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Strategies for the Prevention of Meningitis

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1. Introduction

Meningitis is a clinical condition involving inflammation of the meninges that most commonly affects otherwise healthy people. Generally, the meningitides are of infectious etiology that can be viral, bacterial, fungal, or parasitic in nature, although iatrogenic causes are rarely reported (Table 1). Inflammation of the meninges can pose serious dangers to patients, given that many of the areas affected are encased by bony structures that can exacerbate tissue damage caused by swelling. Collapse of the blood vessels, causing hypoxic damage, is a particularly dangerous effect of inflammation in the brain. In fact, permanent disability and death may result from all forms of meningitis. Further, sepsis, bacteremia, or other disease processes can be caused by the same infectious agents that cause meningitis. Epidemics associated with certain pathogens, like the meningococcus, pose a serious public health risk, and therefore require prevention and control strategies. The quest to limit the

	Viruses*	Bacteria	Fungi
Vaccine preventable	Japanese and tick-borne encephalitis Polio Measles Mumps	*Streptococcus pneumoniae* ("Pneumococcus") *Neisseria meningitidis* serogroups A, C, W-135, Y *Haemophilus influenzae* type b Tuberculosis	
Vaccines under clinical investigation		Group B streptococcus *Neisseria meningitidis* serogroup B *Staphylococcus aureus*	
No vaccines available	West Nile Herpes simplex	*Neisseria meningitidis* serogroup X *Escherichia coli* *Listeria monocytogenes* Lyme (*Borrelia burgdorferi*)	*Candida albicans* *Cryptococcus neoformans* Histoplasma

*Most commonly enteroviruses, arboviruses, herpes, measles and mumps
Rarely, meningitis may be caused by parasites or as a side effect of medication.

Table 1. Examples of pathogens associated with meningitides, encephalitis, or sepsis (2-3)

public health impact of meningitis has led to the application of various public health strategies, including vaccine campaigns, over the last century (1-2). This chapter places meningitis vaccine policy in the context of several forces: public perception and media activity, clinical diagnosis and laboratory testing, antibiotic effectiveness and vaccine safety, efficacy and cost-effectiveness. Country and situational examples will be given.

2. Disease factors that impact policy decisions

The global epidemiology of meningitis changed dramatically during the twentieth century as vaccines and antibiotics became available to prevent and treat this deadly disease (4-5). The potential public health impact of meningitis-causing organisms is affected by disease incidence, severity and scope, case fatality ratio, risk of contagion, rate of disease progression and additional acute and chronic disease caused by the pathogen. The Meningitis Research Foundation notes that, with the exception of measles and mumps (6) which have been vaccine-preventable for decades, the relatively mild severity and generally good prognosis associated with the viral meningitides makes for mild concern among policymakers (3). The World Health Organization and the Pan American Health Organization consider bacterial, particularly meningococcal, meningitis to be among the world's most important public health problems (2).

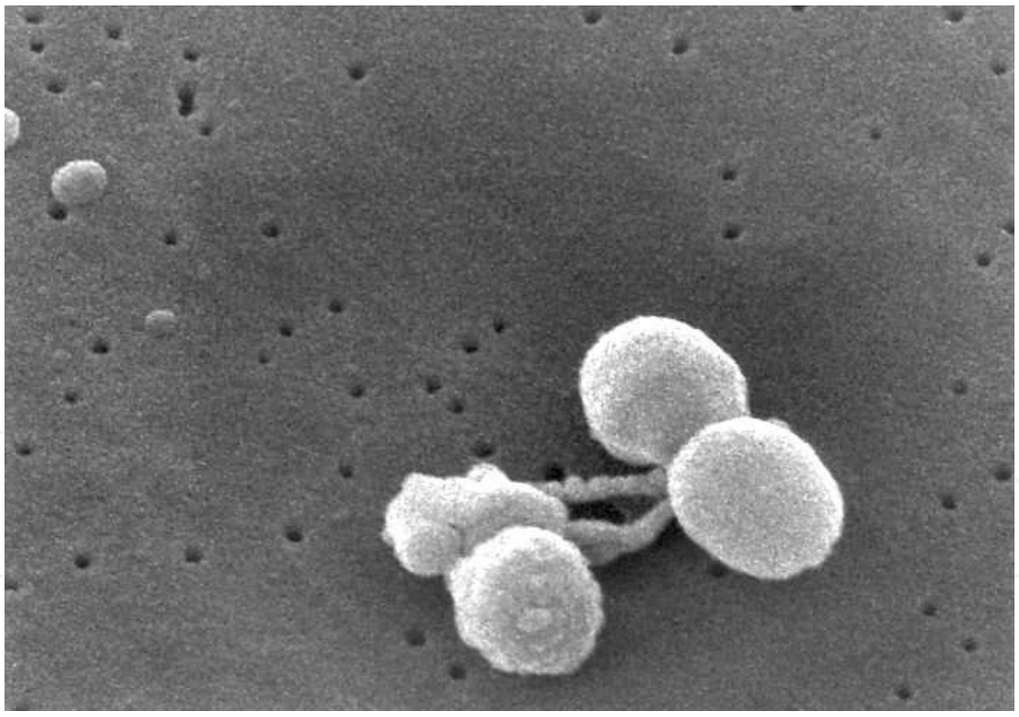

Fig. 1. Scanning electromicrograph of the pneumococcus. photo by Janice Haney Carr. Centers for Disease Control and Prevention Public Health Image Library ID # 265. (15)

