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Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada

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ABSTRACT

Objective: Invasive *Neisseria meningitidis* serogroup B (MenB) disease is a low incidence but severe infection (mean annual incidence 0.19/100,000/year, case fatality 11%, major long-term sequelae 10%) in Ontario, Canada. This study assesses the cost-effectiveness of a novel MenB vaccine from the Ontario healthcare payer perspective.
Methods: A Markov cohort model of invasive MenB disease based on high quality local data and data from the literature was developed. A 4-dose vaccination schedule, 97% coverage, 90% effectiveness, 66% strain coverage, 10-year duration of protection, and vaccine cost of C$75/dose were assumed. A hypothetical Ontario birth cohort ($n = 150{,}000$) was simulated to estimate expected lifetime health outcomes, quality-adjusted life years (QALYs), and costs, discounted at 5%.
Results: A MenB infant vaccination program is expected to prevent 4.6 invasive MenB disease cases over the lifetime of an Ontario birth cohort, equivalent to 10 QALYs gained. The estimated program cost of C$46.6 million per cohort (including C$318,383 for treatment of vaccine-associated adverse events) were not offset by healthcare cost savings of C$150,522 from preventing MenB cases, resulting in an incremental cost of C$4.76 million per QALY gained. Sensitivity analyses showed the findings to be robust.
Conclusions: An infant MenB vaccination program significantly exceeds commonly used cost-effectiveness thresholds and thus is unlikely to be considered economically attractive in Ontario and comparable jurisdictions.

Abbreviations: AEFI, Adverse events following immunization; CCC, Complex chronic condition; CFR, Case fatality ratio; hSBA, Human serum bactericidal assay; ICER, Incremental cost-effectiveness ratio; IMD, Invasive meningococcal disease; IMPACT, Immunization Monitoring Program ACTive; MATS, Meningococcal antigen typing system; MenB, Serogroup B *N. meningitides*; MOHLTC, Ministry of Health and Long-Term Care; OCCI, Ontario Case Costing Initiative; OHIP, Ontario Health Insurance Program; QALY, Quality adjusted life year; QoL, Quality of life; TA, Technical assistance; UK, United Kingdom.

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1. Introduction

Annually, 500,000 cases of invasive meningococcal disease (IMD) lead to over 50,000 deaths worldwide [1,2]. In countries where serogroup C meningococcal vaccines are used, most IMD is caused by serogroup B *Neisseria meningitidis* (MenB) [1,2]. Invasive MenB disease largely affects children <5 years of age, with a 5–11% case-fatality ratio (CFR) [3,4]. In Ontario, the most populous Canadian province (population approximately 13 million), 713 IMD cases were reported between 2000 and 2010, of which 259 were caused by serogroup B (36.3%), followed by serogroups C (21.7%), Y (21.5%), and W135 (7.2%) [3]. Serogroup B has emerged as the dominant serogroup. The proportion of IMD caused by serogroup B increased from 25.0% in 2000 to 53.2% in 2008 [3].

Several regulatory agencies have recently provided marketing authorization to Novartis for Bexsero® (Meningococcal Group B Vaccine [rDNA, component, adsorbed]) [5–8]. Although no efficacy or effectiveness studies have yet been published, immunogenicity studies suggest 74–100% of vaccine recipients produce an immune response, depending on the MenB strain [9–11].

Two studies explored the cost-effectiveness of a potential MenB vaccination program [12,13]. In the United Kingdom (UK), routine infant MenB vaccination was anticipated to prevent 27–56% of cases (without and with herd immunity, respectively) over the lifetime of a birth cohort. However, the MenB vaccine's effect on carriage, the mechanism of generating herd immunity, remains unknown. Vaccination was not considered cost-effective from the healthcare perspective (except at a very low vaccine price) [13]. Similarly, in the Netherlands, routine infant MenB vaccination was estimated to prevent 14% of cases over the lifetime of a birth cohort and was not considered cost-effective from the societal perspective [12]. Since invasive MenB disease incidence and vaccine price were identified as critical, cost-effectiveness should be evaluated within the local context.

