Meningococcal disease: Oh no, not another childhood vaccine

Epidemiology and background: The epidemiology of bacterial meningitis changed dramatically a decade ago with the advent of the *Haemophilus influenzae* type b (Hib) conjugate polysaccharide vaccine. The incidence of Hib infection dropped by as much as 99%,[1] which left 2 other encapsulated pathogens — *Streptococcus pneumoniae* and *Neisseria meningitidis* — to head the list of etiologic agents of bacterial meningitis. However, with the recent availability of conjugated vaccines for certain strains of these 2 pathogens, we may witness parallel drops in the burden of disease they cause.

The annual incidence of invasive meningococcal disease in Canada — 1 case per 100 000 population[2] — fails to convey the full impact of the disease. Most cases involve people less than 19 years old, with the highest incidence found among infants less than 1 year old (12.9 and 6.5 cases per 100 000 population in 1997 and 1998 respectively[3]). The second peak incidence occurs among older teenagers.

Case-fatality rates range from 10% to 20%, even with early and appropriate treatment, and about 15% of survivors bear serious long-term sequelae such as scars, amputations, hearing loss and renal problems.[4] In Canada most cases involve sporadic, random strikes against a previously healthy child, with no evident epidemiologic link to another case. Each incident requires a labour- and time-intensive public health response involving risk assessment, contact tracing, antimicrobial chemoprophylaxis, laboratory confirmation of the serotype and, occasionally, vaccination and public education campaigns. Thus, prevention of meningococcal disease is a public health priority.[1]

Five serogroups of *N. meningitidis* (A, B, C, Y and W-135), formed on the basis of capsular polysaccharide antigens, have been responsible for most of the disease in North America over the past 70 years. In recent decades serogroups B and C have predominated.[2,3] In 1997/98, serogroup B was isolated in about 50% of Canadian cases of invasive disease and serogroup C in 30%.[3] An increasing incidence of serogroup Y disease has been observed in the United States during the past decade, but the Canadian National Advisory Committee on Immunization (NACI) says a similar trend has not been seen here.[2] Serogroups A and W-135 pose risks primarily for travellers to endemic areas outside Canada.

The bacterium itself is ubiquitous. The human nasopharynx is a natural reservoir, and about 10% of adults harbour *N. meningitidis* in the nose.[5] Consequently, isolation of this organism from a throat swab, nasopharyngeal aspirate or conjunctival swab provides no information about the cause of invasive disease.[6] Infection usually causes only a subclinical mucosal infection. Invasive disease occurs only when the following conditions are met: contact with and colonization by a virulent strain, penetration of that strain through the mucosa and its subsequent spread into the blood stream.[5]

The course of infection depends on the host's ability to launch a rapid antibody response. Massive outgrowth can lead to fulminant sepsis within 12 hours, often before signs of meningitis have developed. Host factors that appear to increase the risk of invasive disease include low age, certain immunodeficiencies (asplenia, hypogammaglobulinemia, complement deficiencies), a recent respiratory tract infection, exposure to cigarette smoke and overcrowded living conditions.[2] Transmission occurs person-to-person through respiratory droplets. A person is infectious until meningococci are no longer present in discharges from the nose or mouth — usually within 24 hours after starting appropriate antibiotic treatment.[7]

Clinical management: Meningococcal disease usually presents as a sudden-onset febrile disease with signs of meningitis (drowsiness, headache, stiff neck, photophobia) or septicemia. In two-thirds of cases it is accompanied by a characteristic, nonblanching petechial or purpuric rash that frequently involves the trunk and extremities first. A patient with a confirmed case is currently defined as "one with clinical features compatible with meningococcal disease with laboratory confirmation of infection through isolation of *N. meningitidis* from a normally sterile site (blood, cerebral spinal fluid [CSF] or joint, pleural or pericardial fluid) or demonstration of *N. meningitidis* Ag in CSF."[1] A probable case is defined as "invasive disease with purpura fulminans or petechiae in the absence of a positive blood culture and no other apparent cause."[2] The bacterium may be isolated by either Gram staining or culture. An antibody detection or polymerase chain reaction method, now available in several centres including Health Canada's National Microbiology Laboratory, can be used to determine the serogroup.[2]

To treat meningitis in adults and children more than 2 months old before laboratory results have arrived, high-dose cefotaxime or ceftriaxone therapy is generally recommended, plus vancomycin with or without rifampin.[8] For patients in the first 2 months of life, many consultants use ampicillin plus cefotaxime, with or without gentamicin, while awaiting these results.[8] *N. meningitidis* with decreased susceptibility to penicillin has been observed in some parts of Canada. In Ontario, 35% of invasive meningococcal isolates identified in 2000 had decreased susceptibility to penicillin. The serogroup W-135 had a much higher rate of decreased susceptibility than did other serogroups.[2]