The most common causes of bacterial meningitis in the United States, Europe and many other developed countries since the 1980s have been the pneumococcus, *Haemophilus influenzae* type b, the meningococcus, group B streptococcus, and *Listeria monocytogenes* (4-5, 7). In Africa, seasonal outbreaks and epidemics of meningococcal meningitis and

septicemia numerically represent the greatest public health impact in this context (1, 8-9). The three polysaccharide-encapsulated bacteria for which licensed vaccines are widely available, the pneumococcus, *Haemophilus influenzae* type b , and the meningococcal serogroups A, C, W-135 and Y, have been the major focus of vaccine development and policy efforts (1-2, 10-11). Following the initial introduction of conjugate polysaccharide vaccines against these pathogens during the 1980s and 1990s the epidemiology of bacterial meningitis has changed dramatically. Further challenges to reducing the global burden of meningitis remain, among them the need for vaccines against Group B streptococcus, which accounts for a large proportion of newborn and very young infant infections, and meningococcal serogroup B (11-12). Indeed, in a recent report, Group B streptococcus was responsible for more than 85% of bacterial meningitis among US infants less than 2 months of age (5). In regions where vaccines against pneumococcus and *Haemophilus influenzae* type b are not available, Group B streptococcus is also an important cause of meningitis in the first 3 months of life (13-14).

The clinical characteristics of various meningitides are discussed in detail in other chapters. Risk factors for bacterial meningitis include age (the very young, the elderly, adolescents), underlying medical conditions (innate or acquired immunosuppression, complement deficiency, shunts, cochlear implants) and lifestyle factors such as poverty, college attendance, or travel. Increasing evidence suggests that genetic factors increase the risk of contracting bacterial meningitis (Table 2).

Genetic condition	**Arising infection**
Severe congenital neutropenia	Recurrent infections
Immunoglobulin deficiency	Pneumococcal infection
Severe combined immune deficiency	Recurrent infections
Complement deficiency	Meningococcal infection
TLR and NEMO	Pneumococcal infection
Mal/TIRAP gene	*Haemophilus influenzae* type b vaccine failure

TLR: toll-like receptor; NEMO: NF-kappa-B essential modulator; TIRAP: toll-interleukin 1 receptor (TIR) domain containing adaptor protein.
(1, 16-20)

Table 2. Known genetic predispositions to bacterial meningitis

Unique risk factors (Table 3) for meningococcal meningitis have been observed in adolescents and young adults: close social contact (e.g. bars, discotheques, dormitories), kissing, smoking (1, 3, 17-18). For *Haemophilus influenzae* type b, and pneumococcus, low socioeconomic status and ethnic minority group status represent risk factors of special note (5).

Exposure to antibiotics can increase the risk of infection with an antibiotic-resistant organism, as observed for pneumococcal infections, while vaccine policy has exerted a downward pressure on antibiotic resistance (26). For newborn Group B streptococcus infection, maternal colonization alone is a risk factor – accordingly, some regions recommend administration of prophylactic antibiotics during labor and delivery for all women known to be colonized (27).

Crowding factors
Moving into a college dormitory, particularly freshmen
Moving into army barracks, particularly new military recruits
Travel
Attendance at the Hajj or Umrah pilgrimages
Travel to areas with hyperendemic or epidemic disease
Social factors
Pub or discotheque attendance
Kissing
Smoking and exposure to second-hand smoke

(1,21-25)

Table 3. Examples of risk factors for developing meningococcal meningitis

Rates of asymptomatic carriage may affect the transmission of encapsulated pathogenic bacteria and thereby lead to colonization, invasion and invasive disease. The ability to adhere to or penetrate the mucosa, or to survive and multiply in blood or infect organs (especially the brain) are commonly-recognized virulence factors that, like epidemiology, may differ among strains, serogroups or types of encapsulated bacteria within a species (1, 5, 24, 28-32). Susceptibility to disease or asymptomatic carriage may coincide or occur in distinct population groups (Table 4).

Carriage in infants, disease in infants
Pneumococcal diseases: bacteremia, meningitis, otitis media, pneumonia
Invasive *Haemophilus influenzae* type b disease: bacteremia, meningitis, epiglotitis
Carriage in adolescents and/or adults, disease in adolescents and/or adults
Invasive meningococcal meningitis and septicemia in travelers
Invasive meningococcal meningitis and septicemia in military recruits
Carriage in adolescents and adults, disease in infants
Invasive meningococcal meningitis in infants in developed countries
Maternal colonization with Group B streptococcus, disease in infants

(1,5, 16, 20, 22-23, 31-32)

Table 4. Examples of carriage versus invasive disease profiles

Ideally, definitive laboratory tests would rapidly confirm or exclude bacterial meningitis, determine the organism and identify its pattern of antibiotic susceptibility. Unfortunately, diagnosis of bacterial meningitis in the absence of a positive culture remains at best imprecise, despite numerous algorithms and putative biomarkers (Table 5). A recent early diagnostic model relies on dichotomized variables of peripheral blood polymorphonuclear cell count >16 × 10^9/l, serum C-reactive protein >100 mg/l and hemorrhagic rash, with a predicted probability of bacterial meningitis or meningococcal septicemia >95% with the presence of any one variable and >99% for two or more (33). Serum procalcitonin

distinguished viral from bacterial meningitis more effectively than C-reactive protein or leukocyte counts (34-35). However, methods must approach 100% sensitivity to avoid missed cases. Immediate and urgent administration of antibiotics until the results of microbiological tests become available is therefore recommended, (24, 36-37) although this practice may hinder diagnostic methods and surveillance that rely on culture. More sensitive molecular diagnostic techniques such as polymerase chain reaction (PCR) can enable definitive diagnosis in these cases (1, 38). Administration of preemptive antibiotics to viral meningitis patients can be costly and may indirectly contribute to antibiotic resistance. Suboptimal dosing of preemptive antibiotics may result in penetration into the cerebrospinal fluid or across the blood-brain barrier that is inadequate to eradicate bacterial pathogens (36-37).

