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Residual economic burden of *Streptococcus pneumoniae*- and nontypeable *Haemophilus influenzae*- associated disease following vaccination with PCV-7: A multicountry analysis

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ABSTRACT

This paper estimates the annual direct medical and caregiver costs of *Streptococcus pneumoniae* (*Sp*) and nontypeable *Haemophilus influenzae* (NT*Hi*)-associated diseases in children younger than 10 years in Canada, Germany, Mexico, and Norway after vaccination with the 7-valent pneumococcal conjugate vaccine (PCV-7). Per-episode direct medical costs for treating *Sp*- and NT*Hi*-associated diseases were summarised from the literature for three countries, and a Delphi panel was used to estimate resource use and the per-episode costs for Mexico. Per-episode or annual costs were inflated to 2008 local currency and converted to 2008 United States (US) dollars using purchasing power parities. The analysis was for 1 year; therefore, costs were not discounted. *Sp*- and NT*Hi*-associated diseases resulted in current annual national costs of $179–$260 million ($5.43–$7.89 per capita) in Canada, $290–$435 million ($3.53–$5.29 per capita) in Germany, $277–$432 million ($2.59–$4.05 per capita) in Mexico, and $20–$28 million ($4.35–$6.17 per capita) in Norway. Although acute otitis media (AOM) was associated with the lowest per-case costs, it accounted for between 45% and 88% of the national direct medical costs and between 67% and 96% of caregiver costs for *Sp*- and NT*Hi*-associated diseases. *Sp*- and NT*Hi*-associated diseases continue to result in substantial direct medical and caregiver costs despite current PCV-7 vaccination programs.

1. Introduction

Invasive pneumococcal disease (IPD) (including meningitis and bacteraemia), pneumonia, and acute otitis media (AOM), all caused by the gram-positive bacterium *Streptococcus pneumoniae* (*Sp*), are common infectious diseases in children worldwide. Nontypeable *Haemophilus influenzae* (NT*Hi*) is an important cause of AOM in children and is also the cause of some cases of bacterial meningitis and bacteraemia [1–5]. These diseases are associated with substantial morbidity and mortality. In addition, each year they are responsible for many hospitalisations, physician visits, and antibiotic prescriptions, as well as productivity losses for parents or other informal caregivers [6].

Since 2000, a 7-valent pneumococcal conjugate vaccine (PCV-7) has been available for use in young children. Vaccination of infants with PCV-7 has been shown to significantly reduce the incidence of IPD and, to a lesser extent, the incidence of all-cause pneumonia and AOM [7–10]. In addition, a protective benefit among nonvaccinated individuals has been observed following routine vaccination of infants in the United States (US) [11–13].

Since routine vaccination programs with PCV-7 have been in place, important changes in the causes of pneumonia and AOM have also occurred in the US and many countries around the world. Following vaccination with PCV-7, a large decrease in the frequency of pneumococcal pneumonia and a smaller increase (i.e., replacement) in the frequency of unspecified pneumonia has been observed among children [13,14]; thus, there has been an overall reduction in all-cause pneumonia. Although the proportion of paediatric pneumonia attributable to *Sp* is difficult to measure, evidence suggests that the proportion has decreased since the introduction of PCV-7 [15]. Similarly, the reduction in frequency of physician visits for AOM since the introduction of PCV-7 [16] is likely associated with a reduction in cases of AOM caused by *Sp*. This shift in causative pathogens of AOM has led not only to a moderate

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decrease in the proportion of cases of AOM attributable to *Sp* but also to an increase in the proportion of cases attributable to NT*Hi* [1,2].

A new pneumococcal vaccine, PHiD-CV (pneumococcal nontypeable *H. influenzae* protein D conjugate vaccine), active against 10 *Sp* strains and NT*Hi*, was recently approved (or recommended) in 47 countries, including Canada, Germany, Mexico, and Norway. PCV-13, active against 13 *Sp* strains, has also been approved in Canada, Germany, Mexico, and Norway. To understand the potential impact of the PHiD-CV and PCV-13 vaccines in countries with current PCV-7 programs in place, it is important to estimate the residual health and economic burdens of both *Sp*- and NT*Hi*-related diseases in children younger than 10 years in the post-PCV-7 vaccine era.

This paper estimates the health service use, direct medical costs, and informal care costs to provide care for sick children (caregiver costs) associated with diseases attributable to both *Sp* and NT*Hi* in children younger than 10 years after implementation of vaccination with PCV-7 in four countries: Canada, Germany, Mexico, and Norway. These countries were selected because each has routine vaccination with PCV-7 with high coverage rates; thus, the cost burden would be expected to have decreased substantially since PCV-7 vaccination was introduced.

