Invasive disease due to *Haemophilus influenzae* type A in children in Canada’s north: A priority for prevention

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*Haemophilus influenzae* type B (HiB) was the major cause of meningitis and a frequent cause of other invasive infections in young children until an effective vaccine became available in the early 1990s. In the prevaccine era, the estimated yearly incidence of invasive disease in the United States (US) for children <5 years of age was 40 to 100 cases per 100,000. Infection rates were highest in Aboriginal children (1). For Inuit children <5 years of age residing in the Keewatin district of Nunavut, the rate of HiB meningitis alone was 530 cases per 100,000 (2); however, HiB infection is now rare.

Immunization against HiB protects against disease and also reduces carriage of this organism. After the remarkable success of the conjugate HiB vaccine in controlling HiB, there has been concern about the possibility of serotype replacement, as has been observed with pneumococcus (1,3,4). Historically, invasive infections involving *H influenza* serotypes other than B were sporadic and rare (5).

However, in recent years, increasing rates of invasive infection due to *H influenza* type A (HiA) have been reported in the Canadian north, as well as in Alaska (USA) and in Aboriginal populations in the southwestern US and Australia (1,6,7). In Alaska, where surveillance for all invasive *H influenzae* infections has been ongoing since 1983, HiA was not detected before 2002 (8). Between 2002 and 2005, rates for Indigenous children <2 years of age in northern Canada and Alaska were 101.9 and 20.9 per 100,000, respectively (3). An incidence of 87.5 per 100,000 for children <2 years of age was reported in the Canadian circumpolar region from 2000 to 2010 (6). In 2001, in the Keewatin region of Nunavut, the rate for children <5 years of age was 418.8 per 100,000 (9). Outbreaks occurred in Alaska in 2003 and 2009 to 2011 (3,8), as well as in Nunavik, northern Quebec, from 2012 to 2013 (10). Recurrent disease has been reported in three apparently healthy children who were <10 months of age at initial infection (11,12). Case fatality rates of 5.5% to 16% have been observed (6,8,9). HiA infections in the non-Aboriginal population in the US remain rare (13).

In Quebec, before 2010, there were one or two cases of invasive HiA infection per year, with no cases from Nunavik. There was an average of four cases per year in Nunavik from 2010 to 2012, and 10 cases in 2013. Most cases involved young children, and presentations included meningitis, septicemia, septic arthritis and bacteremic pneumonia. Infection rates for 2010 to 2013 were 330.1 and 191.4 cases per 100,000 for children <1 year of age and one to four years of age, respectively, compared with an overall rate in Quebec of 2.0 and 0.8 for children <1 year of age and another 10 months of age (10).

Children from Nunavik are transferred to the Montreal Children’s Hospital (Montreal, Quebec) if they require care that cannot be provided in the north. There were no children transferred with invasive HiA disease before 2010, one in 2010, none in 2011; however, 12 were transferred from 2012 to 2013. In 2013, two cases were from the same household, with onset of illness 24 h apart. In November 2013, the Institut national de santé publique du Québec made interim recommendations for Nunavik to provide chemoprophylaxis to household and other close contacts of children with HiA infection (10), as was used for HiB (14). Final data for the region for 2014 and 2015 are not available; however, since November 2013, there has been only one case of HiA infection transferred to Montreal Children’s Hospital.

Information regarding rates of HiA carriage is sparse. Overall, rates of <1% to 3.5% for children have been reported from cities in Mexico and Brazil, and from an Aboriginal population in Australia (15-17); however, there are no data from North America. Studies involving a small number of close contacts of children with invasive HiA disease in Alaska reported carriage rates of 16% and 45% (11,18).

Serological studies involving Aboriginal adults in northern Ontario from 2010 to 2012 showed a high prevalence of anti-HiA antibodies with elevated immunoglobulin (Ig) M levels relative to IgG, whereas anti-HiB levels were lower and IgG predominated (19). This suggested that HiA had only recently become widespread in the area, as reflected by the increase in reports of invasive HiA disease.

The pathogenicity and virulence of HiA are similar to that of HiB (20), and the diseases it causes are similar (7). This may be explained by similar capsule structures and resistance to antibody-independent lysis by complement. The other four serotypes (C to F), which occur sporadically, are less virulent in animal models, have different capsule structures and are susceptible or less resistant to complement-mediated lysis (20).

The HiA infection rate in young children in northern Canada is now above the rate observed in the general population when the HiB vaccine was introduced. Applying conjugates and methods used in the development of the HiB vaccine, the development of an HiA vaccine is technically feasible. To date, the population at risk is small and underprivileged. Production of an HiA vaccine for this group is unlikely to attract the attention of vaccine manufacturers. Individuals residing in Canada’s north have unique health care needs that require government leadership and initiatives to ensure that they are met. To this end, a collaboration between the Public Health Agency of Canada, the National Research Council and the Northern Ontario School of Medicine launched a project in 2013, with the goal of developing a vaccine against HiA and a better understanding of HiA epidemiology through improved surveillance (21).