Clinical criteria: hemorrhagic nonblanching rash, neck stiffness, altered mental state, shock, hypotension, back rigidity, photophobia, toxic or moribund state, seizures headache, vomiting, fever, etc.
Bacterial antigen testing
Gram staining
Blood markers: C-reactive protein level, white blood cell count
Cerebrospinal fluid markers: protein level, glucose level, white blood cell count, neutrophil count
Cultures of blood or cerebrospinal fluid
Serum procalcitonin
Blood polymorphonuclear cell count >16 × 10^9/l, serum C-reactive protein >100 mg/l and/or hemorrhagic rash

(33-39)

Table 5. Examples of algorithms and biomarkers for bacterial meningitis.

Difficulties in differential diagnosis, combined with the severe consequences of disease, including sepsis, shock, gangrene, deafness, seizures, CNS damage, or limb amputation, taken together support vaccination as the best approach for preventing the most epidemiologically and clinically important forms of bacterial meningitis.

While the brain and meninges are relatively anatomically inaccessible, once breached by a pathogen the blood-brain barrier tends to become more permeable to medicines because of resultant inflammation. *Haemophilus influenzae* type b, the meningococcus and the pneumococcus are generally highly sensitive to antibiotics, although resistance has been increasingly reported with pneumococci and a few meningococcal strains, leading to recommendations for the empiric use of third-generation cephalosporins. Therapies are also available for other forms of meningitis. Corticosteroids may be recommended as adjunctive therapy to reduce some symptoms (36-37).

3. Prevention of meningitis

Strategies and policies to prevent and control meningitis tend to involve narrow, categorical, pathogen-specific programs. Few if any broad policies spanning the gamut of pathogens responsible for causing meningitis exist. This shortcoming reflects the differences in the

epidemiology of the etiologic agents, the limited antigenic composition and coverage of the available vaccines, the complexity of primary prevention and secondary prevention modalities, and the cost and complexity of instituting large scale programs.

In epidemic situations, antibiotics may be used to prevent bacterial meningitis in close contacts or communities within a reasonable period (1 week in the case of meningococcal meningitis) from the diagnosis of an index case. Current recommendations often call for third-generation cephalosporins to address possible drug-resistant strains. (22-23, 36-37). In addition, intrapartum antibiotics are routinely administered to mothers colonized with Group B streptococcus to prevent infant disease. Nevertheless, vaccination remains the most effective means of preventing both the most common causes of bacterial meningitis and some viral pathogens, like measles and mumps. Although vaccines have been licensed steadily throughout the late twentieth and early twenty-first centuries for encapsulated bacteria, areas for improvement remain.

Investigation into vaccines that limit meningitis followed work against other deadly diseases such as rabies, yellow fever, and smallpox. The diphtheria and tetanus toxoid vaccines originally designed in the 1920s were later adapted to act as protein carriers in the current polysaccharide-protein conjugate vaccines. Another early twentieth-century vaccine to prevent a range of illnesses, including meningitis, was the Bacille Calmette-Guérin (BCG) vaccine against tuberculosis, which has become the most widely used vaccine in the WHO Expanded Programme for Immunisation. Measles and mumps vaccines were developed during the second half of the twentieth century, and, like diphtheria and tetanus vaccines, remain an essential part of early childhood universal vaccination programs (40).

The first vaccines against encapsulated bacterial meningitis-causing pathogens during the 1960s and 1970s employed the purified outer polysaccharide capsule to provide immune responses in persons over 2 years of age who were able to mount B-cell responses. Such vaccines have been used successfully in situations where individual protection is needed for a limited amount of time. However, these vaccines may have blunted or diminished responses with repeat dosing, possibly due to B-cell depletion and do not offer protection in infants and others who cannot mount B-cell responses. The next generation of conjugated pneumococcal, meningococcal and *Haemophilus influenzae* type b vaccines offer protection to infants and young children and allow for booster responses with repeat dosing. Extensive vaccination of infants and young children with pneumococcal vaccines has led to considerable reductions in disease in non-target age groups by means of herd protection, which was also evident in meningococcal serogroup C vaccine programs that include the primary carriage population (1, 2, 40-41).

Policy makers and health care providers generally consider the full spectrum of clinical disease caused by meningitis-causing pathogens when making decisions about therapy, prevention, or vaccination. For example, meningococci can cause a range of clinical syndromes including septicemia, bacteremia, and localized suppurative infections such as arthritis. Similarly, pneumococci cause otitis media and pneumonia, which create serious public health consequences. Further, *Haemophilus influenzae* type b vaccine policy was strongly affected by the possibility to prevent pneumonia and epiglottitis, which is very difficult to manage. Meningococcal vaccine policy must also address the possibility for unpredictable, severe