2. Methods

2.1. Overview

The national financial burden estimates are part of a comprehensive disease model developed to estimate the impact and cost-effectiveness of different vaccination strategies. Both direct medical costs and caregiver productivity loss costs were estimated for each case of illness. Direct medical costs included costs incurred for medical treatment of the acute condition on an inpatient or outpatient basis, as well as 1-year costs of treating cases of sequelae. Nonmedical costs included costs related to cases of sequelae such as incremental educational costs, disability payments, and the cost of a parent's or caregiver's productivity loss due to time to care for a child during the acute episode of a pneumococcal or NT*Hi*-related illness. Caregiver productivity loss costs were estimated using the human capital approach.

To estimate the current national burden of *Sp*- and NT*Hi*-associated diseases in the four countries, the cost per case of the disease was multiplied by the estimated number of cases of each disease in 2008 using current PCV-7 coverage rates (91% in Canada, 90% in Germany, 95% in Mexico, 80% in Norway) [17,18]. Because of the dynamics of the disease (e.g., herd effects) over time, we conducted the analysis for each country under the assumption that the full herd effect (from PCV-7 vaccination) had been realised. For long-term outcomes such as meningitis sequelae, the number of cases of sequelae occurring in 2008 in addition to the number of cases of sequelae that developed in previous years and required treatment in 2008 were estimated. The analysis was limited to children younger than 10 years to focus on the target age group for vaccination and to compare results with other published studies.

2.2. Cases of Sp- and NTHi-associated disease with the PCV-7 vaccination program

The estimated number of acute cases of each disease in 2008 in the four countries, all of which had routine vaccination with PCV-7, was taken from the full disease model explained in a companion paper in this supplement [19]. In summary, the model used prevaccination incidence data for pneumococcal meningitis, pneumococcal bacteraemia, all-cause pneumonia, and all-cause AOM and then applied direct and indirect effects of PCV-7 to estimate the number of remaining cases of disease after vaccination. Indirect effects (i.e., the net effect of herd protection and serotype replacement) were included only for pneumococcal meningitis and bacteraemia, and not for pneumonia or AOM, because evidence of sustained herd protection is limited for these diseases [20].

For long-term outcomes such as meningitis sequelae, a prevalence-based approach was used, where the number of cases of meningitis sequelae that developed in previous years that would require treatment in 2008 was calculated using meningitis sequelae rates and age-specific survival probabilities. For Canada, Mexico, and Norway, meningitis sequelae rates (7% for neurological sequelae, 13.3% for long-term hearing loss) were based on data from a review of multiple studies in North America used in another model [6,21,22]. For Germany, meningitis sequelae rates (5.7% for neurological sequelae, 8.3% for long-term hearing loss) were based on a single study in Germany [23]. The number of prevalent sequelae cases was estimated by applying age-specific survival probabilities to children from infancy to 9 years. The equation for calculating the expected number of prevalent cases of sequelae among children younger than 10 years in 2008 is as follows:

$$\sum_{i=0}^{9}\left(s_i + \sum_{t=1}^{9-i} p_{i,t}s_i\right)$$

where

s_i = the number of incident cases of sequelae at age i.
$p_{i,t}$ = the probability that a person age i at the time of developing sequelae will survive t years.

The proportion of cases of pneumonia attributable to *Sp* decreased after the introduction of PCV-7, but it is difficult to quantify the proportion of cases of pneumonia still attributable to *Sp*. Therefore, a range of 13–37% was applied to cases of all-cause pneumonia (generated by the model) to estimate only the proportion due to *Sp* [6,15,24]. For AOM, a shift in aetiology similar to pneumonia has been observed since the introduction of PCV-7, with fewer cases caused by *Sp* and possibly more caused by NT*Hi*. Therefore, a range of 30–38% [1,2,25,26] was applied to cases of all-cause AOM (generated by the model) to estimate the proportion due to *Sp*. A range of 38–57% [1,2,26] was used to estimate the proportion due to NT*Hi*.

To estimate the number of cases of invasive disease (meningitis and/or bacteraemia) caused by NT*Hi* among children, we assumed that the ratio of NT*Hi* cases to *Sp* cases was 5%. This estimate was based on expert opinion because, although there is evidence of invasive disease caused by NT*Hi*, [5,27] the precise proportion of invasive disease caused by NT*Hi* is not well established. We did not attempt to quantify meningitis and bacteraemia separately for cases of invasive disease caused by NT*Hi* because of the relatively small numbers of cases. Although some studies have examined the role of NT*Hi* in pneumonia, it is unclear whether NT*Hi* is an important cause of paediatric pneumonia [15]; therefore, pneumonia cases attributable to NT*Hi* were excluded from this analysis.

2.3. Direct medical costs per case

For all acute disease outcomes, direct medical costs per case were applied to the annual number of cases of each disease assuming current PCV-7 vaccination coverage rates. For prevalent cases of meningitis sequelae, the direct medical and nonmedical costs associated with meningitis sequelae for 1 year were applied to the number of prevalent cases of sequelae in 2008 among children younger than 10 years. This approach of estimating the cost of treating all acute cases of disease and prevalent cases of sequelae