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Dynamics of naturally acquired antibody against *Haemophilus influenzae* type a capsular polysaccharide in a Canadian Aboriginal population

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ABSTRACT

Severe infections caused by *Haemophilus influenzae* type a (Hia) have reached alarming rates in some Canadian Aboriginal communities. We sought to estimate the frequency of exposure to this pathogen and timelines for boosting protective antibodies.

We developed a model of secondary antigenic challenge (natural exposure), and used data for anti-Hia antibodies in serum samples of healthy and immunocompromised adults in a population of Northwestern Ontario, Canada. We parameterized the model with available estimates from previous studies for the decay rate of antibody and its protective levels against both Hia carriage and invasive disease. Simulations were initialized using antibody concentrations from data. We investigated both the duration of immunity without secondary antigenic challenge and the average time between subsequent exposures to Hia.

When there was no new natural exposure, serum antibody concentrations in healthy Aboriginal individuals decreased below the level (1 μg/ml) assumed for protection against invasive Hia disease 3 years after primary exposure. This period was shorter (about 2 years) for Aboriginal individuals suffering from chronic renal failure. We estimated that a new antigenic challenge occurs once in 5 and 2 years for healthy and immunocompromised Aboriginal individuals, respectively. More frequent natural exposure was required to maintain protective antibody levels for non-Aboriginal individuals compared to Aboriginal individuals.

The findings suggest that frequent boosting of natural immunity is required to maintain the anti-Hia antibody levels protecting against invasive Hia disease, particularly in individuals with underlying medical conditions. This information has important implications for immunization when an anti-Hia vaccine becomes available.

Background

Haemophilus influenzae type a (Hia) is an important bacterial pathogen, which can cause severe invasive disease (Ulanova and Tsang, 2014). The invasive disease manifestation occurs mainly in young children (younger than 2 years of age), the elderly, and immunocompromised individuals (Ulanova, 2013). Hia is one of the 6 known encapsulated strains of *H. influenzae* classified based on their distinct capsular antigens (Ryan and Ray, 2004). *H. influenzae* serotype b (Hib) was the major cause of bacterial meningitis in young children worldwide before the introduction of an effective conjugate Hib vaccine in the late 1980s (Adams et al., 1993). Routine vaccination against Hib dramatically decreased the incidence of invasive Hib disease and carriage of the pathogen in the countries where vaccination programs were implemented (Ulanova and Tsang, 2009). Since protection conferred by the Hib vaccine is specific to the type b polysaccharide capsule, widespread vaccination against Hib may have unmasked the disease caused by other serotypes (Lipsitch, 1999).

The preceding decade has witnessed the emergence of Hia as the dominant encapsulated strain of *H. influenzae* in several specific geographic locations and populations, including Aboriginal populations in North America (Rotondo et al., 2013; Bruce et al., 2013). Clinical and epidemiological studies of Hia indicate that Aboriginal children (younger than 5 years of age) and adults with predisposing medical conditions are most affected by invasive Hia disease (Ulanova, 2013). While currently there is no vaccine to prevent Hia infection, understanding of the immunological and epidemiological characteristics of this pathogen is imperative to develop preventive measures with long-lasting effects. Similar to Hib, since vaccination with a conjugate vaccine specific to Hia could reduce the circulation of Hia bacteria, and therefore the incidence of Hia carriage in the population, determining timelines for boosting of protective immunity will be essential for maintaining a high level of herd immunity (Konini and Moghadas, 2015). In case of Hib, the frequency of new exposure required to maintain protective serum

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antibody concentrations ≥ 1.0 μg/ml was estimated at a minimum of 1 in 4 years prior to the introduction of conjugated Hib vaccine (Leino et al., 2000). Currently, there are no estimates on timelines for Hia recurrent natural exposure and boosting of antibody concentration.

In this study, we developed a model of secondary antigenic response using data for anti-Hia antibody concentrations in the serum samples of the participants in a population of Northwestern Ontario, Canada. Our aim was to estimate the timelines for boosting antibody concentrations following priming for different populations' characteristics. We considered the age, sex, ethnicity (Aboriginal and non-Aboriginal), and health status (including those presenting chronic renal failure) of individuals in stratifying collected data. Since the rates of antibody decay against Hia are still unknown, we parameterized the model using available estimates from the published studies for Hib. We based this assumption on the similarities between Hia and Hib capsular polysaccharide antigens (Branefors-helander, 1977; Crisel et al., 1975).

Materials and methods

Our methodology included sample collection and laboratory assays, data analysis, model development, simulation experiments and sensitivity analysis of the model outcomes. Details of laboratory assays are provided in the Appendix. Data collection and analysis were approved by the Thunder Bay Regional Health Sciences and Lakehead University research ethics boards.

Study population

This study is based on the analysis of Hia seroprevalence data in a population of Northwestern Ontario, Canada, which is characterized by a presence of a significant proportion of indigenous people, i.e., 19.6% of the total population in this area (Statistics Canada, 2006). In comparison, according to the 2006 Canadian Census, indigenous people comprise 3.8% of the Canadian population (Anon., 2006). Healthy adults aged 19–80 years who self-identified as either Aboriginal or non-Aboriginal were recruited from the Thunder Bay area. Individuals with chronic renal failure (CRF) aged 24–91 years were recruited from the Renal Services, Thunder Bay Regional Health Sciences Centre. The characteristics of the study groups are presented in a recently published study (Nix et al., 2015). Table 1 summarizes the demographic and health status of the participating subjects.