The appropriate management of close contacts of HiA cases remains to be determined. Before the HiB vaccine became available, secondary cases occurred in 2% of household and 1% of day care contacts (14). Chemoprophylaxis has been suggested for contacts of individuals with HiA (1,7,11), used by some (3,10,18) and discouraged by others because of an absence of data regarding carriage and efficacy (9,22). If carriage rates in close contacts are, in fact, in the range of 16% to 45%, it would be warranted. Studies investigating the effectiveness of HiA eradication using the antibiotic regimens used for HiB are needed. While awaiting further data and guidance, physicians and public health authorities will have to use judgement and knowledge of local epidemiology to decide whether prophylaxis is warranted.
REFERENCES

1. Tsang RSW, Bruce MG, Lem M, et al. A review of invasive Haemophilus influenzae disease in the Indigenous populations of North America. Epidemiol Infect 2014;142:1344-54.

2. Hammond GW, Rutherford BE, Malandrewicz R, et al. Haemophilus influenzae meningitis in Manitoba and the Keewatin District, NWT: Potential for mass vaccination. CMAJ 1988;139:743-7.

3. Bruce MG, Deeks SL, Zulz T, et al. Epidemiology of Haemophilus influenzae serotype A, North American Arctic, 2000-2005. Emerg Infect Dis 2008;14:48-55.

4. Adam HJ, Richardson SE, Jamieson FB, et al. Changing epidemiology of invasive Haemophilus influenzae in Ontario, Canada: Evidence for herd effects and strain replacement due to Hib vaccination. Vaccine 2010;28:4073-8.

5. Ulanova M, Tsang RSW. Invasive Haemophilus influenzae disease: Changing epidemiology and host-parasite interactions in the 21st century. Infect Genet Evol 2009;9:594-605.

6. Rotondo JL, Sherrard L, Hellierty M, Tsang R, Desai S. The epidemiology of invasive disease due to Haemophilus influenzae serotype a in the Canadian North from 2000 to 2010. Int J Circumpolar Health 2013;72:21142.

7. Ulanova M, Tsang RSW. Haemophilus influenzae serotype A as a cause of serious invasive infections. Lancet Infectious Diseases 2014;14:70-82.

8. Bruce MG, Zulz T, DeByle C, et al. Haemophilus influenzae serotype a invasive disease, Alaska, USA, 1983-2011. Emerg Infect Dis 2013;19:932-7.

9. McConnell A, Tab B, Scheifele D, et al. Invasive infections caused by serotypes in twelve Canadian IMPACT centers, 1996-2001. Pediatr Infect Dis J 2007;26:1025-31.

10. Bureau de surveillance et de vigie de la Direction de la protection de la santé publique du ministère de la Santé et des Services sociaux du Québec. Haemophilus influenzae au Nunavik. FlashVigie 2013;8:10. <http://publications.msss.gouv.qc.ca/msss/fichiers/flashvigie/06-271-02W-vol8_no10.pdf> (Accessed October 28, 2015).

11. Hammitt LL, Block S, Hennessy TW, et al. Outbreak of invasive Haemophilus influenzae serotype A disease. Pediatr Infect Dis J 2005;24:453-6.

12. Whyte K, Levent PN, Horsman GB, et al. Recurrent invasive Haemophilus influenzae serotype A infection in an infant. Microbiol Discov 2015;3:4. <http://dx.doi.org/10.7243/2052-6180-3-4> (Accessed October 28, 2015).

13. Langley G, Schaffner W, Farley MM, et al. Twenty years of active bacterial core surveillance. Emerg Infect Dis 2015;21:1320-8. <http://www.cdc.gov/abcs/index.html> (Accessed October 28, 2015).

14. Centers for Disease Control. Current trends. Prevention of secondary cases of Haemophilus influenzae type B disease. <www.cdc.gov/mmwr/preview/mmwrhtml/00001210.htm> (Accessed October 28, 2015).

15. Solórzano-Santos F, Miranda-Novales MG, Leaños-Miranda B, et al. [Haemophilus influenzae nasopharyngeal colonization in children]. Rev Med Inst Mex Seguro Soc 2011;49:499-502. (in Spanish)

16. de Carvalho CX, Kipnis A, Thorin L, et al. Carriage of Haemophilus influenzae among Brazilian children attending day care centers in the era of widespread Hib vaccination. Vaccine 2011;29:1438-42.

17. Gratten M, Manning K, Dixon J, et al. Upper airway carriage by Haemophilus influenzae and Streptococcus pneumoniae in Australian Aboriginal children hospitalised with acute lower respiratory infection. Southeast Asian J Trop Med Public Health 1994;25:123-31.

18. Hammitt LL, Hennessy TW, Romero-Steiner S, Butler JC. Assessment of carriage of Haemophilus influenzae type A after a case of invasive disease. Clin Infect Dis 2006;43:386-7.

19. Nix EB, Williams K, Cox AD, et al. Naturally acquired antibodies against Haemophilus influenzae type A in Aboriginal adults, Canada. Emerg Infect Dis 2015;21:273-9.

20. Jin Z, Romero-Steiner S, Carlone JM, et al. Haemophilus influenzae type A infection and its prevention. Infect Immun 2007;75:2650-4.

21. Desai S, Tsang R, St Laurent M, Cox A. Collaboration on a public health-driven vaccine initiative. CDDR 2014;40-17:365-8. <www.phac-aspc.gc.ca/publicat/ccdr-rmtc/14vol40/dr-rm40-17/dr-rm40-17-vaccin-eng.php> (Accessed October 28, 2015).

22. Murray DL. Chemoprophylaxis for household contacts of index cases of invasive non-type B Haemophilus influenzae disease. Pediatr Infect Dis J 2001;20:1099-100.