | 54% (3.1) | 16% (0.8) |
| 30 to 39 | | 70% | 20% | | 45% (4.2) | 24% (0.8) |
| 40 to 49 | | 85% | 60% | | 63% (7.9) | 21% (0.6) |
| 50 to 59 | | 78% | | | 61% (5.9) | 43% (1.4) |
| 60+ | | 93% | | | 66% (6.7) | 43% (1.2) |

*Not all studies reported age groups at the detail shown in column 1. The CFRs in Burkina Faso for persons age 5 to 14 and 15+ years, in Niger for persons 40+ years, and in Ghana for all ages combined were 45%, 44%, 60%, and 44%, respectively.

†Weighted mean based on population under surveillance; Ghana was not included in the weighted means. Where data were not available from a study site for a specific age group, the next oldest age group was used in the calculation of the weighted mean.

‡ Nm = *Neisseria meningitidis*. For comparison, data on Nm are presented for the same surveillance periods and sites except for Ghana, which did not report these data.

§Mortality rate per 100,000 per year, based on the product of the meningitis incidence rate and the case fatality ratio.

who usually are not targeted by vaccination programs, experienced 59% of cases and 57% of deaths.

The cumulative risk of pneumococcal meningitis and meningitis death increased at a relatively constant rate after age 5 years (Figure 1). The number of new cases decreased among older persons despite a modest increase in incidence rates because fewer and fewer people remained alive to experience outcomes. The total number of outcomes was greatest during the first year of life (Table 5). Nevertheless, the number of new cases occurring during each age decade after 20 years was comparable to that during infancy and up to three times greater than that during the age category of 1-9 years.

## Discussion

### Meningitis

The current analysis showed that for at least the last 35 years, and based on approximately 35 years of surveillance occurring in four countries, pneumococcal meningitis in the meningitis belt has caused a high burden of

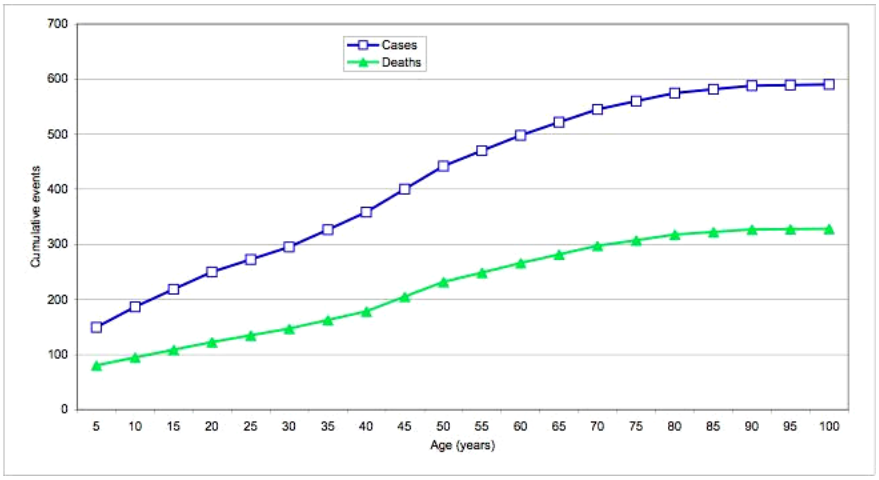


**Figure 1 Cumulative *Streptococcus pneumoniae* meningitis and meningitis death cases**. Among a hypothetical population of 100,000 persons living in the meningitis belt and followed from birth to death, the cumulative number of *Streptococcus pneumoniae* meningitis and meningitis death cases occurring by 5-year age increments.