VACCINE	PRIMARY DISEASE TARGETED	CURRENT ROUTINE USE EXAMPLES
Early Twentieth Century		
Bacille-Calmette-Guérin (BCG) Vaccine	Tuberculosis	WHO countries
Mid-Twentieth Century		
Measles virus vaccine	Measles	Infants and toddlers
Mumps virus vaccine	Mumps	Infants and toddlers
Late twentieth Century		
Meningococcal polysaccharide vaccines	Meningitis and septicemia	Hajj travel in countries without access to conjugate vaccines
Pneumococcal polysaccharide vaccine	Meningitis and pneumonia	Elderly persons in countries without conjugate vaccines against all significant serotypes
Haemophilus influenzae type b conjugate vaccine	Meningitis and epiglotitis	Infants and toddlers
Pneumococcal conjugate vaccine	Meningitis, pneumonia and otitis media	Infants and toddlers
Meningococcal conjugate vaccines	Meningitis and septicemia	Infants, toddlers, adolescents, travelers, Hajj pilgrims

Note: vaccines against Japanese and tick-borne encephalitis also became available during the twentieth century. (1,2, 5, 40-41)

Table 6. Vaccines against pathogens that cause meningitis

outbreaks and epidemics that may prevent adequate distribution of antibiotics fast enough to treat individuals and to curtail the spread of infection through a community. The possibility of drug resistance can also impact vaccine policy and treatment decisions (2).

3.1 *Haemophilus influenza* type b vaccines

No single intervention has done more to prevent cases of bacterial meningitis than the successful introduction of conjugate *Haemophilus influenzae* type b vaccines, which stands as a major triumph in the history of vaccinology (42-43). The virulence of *Haemophilus influenzae* type b results from its unique polyribosylribitol phosphate (PRP) capsule, which is thought to be particularly effective at enabling the organism to evade complement-mediated lysis and avoid splenic clearance (44-45). Previous to the development of conjugate vaccines, *Haemophilus influenzae* type b was the most common cause of bacterial meningitis, and disease incidence remains high in countries that do not immunize infants (42-43). *Haemophilus influenzae* type b meningitis occurs primarily in older infants and toddlers, during a "window of vulnerability" corresponding to a gap in anti-capsular antibody titers that occurs between a decline in maternal antibody and the second year of life. Conjugated *Haemophilus influenzae* type b PRP (or PRP derivative) vaccines enabled the

Vaccine	Diseases/pathogens covered	Regions used
Haemophilus influenzae type b (Hib) conjugate vaccines		
PRP-T PRP-OMPC PRP-D PRP-CRM197	*Haemophilus influenzae* type b	North America and Europe
Haemophilus influenzae type b and pertussis-containing vaccine combinations		
DTaP-IPV/Hib	Diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b	North America
DTaP-IPV/Hib-HBV	Diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b , hepatitis B	Europe
DTP-Hib	Diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b	Africa, Asia, Latin America
DTP-Hib-HBV	Diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b , hepatitis B	Africa, Asia, Latin America
Haemophilus influenzae type b meningitis combinations		
MenCY-Hib	Meningococcal serogroups C and Y, *Haemophilus influenzae* type b	Not yet in use
MenC-Hib	Meningococcal serogroup C, *Haemophilus influenzae* type b	UK
Other *Haemophilus influenzae* type b combinations		
Hib-HBV	*Haemophilus influenzae* type b and hepatitis B	North America Europe

-aP: acellular pertussis; CRM197: cross-reacting material; D: diphtheria toxoid; HBV: hepatitis B virus; IPV: inactivated poliovirus vaccine; MenC meningococcal serogroup C; MenCY: meningococcal serogroups C and Y; OMPC: outer membrane protein complex; P: whole-cell pertussis; PRP: polyribosylribitol phosphate; T: tetanus toxoid. (40-52)

Table 7. Examples of vaccines against *Haemophilus influenzae* type b

institution of immunization policies shaped by an understanding of epidemiology. Universal use of *Haemophilus influenzae* type b conjugate vaccines in the first year of life provided protection from invasive disease, reductions in carriage, and herd effects, an approach that was tailored to fit existing routine infant immunization schedules. Combining conjugate *Haemophilus influenzae* type b vaccine with other routine infant vaccines has allowed for ease of implementation in increasingly crowded immunization schedules (42-52).

3.1.1 Pneumococcal vaccines

The pneumococcus comprises antigenically distinct types based on the chemistry of the polysaccharide outer capsule. Vaccines have therefore been designed to provide protection against the broadest number of serotypes in a specific population (Table 8).

Pneumococcal Types	23-valent polysaccharide vaccine	7-valent CRM-conjugate vaccine	10-valent protein D-conjugate	13-valent CRM-conjugate vaccine
Target age group	Adults	Infants	Infants	infants
1	X		X	X
2	X			
3	X			X
4	X	X	X	X
5	X		X	X
6A				X
6B	X	X	X	X
7F	X		X	X
8	X			
9N	X			
9V	X	X	X	X
10A	X			
11A	X			
12F	X			
14	X	X	X	X
15B	X			
17F	X			
18C	X	X	X	X
19F	X	X	X	X
19A	X			X
20	X			
22F	X			
23F	X	X	X	X
33F	X			

CRM: cross reacting material 197; protein D is derived from nontypeable *Haemophilus influenzae* (40, 63)

Table 8. Pneumococcal types covered by available polysaccharide vaccines for use in adults and polysaccharide-protein conjugate vaccine for use in infants and young children

The UK has been a leader in implementing universal infant vaccination against bacterial meningitides. Awareness raised by charities such as the Meningitis Research Foundation or the Meningitis Trust and the media helped support the inclusion of pneumococcal vaccines in not only routine infant schedules but also into at-risk programs. At-risk programs may

have little impact on disease burden (54), particularly given that immunization of infants and young children provides some protection in older age groups by virtue of herd protection (55). Pneumococcal conjugate vaccine also provided unexpected benefits such as the prevention of secondary bacterial super-infection in influenza (56).