The patient should be placed in respiratory isolation for 24 hours after antibiotic therapy is started, with concurrent disinfection of all materials soiled by discharges from the nose and throat.[7] All confirmed and probable cases of men-

ingococcal meningitis must be reported to the local medical officer of health, and assessment and control of outbreaks should be done in consultation with this physician. Close contacts, defined practically as "any individual who frequently has slept or eaten in the same dwelling with the index case" or who had direct exposure to salivary secretions are at increased risk and require chemoprophylaxis.[6] For most contacts, rifampin, ceftriaxone or ciprofloxacin are appropriate drugs for this purpose (Table 1).[6,9]

Prevention: No serogroup B meningococcal vaccines are currently licensed for use in Canada. Developing effective vaccines against this serogroup has been challenging because the group B polysaccharide is poorly immunogenic in humans.[2] In contrast, purified capsular polysaccharide meningococcal vaccines against serogroups A, C, Y and W-135 (MenACYW-Ps) have been licensed in North America for several years and have been widely used to control outbreaks and epidemics. However, these polysaccharide vaccines are not recommended for routine vaccination because they provide relatively short-term protection[9] and have low efficacy in children aged 2–10 years. They are ineffective in children younger than 2 years because the immune system at that age is too immature to launch a sustained (T-cell dependent) response.

A monovalent serogroup C conjugate vaccine (MenC-conjugate), which is effective in inducing immunologic memory in children under age 2 for at least 5 years, has recently been licensed in Canada and has demonstrated a very acceptable safety profile. No serious adverse effects were noted in clinical trials, although local reactions were common in infants and toddlers. Headaches occurred in about 10% of older children.[10] Last year NACI recommended that meningococcal protein-polysaccharide conjugate vaccines be used for the routine vaccination of infants, children aged 1 to 4, adolescents and young adults (see box).[2] The recommendation followed a comprehensive 1999 public health campaign in the United Kingdom to vaccinate all people less than 18 years of age against meningococcus serogroup C. Rates of invasive meningococcal disease caused by this serogroup are twice as high in the United Kingdom as they are in North America. Vaccine advisory committees in the United States are developing recommendations on the basis of evidence that is accumulating. One American model projected that the routine vaccination of infants, toddlers and adolescents with a serogroup C+Y conjugated vaccine, assuming current rates of coverage, would reduce the cumulative incidence of meningococcal disease over 10 years by 54%, 48% and 25% respectively.[1]

The conjugated vaccine costs about $120 per dose and is not covered by most provincial health care plans. Canadian cost-effectiveness data and information on parental attitudes toward the need for another childhood vaccine are not currently available. According to the American National Immunization Program, about 25% of parents believe that infants get more vaccines than are good for them.[11] To address parental concerns, the Institute of Medicine estab-

Recommendations for routine vaccination with meningococcal C-conjugate vaccine

Infants

- The new protein-polysaccharide conjugate vaccine (MenC-conjugate) is recommended for routine vaccination of infants at 2, 4 and 6 months of age (3 doses, at least 4 weeks apart) at the same visit as primary vaccination for diphtheria–tetanus–pertussis, polio and *Haemophilus influenzae* type b.
- Infants 4 to 11 months of age who have not previously received the vaccine should be given 2 doses at least 4 weeks apart.
- Infants born prematurely should receive the vaccine at the same chronological age as term infants.
- Purified polysaccharide vaccines (MenACYW-Ps or MenAC-Ps) are not recommended for routine vaccination of infants.

People ≥ 1 year old

- A single dose of MenC-conjugate vaccine is recommended for children 1–4 years of age and for adolescents and young adults.
- It may also be considered for children > 4 years of age who have not reached adolescence.
- Purified polysaccharide vaccines (MenACYW-Ps or MenAC-Ps) are not recommended for routine vaccination of children and young adults.

Source: National Advisory Committee on Immunization.[2]

Table 1: Chemoprophylaxis regimens for close contacts of people with invasive meningococcal disease

Drug	Age group	Dosage	Duration
Rifampin*	< 1 mo	5 mg/kg orally every 12 h	2 d
	≥ 1 mo	10 mg/kg orally every 12 h	2 d
	≥ 18 yr	600 mg orally every 12 h	2 d
Ciprofloxacin*	≥ 18 yr	500 mg orally	Single dose
Ceftriaxone	< 15 yr	125 mg intramuscularly	Single dose
	≥ 15 yr	250 mg intramuscularly	Single dose

*Not recommended for use in pregnant women. Also, rifampin may interfere with efficacy of certain medications such as oral contraceptives.
Source: Adapted from reference 9.

lished an independent expert committee to review hypotheses about existing safety concerns, and it found no evidence that the infant immune system is inherently incapable of handling the number of antigens children are exposed to during routine vaccination or that there is a causal relation between multiple vaccinations and increased risks of infections or type 1 diabetes mellitus. There was insufficient evidence to accept or reject a causal relation between vaccination and increased risk of allergic diseases, such as asthma.[11]

With the advent of the new MenC-conjugate vaccine, parents are asked to choose between the highly improbable, less-than-1-in-10 000 chance meningococcal disease will develop in a healthy infant, and the unbearable thought of a child moribund with meningococcal disease. The Canadian Immunization Awareness Program is designed to counsel parents about vaccination concerns (www.immunize.cpha.ca).

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