**Table 5 Estimates of laboratory-confirmed *Streptococcus pneumoniae* (Sp) meningitis cases and deaths within age groups**

| Age group in years | Meningitis cases | Meningitis deaths |
|---|---|---|
| <1 | 98 | 53 |
| 1 to 4 | 52 | 27 |
| 5 to 9 | 37 | 15 |
| 10 to 14 | 32 | 14 |
| 15 to 19 | 31 | 14 |
| 20 to 29 | 45 | 24 |
| 30 to 39 | 64 | 31 |
| 40 to 49 | 83 | 53 |
| 50 to 59 | 56 | 34 |
| 60 to 69 | 47 | 32 |
| 70 to 79 | 30 | 20 |
| 80 to 89 | 10 | 7 |
| 90 to 99 | 2 | 1 |
| Total | 587 | 326 |

These estimates were made for a hypothetical population of 100,000 persons in the African meningitis belt followed from birth through age 99 years [4,5,7-9].

disease and high mortality in older children and working age adults, primarily during the epidemic meningitis season. Of the estimated 1 in 170 persons that will experience laboratory-confirmed pneumococcal meningitis, many will develop sequelae such as hearing and vision loss, seizure disorder, cerebral palsy, and mental retardation [11], although no specific data exist from the meningitis belt on these sequelae among older children and adults. Beyond laboratory-confirmed cases, an unknown burden of unconfirmed cases exists, since some persons do not present for care or receive a lumbar puncture, others have received pretreatment with antibiotics, and laboratory limitations may prevent etiologic identification. This issue may be accentuated for mortality, since lumbar punctures may be less likely to be performed in critically ill and unstable patients. Consequently, data presented very here should be considered minimum estimates.

Within the limits of our analysis, pneumococcal meningitis burden among older children and working age adults may surpass that for diseases currently targeted for routine immunization in meningitis belt countries. For example, WHO has recommended universal infant Hib vaccination [12], and the meningitis belt in particular has among the world's highest annual incidence rates at 34-60 per 100,000 children aged under 5 years [13]. Almost the entire risk of Hib disease, though, occurs during childhood. By contrast, the high pneumococcal meningitis incidences that occur throughout life result in a higher pneumococcal meningitis risk during ages 5 to 49 years than Hib meningitis during childhood. Beyond the higher cumulative risk of pneumococcal outcomes, disease, disability, and death among working adults may impoverish entire families or extended families, triggering a cascade of adverse health events [14].

Compared to the United States and Europe, where a bimodal meningitis age distribution with peaks in infants and the elderly is observed, pneumococcal meningitis epidemiology in the meningitis belt appears distinctly different, with strong seasonality, predominance of serotype 1 outside of childhood, higher incidences, higher case fatality ratios, and an age distribution with a concentration on older children and working age adults [15-19]. Indigenous persons of North

America and Australia have overall pneumococcal disease incidences that are among the world's highest. However, Sp meningitis incidence in these populations is still relatively low compared to incidence rates observed in the African meningitis belt, and other aspects of Sp epidemiology are similar to what is seen in developed country populations [16,20,21]. African countries outside the meningitis belt have, not reported population-based pneumococcal meningitis data across the entire life span. An unpublished study from Kenya [22] reported annual incidence rates among adults for all invasive pneumococcal disease - including bacteremia, which can cause 10-20 fold more invasive disease than meningitis [15] - of 261 and 3.3 per 100,000 among, respectively, persons with and without confirmed human immunodeficiency virus (HIV) infection. The latter rate for all invasive disease is substantially lower than the Sp meningitis incidence seen in the meningitis belt. North-central Uganda, which borders the meningitis belt, reported an annual pneumococcal meningitis incidence among children under age 5 years of 28 to 42 per 100,000 versus 3 to 20 per 100,000 reported in tropical Kampala [23]. These data suggest that the meningitis belt has a unique pneumococcal disease epidemiology even within Africa.

The mechanisms responsible for the Sp epidemiology found in the meningitis belt remain unknown. The observed seasonal pattern indicates some overlap in risk factors with meningococcal meningitis [24] including climatic conditions, concurrent respiratory infections, decreased host immunity and others. Although HIV plays an important role in many African countries [22], meningitis belt countries have relatively low HIV prevalences and the epidemiology of pneumococcal meningitis in the region has been relatively stable since the 1970s when HIV was presumably of little importance. It is unlikely that circulation and transmission of serotype 1 alone explains the observed patterns since Asia, with the world's lowest documented pneumococcal meningitis incidences, reports serotype 1 as the most common cause of meningitis in all age groups [25]. Lastly, meningitis belt countries have a high prevalence of hemoglobinopathies mainly due to hemoglobin S and C [26], and these greatly increase the risk of invasive pneumococcal disease [27]. High hemoglobinopathy prevalence, however, is not unique to the meningitis belt.