The 7-valent pneumococcal conjugate vaccine has been in use in the US since 2000 with subsequent licensing in the EU and elsewhere. Although the initial European recommendation was for at-risk groups, by 2006 more countries were making universal recommendations and providing funding. Cost-effectiveness data from the US, some European countries and Australia (57) have been reported and indicate that vaccination can be cost-saving, as in Germany, partly as a result of reduction of high-incidence but also lower severity infections such as otitis media. Favorable pharmacoeconomic results tend to drive routine (universal use) policy implementation. Pneumococcal conjugate vaccine is funded in many countries including Turkey, Mexico, and South Africa, and in some GAVI-eligible countries.

The safety, efficacy and effectiveness of the 7-valent pneumococcal conjugate vaccine were established through pivotal trials, long-term surveillance, and monitoring. In a multi-centre study of 1379 pneumococcal meningitis cases in the US from 1998 to 2005 (58), incidence declined from 1.13 to 0.79 cases per 100,000 persons, a 30.1% reduction ($P<0.001$). Reductions were most marked in those less than 2 years and more than 65 years of age, respectively 64.0% and 54.0% ($P<0.001$). Non-vaccine serotypes were noted to cause more disease after the introduction of vaccine. Newer 10- and 13-valent pneumococcal vaccines have been studied in clinical trials and are appearing in some markets. A 15-valent pneumococcal conjugate vaccine is also in clinical trials.

Questions regarding the efficacy of 23-valent pneumococcal polysaccharide vaccine have led the UK to consider eliminating its routine use in the elderly and confining use to specific at-risk groups (59). Licensing of the 13-valent pneumococcal conjugate vaccine for adults should provide an alternative. In France, the 13-valent pneumococcal vaccine, which is already licensed for use in children, may reduce disease where serotypes 7F and 19A have come to predominate (60) while in the African meningitis belt there is potential for the reduction in the burden of disease through coverage of serotype 1 (61).

3.2 Meningococcal vaccines

The epidemiology of meningococcal disease is characterized by dynamic shifts in serogroup incidence over time and across geography. In addition, hypervirulent strains cause unpredictable outbreaks, and epidemics are reported annually in the sub-Saharan meningitis belt. Six meningococcal serogroups, A, B, C, W-135, X, and Y cause the majority of disease worldwide and are considered epidemiologically important by the WHO (1, 5, 9). Currently, conjugate vaccines are available against serogroups A, C, W-135 and Y. Routine immunization with the serogroup C conjugate vaccines dramatically reduced disease incidence and asymptomatic carriage, thus leading to herd protection in many countries including the UK, Ireland, the Netherlands, and Canada. Effective vaccination policy mandated immunization of both infants and adolescents, an important reservoir for meningococcal carriage. These findings have yet to be replicated with additional serogroups (1, 9). Quadrivalent meningococcal vaccines against serogroups A, C, W-135 and Y are routinely recommended in North America for use in adolescents, and a booster dose is

recommended in the US. Additional recommendations for meningococcal vaccination include the military, persons travelling to regions with endemic or epidemic disease, and those attending the annual Hajj pilgrimage to Mecca (1, 25, 62). A very significant new advance in this field is the recent implementation of serogroup A conjugate vaccine in the African meningitis belt (8).

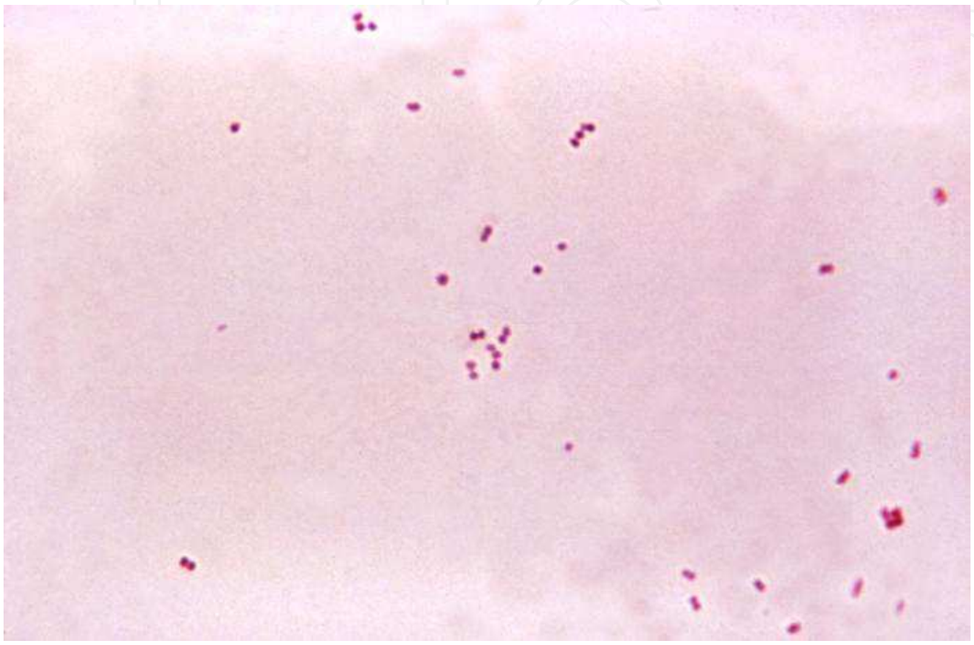

Fig. 2. Micrograph at 1150 X magnification of meningococci. Image by Dr Brodsky c. 1966. Centers for Disease Control and Prevention Public Health Image Library ID #6423 (15).