In designing and conducting this research, we have fully adhered to the core principles of ownership, control, access, and possession as defined by the National Aboriginal Health Organization and the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans, specifically those outlined in Chapter 9 of the 'Research Involving the First Nations, Inuit and Métis Peoples of Canada' (Anon., 2015; Schnarch, 2004). In particular, prior to the beginning of the study we engaged in an extensive consultation with a variety of stakeholders and received letters of endorsement from several regional Aboriginal organizations including the Nishnawbe Aski Nation (political territorial organization representing 49 First Nation communities in Northern Ontario), the Métis Nation of Ontario, the Red Rock Indian Band (Lake Helen First Nation), the Bingwi Neyaashi Anishinaabek (Sand Point First Nation), and the Fort William First Nation. During the data collection phase, we have regularly updated our Aboriginal partners through information sessions and progress reports as results are analyzed.

Table 1
Summary of the data collected based on the analysis of Hia seroprevalence in a population of Northwestern Ontario, Canada.

Age/Sex	Aboriginal				Non-Aboriginal			
	Healthy		CRF		Healthy		CRF	
	F	M	F	M	F	M	F	M
19–34	29	5	2	4	10	7	2	0
35–59	23	5	14	7	13	7	4	4
≥60	3	1	8	2	5	6	6	19
All	55	11	24	13	28	20	12	23

F: female; M: male; CRF: chronic renal failure.

Antibody concentration

On the basis of previous findings on immunological correlates of protection against Hib disease (Leino et al., 2000; Eskola et al., 1985; Käyhty et al., 1983), we hypothesized that anti-Hia polysaccharide antibody concentrations of 1 μg/ml or above provide long-term protection against invasive Hia disease and concentrations of 5 μg/ml or above prevent colonization of the upper airways. We stratified the collected data for the level of antibody concentrations and the corresponding average ages of individuals in Fig. 1. In all categories of healthy and CRF participants, the level of antibody concentration <1 μg/ml corresponds to the lowest fraction of individuals, with an average age older than 50 years.

The model

We first used logistic regression to investigate the effect of age and sex on the concentration of anti-Hia capsular polysaccharide antibody in the serum samples of the study participants. The statistical significance of adding the interaction term for age and sex was assessed by using a likelihood ratio test. We performed this analysis for both Aboriginal and non-Aboriginal participants. All tests were at two-sided significance level of 0.05. The results of this analysis indicated that variables of sex and age were not significant on the level of antibody concentration,

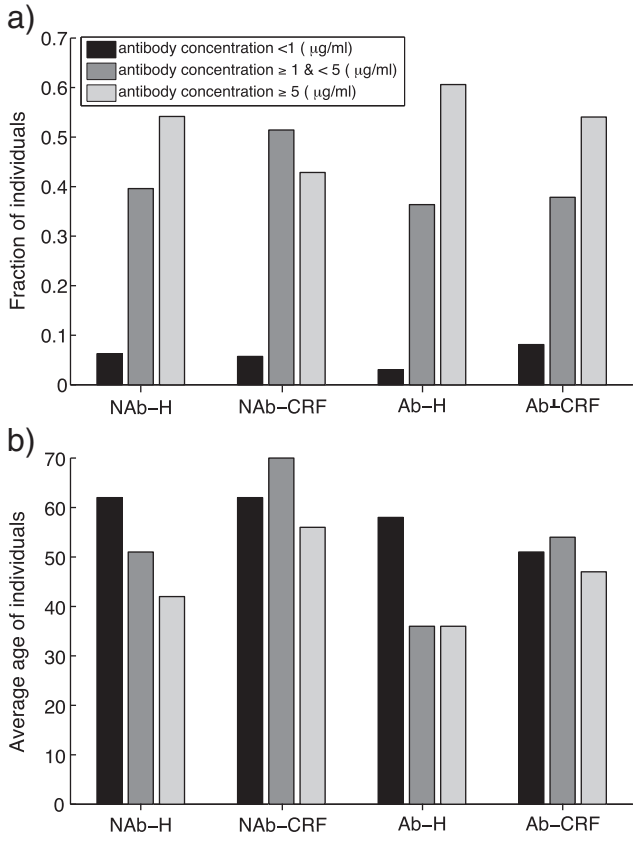

Fig. 1. (a) The fraction of individuals at low risk of infection (AC ≥ 5 μg/ml; light grey), low risk of invasive disease (1 μg/ml ≤ AC < 5 μg/ml; dark grey); and high risk of invasive disease (AC < 1 μg/ml; black). (b) The corresponding average ages of individuals identified as healthy Non-Aboriginal (NAb-H); Non-Aboriginal with chronic renal failure (NAb-CRF); healthy Aboriginals (Ab-H); and Aboriginals with chronic renal failure (Ab-CRF). (AC: total IgG and IgM antibody concentration).