### Implications for pneumococcal pneumonia

The African meningitis belt, home to about 350 million people, is characterized by an extraordinarily high incidence of acute bacterial meningitis, occurring mainly during the dry season. No data, however, exist from the meningitis belt on age specific pneumonia incidence, either overall or specifically for pneumococcus. Thus, it remains unknown if the high pneumococcal meningitis disease burden occurs in association with a high pneumococcal pneumonia burden. In industrialized countries, numerous studies have estimated the ratio of bacteremic pneumococcal pneumonia to meningitis [15-21,28,29]. Examination of data from these studies (Additional file 1, Table S1) illustrates that this ratio remains relatively stable across populations (including high incidence populations such as Alaska Native people) and increases sharply with age. If ratios seen in developed countries hold true for meningitis belt countries, it would imply a very high risk of pneumococcal pneumonia (estimated as 1 in every 15 persons using the presented meningitis data) and overall pneumococcal mortality (estimated as 1 in every 62 persons) with a risk even more weighted toward ages outside of early childhood than that seen for meningitis.

The applicability of this ratio for meningitis belt populations, however, is unknown. The only relevant current data point from in or near the meningitis belt is the pneumococcal conjugate vaccine trial (using a serotype 1 containing vaccine) from The Gambia, located just outside the Western edge of the meningitis belt [30]. Based on reported vaccine-preventable disease incidences for various outcomes, the ratio of vaccine-preventable pneumococcal pneumonia (bacteremic and non-bacteremic) to meningitis was 30 to 1 and the ratio of all pneumococcal mortality to pneumococcal meningitis mortality was 8.8 to 1. These figures would imply an even higher risk of Sp pneumonia and mortality than the values reported in the previous paragraph. The Gambia trial, though, is limited by its location outside of the meningitis belt and a study population limited to children age 6 weeks to 2 years. In summary, there is a need for data on pneumococcal pneumonia across age groups specifically for the meningitis belt.

### Limitations

Our study had at least six limitations. Data were not available from countries located in the eastern part of the meningitis belt such as Sudan and Ethiopia, where pneumococcal disease epidemiology in theory may be different. Meningitis incidence estimates from Niger, Burkina Faso, and Senegal were based on dividing case counts by the population data available, which may be imprecise and therefore overestimate or underestimate true incidence rates. We did not find data on the proportion of all persons with pneumococcal meningitis that present for definitive diagnosis either overall or by syndrome or age group. Although serotype 1 appears to have predominated over many years in the meningitis belt, serotype distribution is a dynamic process. Our results are valid for a situation with predominance of serotype 1 in older children and adults and may require

revision if the serotype distribution should change. Only Senegal provided mortality data restricted to elderly persons and thus estimates for this group are uncertain. Lastly, a quality assessment of the studies was not conducted and approximations in denominators and inclusion of different time periods could have affected results.

#### Implications for vaccine use in the meningitis belt

Existing data indicate that meningitis belt populations need a serotype 1-containing vaccine. The licensed 7-valent pneumococcal conjugate vaccine does not contain serotype 1, may be associated with increases in non-vaccine serotypes [31-34], and thus likely will have little role outside of early childhood in the meningitis belt. Existing 23-valent polysaccharide vaccines could have a role, but these vaccines do not reduce carriage, may be no less expensive than conjugate vaccines, and manufacturers may have little interest in increasing production. Before or concurrent with introduction, the effectiveness of serotype 1 containing vaccine must be confirmed. In The Gambian trial, vaccine was not effective against serotype 1 disease, however the results were based on a total of only six invasive isolates [35]. Other studies - including in The Gambia - have documented robust immunologic response against serotype 1 [35-38] as well as vaccine effectiveness with conjugate [39] or polysaccharide vaccines [40]. The latter finding is encouraging since conjugate vaccines usually elicit more robust immune responses, including for serotype 1 and outside of childhood [41,42]. Nevertheless, questions about serotype 1 conjugate vaccine effectiveness must be resolved before widespread vaccine implementation.