Serogroup B presents special challenges because its capsular polysaccharide is non-immunogenic, resulting in the need for subcapsular antigenic approaches (1, 11). Serogroup B vaccines using outer membrane vesicles (OMVs) as the primary antigen have been used to control specific clonal outbreaks in Cuba, Chile, Brazil, New Zealand, France and Norway. Various other subcapsular antigens have been investigated (10-11). A genomic method known as reverse vaccinology led to the development of 4CMenB, which is the only vaccine that has been shown to generate antibody responses against genetically heterologous serogroup B strains in Phase 3 trials in both infants and adolescents and has been submitted for approval to the European Medicines Agency. 4CMenB is a multicomponent vaccine that combines factor H binding protein, Neisserial adhesin A, and *Neisseria* heparin binding antigen with OMV from the New Zealand outbreak strain. The vaccine promises to be an important advance in vaccine practice (11, 63-65). Other serogroup B vaccines are under development.

An optimal strategy for meningococcal disease control would include broad-coverage vaccines in infants where the disease incidence is highest coupled with immunization of adolescents (where peak carriage occurs) to induce herd effects and prevent secondary peak disease. Vaccine availability, implementation issues and cost have driven meningococcal vaccine policies, which tend to be narrow in scope (65).

4. Policy decisions for the prevention of meningitis

Strategies and policies to prevent and control meningitis tend to be pathogen-specific, because differences in epidemiology, available vaccines, cost and the complexity of instituting large scale programs would make general guidelines unhelpful. Nevertheless, the vision of a meningitis free world is most likely to be realized from innovative approaches to integrated meningitis prevention and control.

Implementation of vaccines against meningitis-causing organisms has been a major priority of global health funding organizations such as the Gates Foundation and the Global Alliance for Vaccines and Immunisation (GAVI). The Gates Foundation alone has committed more than 14 billion dollars toward vaccines for developing countries (66). Investments such as these have led to innovative strategies and partnerships toward vaccines against meningitis. Early efforts focused on introducing existing vaccines, such as *Haemophilus influenzae* type b and pneumococcal conjugate vaccines, to developing countries, while more recent efforts include the development of specialized low-cost vaccines targeted to the needs of developing nations.

A notable GAVI initiative was the introduction of *Haemophilus influenzae* type b vaccine to the world's poorest countries, which began in 2005, on the heels of the WHO global *Haemophilus influenzae* type b vaccine recommendation. By 2008, half of eligible countries, representing 42% of eligible infants, had access to free or subsidized vaccine (67). GAVI has also funded 7-valent pneumococcal vaccine, which has been adopted by a number of countries, the first being Rwanda (68). The Meningitis Vaccine Project recently supported the development of a low-cost (40 cents a dose) tetanus toxoid conjugate vaccine against serogroup A meningococcal disease for use in the meningitis belt. This project was an innovative multi-stakeholder partnership including the WHO, UNICEF, the US Centers for Disease Control, the US Center for Biologics Evaluation and Research (CBER), and the Serum Institute of India. This vaccine has dramatically reduced disease and associated morbidity and mortality after immunization of 19 million residents of Burkina Faso, Mali and Niger in the course of a few weeks (8, 68).

4.1 Considerations for the design of preventative interventions

Vaccine policy for meningitis, as for most infectious diseases, is determined by the burden of disease, public awareness of the problem, availability of vaccines and the ability to fund vaccination campaigns. Yet even with compelling disease burden, clear epidemiologic justification and ample funding, difficulties in vaccine formulation or adding vaccines to crowded schedules may present significant barriers to implementing vaccine policies. The prevention of bacterial meningitis requires vaccinating a large proportion of the community and immunization against relatively rare diseases, thus such programs might not meet pharmacoeconomic parameters in all nations as it did recently in the African meningitis belt (69).

Routine immunization implementation may be necessary to assess clinical effectiveness, cost effectiveness and herd effects; therefore, effective vaccine policies must consider multiple variables in the use of health care resources. The perceived and actual burden of disease may vary because public perception can be skewed by reports of epidemics or small numbers of cases of severe disease. Or, the true burden of disease may be masked by

Epidemiology
Populations suffering from disease
Populations carrying or transmitting the causative organism
Genetic, group, and strain diversity of the organism
Genetic, strain, or serogroup shifts over time and space
Escape mutants
Serogroup or serotype replacement over time and as a result of vaccination campaigns
Proximity of populations (potential for herd effects)
Vaccines
Number and type of available vaccines
Ability for vaccines to protect against circulating pathogens in a given region
Effects on immunogenicity and efficacy when given with existing vaccine schedules
Duration of immunity
Effects in target age groups
Policy
Existing vaccine schedules
Timing of doses
Need for booster doses or catch-up campaigns
Funding
Ability to reach key populations to administer vaccines
Possibility for herd effects
Reduction of the risk for developing antibiotic resistance

Table 9. Considerations for developing vaccine policy

under-diagnosis, under-reporting or, if early antibiotic treatment prevents case confirmation by culture (70-71). Thus, public awareness of disease burden should precede explanations of new vaccines. Media reports may occasionally be counter-productive, especially when considering their treatment of vaccine safety (72).