2. Materials and methods

A cost-utility analysis was conducted from the Ontario healthcare payer's perspective (Ministry of Health and Long-Term Care, MOHLTC), estimating the potential impact of MenB vaccine over the lifetime of a birth cohort. All publicly-funded healthcare costs were included: vaccination program costs (vaccine cost, vaccine administration cost, and costs of treating adverse events following immunization [AEFIs]), treatment costs for invasive MenB disease cases, and public health costs of contact management. Health outcomes included the number of invasive MenB disease cases, morbidity, mortality, and QALYs. The primary outcomes were QALYs, cost (2012 Canadian dollar (C$), where C$1 = United States dollars (US$) 1.01), and the incremental cost-effectiveness ratio (ICER) expressed as cost per QALY gained. Cost-effectiveness was assessed using the commonly used threshold of $50,000 per QALY gained. Costs and QALYs were discounted at 5% as per recommendation [14,15]. Findings are also presented using discount rates of 0% and 3% [14,15].

2.1. Model

A Markov cohort model was developed to capture the natural history of invasive MenB disease, incorporating both acute disease and long-term sequelae [16]. Sequelae were classified as minor or major disease based on Viner et al. [17] The model followed a hypothetical Ontario birth cohort (n = 150,000) over their lifetime using a cycle length of 1 year, i.e. using a 1-year age structure. However, for children aged 0–12 months, monthly incidence and vaccination data were applied to better capture the impact of direct vaccine protection. Fig. 1 presents the natural history model for invasive MenB disease. Key model assumptions were: (i) disease transmission dynamics were not explicitly modelled (i.e., no herd effects); (ii) re-infection with serogroup B *N. meningitidis* was not considered; (iii) acute invasive MenB disease requires hospitalization due to disease severity; and (iv) sequelae are permanent.

2.2. Data

All data and sources are reported in Table 1.

2.2.1. Vaccine effectiveness, strain coverage, schedule, and vaccine coverage

Clinical trials assessing the safety and immunogenicity of Novartis' MenB vaccine in children in Europe showed that the vaccine was immunogenic after ≥2 primary doses, with seroprotection ranging from 74% to 100% against reference strains expressing relevant antigens one month post-vaccination [9–11]. As such, 90% vaccine effectiveness was assumed for the base-case analysis.

The meningococcal antigen typing system (MATS) measures the immunologic cross-reactivity and quantity of component antigens in a meningococcal isolate of a given strain, to estimate "strain coverage". In a MATS study on Canadian isolates, overall "strain coverage" for MenB vaccine was 66% (95% CI: 46–78%) [18]. The base-case analysis assumed 66% strain coverage.

The proposed infant schedule is 4 doses of MenB vaccine administered at 2, 4, and 6 months of age, with a booster dose at 12 months. In the base-case analysis, vaccine protection was assumed to start after completing the second dose of vaccine at 4 months (i.e., no direct protection in infants <4 months). Waning protection was observed within a short period post-vaccination (at 40 months of age for infants) [19]; however, long-term data that could inform a waning rate are currently lacking. A 10-year duration of vaccine protection was therefore assumed (10 years of full protection, no protection after). Vaccine coverage was assumed to be 97%, the national goal for meningococcal C conjugate vaccines [20].

Reported AEFIs from MenB vaccination considered in the analysis were medically attended fever (2% of vaccinated children) and febrile seizure (0.2% of vaccinated children) [9].

2.2.2. Invasive MenB disease incidence and sequelae

The mean annual incidence of microbiologically confirmed age-specific invasive MenB disease in Ontario was obtained from Ontario's reportable disease database and Public Health Ontario Laboratory records (data on file), which is also reported in aggregated age groupings in Dang et al. [3]. Between 2000 and 2010, 259 MenB cases (36.3% of all serogroups) were identified. The overall average annual incidence rate was 0.19 per 100,000 population and the CFR was 10.7% [3]. Age-specific incidence rates were used in the analysis by single year of age (month of age in under 1 year olds), but are presented in aggregated form in the table.

The probability of long-term sequelae was obtained from Viner's population-based, retrospective UK cohort, examining disease burden in survivors of childhood MenB disease [17]. In the absence of Canadian data on risks of sequelae, and given similar overall health status and healthcare systems in the UK and Canada, the UK probabilities of long-term MenB sequelae were applied.

2.2.3. Quality of life (QoL)

Utility weights for acute meningococcal infection and long-term sequelae were derived from Carroll and Downs [21]. Disutilities for AEFI (fever, febrile seizures) were derived from Kuppermann et al. [22]. Age-specific utilities for the well state were obtained from Mittmann et al. [23]. Death was assigned a utility score of 0.

The impact of caregivers' QoL loss was explored in scenario analysis. No studies identified reported QoL loss for caregivers of invasive MenB disease cases. QoL loss of caregivers for children

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