A policy of universal infant pneumococcal vaccination may provide indirect protection to older persons if ongoing Sp carriage and transmission requires young children [43]. If transmission for some serotypes can be maintained solely among older persons, though, infant vaccination will have little impact on the pneumococcal disease burden we describe here. Data on serotype 1 transmission dynamics, including the contribution of different age groups, are lacking in the meningitis belt. Among African populations outside of the meningitis belt, serotype 1 carriage is rarely seen [44-46] but this may indicate a short carriage duration rather than infrequent transmission. During a serogroup A meningococcal epidemic in Burkina Faso, we found among a representative community-based population sample of persons aged 1 to 39 years relatively flat age distributions of overall pneumococcal carriage as well as IgG seroprevalence for serotype 1 similar to other serotypes. Moreover two of three serotype 1 carriage isolates were identified from persons aged greater than 5 years [6].

Most logistical issues associated with delivering pneumococcal vaccine outside of infancy have already been addressed during planning by the GAVI Alliance, WHO, and Unicef for preventive conjugate meningococcal serogroup A vaccine introduction and for the current yellow fever vaccine campaigns in sub-Saharan Africa. For example, one proposed plan for the meningococcal vaccine is to conduct an initial mass vaccination campaign among persons 1 to 29 years of age, followed by continuous routine infant vaccination. Similar mass vaccination campaigns with pneumococcal conjugate vaccine likely would have an immediate and high impact on pneumococcal disease in the region, and possibly higher than that associated with routine infant immunization. Because of longer antibody persistence among individuals older than 1 year, a single dose among persons 1 to 29 years of age probably would have a long-term impact on pneumococcal disease burden. Mass campaigns and routine infant immunization could occur simultaneously, although costs, vaccine availability, and programmatic issues may require a sequential approach. Efforts also should be made to improve and document high vaccination coverage.

## Conclusions

Based on available data for pneumococcal disease epidemiology in the African meningitis belt, policymakers should consider mass vaccination campaigns among older children and adults to precede or accompany routine infant immunization. To guide policy decisions, there remains a substantial need for data on serotype-specific pneumococcal transmission patterns, pneumococcal pneumonia and invasive disease burden across age strata, and pneumonia and meningitis sequelae. A vaccine demonstration project [47] measuring impact on meningitis and pneumonia outcomes could provide this information as well as information on serotype-specific vaccine effectiveness, vaccine impact on meningitis, pneumonia, and carriage, and assessment of programmatic, logistic, and economic issues associated with vaccine introduction.

## List of abbreviations

GAVI: Global Alliance for Vaccines and Immunization; HIV: Human immunodeficiency virus; Sp: *Streptococcus pneumoniae*; WHO: World Health Organization.

**Additional file 1: Table S1**. Table S1: studies reporting the ratio of pneumococcal meningitis to bacteremia globally.
Click here for file
[ http://www.biomedcentral.com/content/supplementary/1471-2334-10-22-S1.DOC ]

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**Authors' contributions**
BDG conceived the analysis, developed the initial model, carried out all analysis, wrote the first draft of the manuscript, and read and approved the final manuscript.
JEM assisted with model development, provided substantial input into the interpretation of results, assisted in the preparation of the final manuscript, and read and approved the final manuscript.
SY provided substantial input into the interpretation of results, assisted in the preparation of the final manuscript, and read and approved the final manuscript.

**Competing interests**
Bradford D. Gessner and Judith E. Mueller work for Agence de Médecine Préventive, which receives substantial financial support for all of its activities from sanofi pasteur, which is currently not involved in the production of pneumococcal conjugate vaccines. Additionally, both have received honoraria from Glaxo-Smith-Kline, a producer of pneumococcal conjugate vaccines.

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