Vaccine availability can be limited by logistical factors like the lack of a universally protective antigen. Thus, not all meningitides are vaccine-preventable in practice (e.g. serogroup B meningococcus, group B streptococcus), nor are many of the encephalitides. Vaccines cannot be considered available unless they have been approved for licensure, yet licensure is necessary but not sufficient for availability to the general public because funding sources have a strong impact on policy decisions. In the public market, pharmacoeconomic considerations may appear calculating or callous to the general public. In a "private" market, the vaccinee must willingly obtain and pay for the vaccine. Although in this context, the decision to receive vaccine is less likely to be driven by a sense of public-mindedness, the near-universal uptake of pneumococcal conjugate vaccine in Portugal indicates that collective responsibility may be powerful in some regions.

4.2 Policy approaches to vaccine against meningitis-causing pathogens

Universal (age-based) routine immunization is a primary model for limiting or eliminating meningitis globally. Prevention in the context of disease outbreaks involves antibiotic chemoprophylaxis as well as targeted vaccine use, generally in the setting of meningococcal disease. Universal vaccination approaches require multiple considerations because successful prevention arises only from a clear understanding of several key factors including the populations at greatest risk of disease, the population where carriage occurs, the features of available vaccines, the feasibility of implementation of immunization policies (Figure 3).

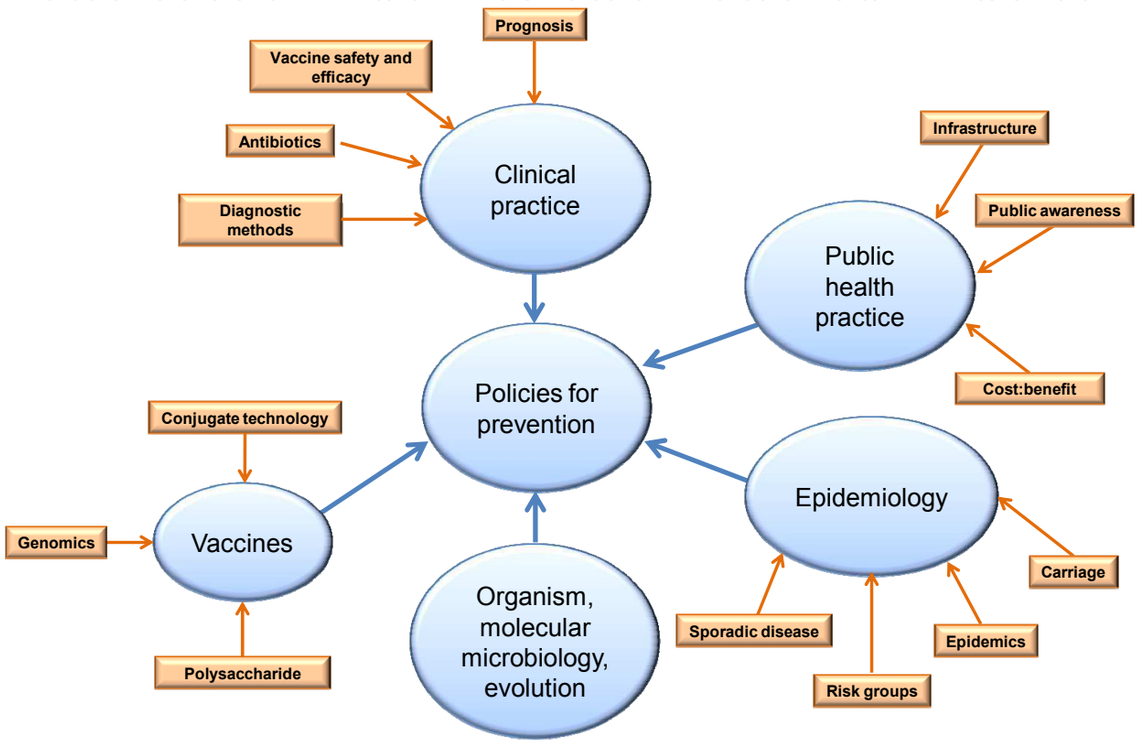

Fig. 3. Considerations that inform policymaking decisions for meningitis prevention

Universal immunization against *Haemophilus influenzae* type b , meningococcal serogroup C and pneumococcal disease stand as exceptionally noteworthy successes in the primary prevention of meningitis. These universal policies are more likely to protect high-risk individuals than selective programs in part because risk factors may be poorly understood. Debates about selective versus universal or voluntary and compulsory vaccination policies remain unresolved.

Primary prevention of other causes of meningitis is somewhat more complex. Control of meningococcal serogroup C resulted through the expansion of the immunization schedule to include older children and adolescents, reducing carriage to provide adequate herd effects and the use of catch-up campaigns to ensure vaccine coverage.

Secondary prevention of meningitis can include interventions, like antibiotic chemoprophylaxis, that can operate at the population level or for an individual. Targeted use of vaccines within communities or geographic areas can also control epidemic as shown

Young children were at the highest risk of disease and also comprised the primary population where carriage occurs
Glycoconjugate vaccines enabled direct protection and reduction in carriage that provided further herd effects in the critical at-risk population simultaneously
Implementation of immunization was straightforward because vaccines fit well into the existing routine infant immunization schedules
Herd effects extended beyond the vaccinated population and into the general population because primary vaccination reduced carriage in the key reservoir for the causative disease pathogens.

Table 10. Considerations that led to the success of universal vaccination policies against *Haemophilus influenzae* type b and pneumococcal diseases

in Cuba, Norway and New Zealand by the use of tailor-made outer membrane vesicle vaccines against meningococcal serogroup B (73). Policy focus in the Middle East has been directed toward the control of meningococcal disease Hajj pilgrims (62, 74). Globally, routine infant immunization schedules commonly include *Haemophilus influenzae* type b and pneumococcal conjugate vaccines within the first six months of life, with a booster in the second year of life, which is important to long-term protection. Meningococcal vaccine schedules are more variable and routine recommendations may target infants, older children, adolescents, or some combination of these.

4.3 Expert commentary and five year view

Where meningitis prevention and control is concerned, optimally, vaccine innovation will involve the development of broadly protective vaccines that are safe and immunogenic across the age spectrum. From a pure feasibility point of view, combining antigens will be critically important given the increasingly crowded immunization schedules. Cost and the crowded immunization schedules are typically cited as the major impediments to making progress in the area of meningitis prevention and control.

The recent advent of vaccines to prevent meningitis and sepsis caused by *Haemophilus influenzae* type b, the pneumococcus and the meningococcus further completes a general picture of universal vaccination to promote public health, beginning with vaccine policies against diseases like measles, mumps, polio, and diphtheria. Yet most of the world's children remain unprotected, which underscores the work of organizations like the WHO, the Gates Foundation and GAVI in limiting infectious disease.

The effects of vaccine programs depend on many factors. Antibody concentration wanes rapidly in infants, and more slowly in toddlers and young children while persons 10 years of age and older can have antibody persistence for five years or more (75). Herd protection may depend on booster dosing in various age groups or catch-up campaigns. Similarly, continued vaccination of infants may be necessary to protect the vulnerable elderly population from pneumococcal disease. Yet, with the dramatic reduction of cases, the political will to support booster vaccinations may be lacking.

Compliance, and therefore vaccine coverage, may be an issue for adolescents, who traditionally visit medical practitioners infrequently, and who often refuse vaccines but represent an important population for meningococcal carriage and also have an increased risk for case fatality. Combined vaccination with other routine vaccinations for this age group, such as Tdap and HPV, may help overcome this difficulty, and are supported by clinical studies (22-23, 76-78). Booster immunizations with DT/IPV/aP combinations, catch-up for MMR/V and depending on the country, catch-up vaccination for hepatitis A or for hepatitis B may provide additional opportunities for vaccination of adolescents. Suboptimal coverage rates, especially for newer vaccines, place substantial numbers of adolescents at risk. One approach to increase adolescent vaccination is to establish routine school-based adolescent immunization programs by primary care trusts, school nursing teams and similar facilities.

In a recent survey analyzed by the Federal Center for Health Education (Bundeszentrale für gesundheitliche Aufklärung) in Germany, 64% of parents had a positive opinion on vaccination, 35% declined individual vaccines due to various reservations and only 1% generally dismissed vaccines. About 50% of the parents with reservations reported that the reason for their reservation was that they assessed the vaccine to be unnecessary, vaccination was discouraged by the physician (41%) or they were afraid of side reactions (40%). The survey data reveal the central role of the medical profession (79).

Education of adolescents, their parents and/or guardians, health care providers, policy makers and physicians is vital to successful implementation of adolescent immunizations and it has to be considered that the role of pediatricians gradually decreases for adolescents older than 14 years, while the role of the family practitioner, internist, and gynecologist increases. Of note, 35% of the preventive care visits made by late adolescent females (18-21 years old) are to obstetricians and gynecologists, which provides an opportunity for concomitant HPV and quadrivalent meningococcal vaccines. Obstetricians may be particularly well positioned to intervene in meningitis affecting the very young infant in the future by administering vaccines to pregnant women to limit infections such as Group B streptococcus, a leading cause of neonatal meningitis. For various reasons, family practitioners are often slower than pediatricians to accept new universal vaccine recommendations (80-81), which might require adjustments in communication about new products.

Achieving reductions in meningitis has to remain a top priority for the modern world. Within this context, a vaccine with the following properties might be considered a magic bullet were it to be developed:

- Multicomponent vaccine with coverage against *Haemophilus influenzae* type b, and PCV (23 - valent), and meningococcus (5 valent: A, B, C, W-135, and Y)
- Safe, immunogenic, and effective in young infants, children, adolescents and adults
- Ability to reduce or eliminate carriage

Such a vaccine, if used appropriately, could help bring us closer to a "meningitis free world". Although a singular such vaccine is not likely to be developed within the next five years, incremental progress is inching us closer toward such broad vaccines. Admittedly, Group B streptococcus remains a critical target, and the new paradigm of maternal immunization will be required for successful control of that disease. Moreover, listerial,

viral, fungal, mycobacterial and other rare forms of meningitis will remain with us for some time to come albeit at low rates. The world is now positioned with an ever growing armamentarium of preventative tools the likes of which physicians and public health officials of past generations could only have dreamed.

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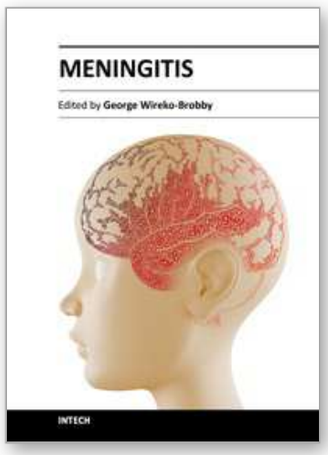

Meningitis

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Meningitis is a medical emergency requiring a rapid diagnosis and an immediate transfer to an institution supplied with appropriate antibiotic and supportive measures. This book aims to provide general practitioners, paediatricians, and specialist physicians with an essential text written in an accessible language, and also to highlight the differences in pathogenesis and causative agents of meningitis in the developed and the developing world.

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