How many individuals with asthma need to be vaccinated to prevent one case of invasive pneumococcal disease?

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BACKGROUND: The American Advisory Committee on Immunization Practices recommended the inclusion of adults with asthma in the high-risk category for pneumococcal vaccination based on a twofold increase in risk of invasive pneumococcal disease (IPD).

OBJECTIVE: To determine whether, among individuals with asthma, the number needed to vaccinate (NNV) using pneumococcal conjugate vaccine (PCV)-13 or 23-valent pneumococcal polysaccharide vaccine (PPV-23) warrants its addition to the high-risk category for pneumococcal vaccination in Canada.

METHODS: Using IPD incidence (per 10,000 individuals) figures from published articles (4.2 in high-risk asthmatics, 2.3 in low-risk asthmatics and 1.2 in healthy individuals), the NNV to prevent one case of IPD in asthmatics five to 17 years of age and 18 to 50 years of age was calculated, factoring in the proportion of pneumococcal serotypes included in vaccines (based on data from Quebec) and accounting for the possibility of waning vaccine efficacy (VE) using four scenarios.

RESULTS: Assuming a VE of 65% for PCV-13 in asthmatics, the NNV would be 704 to 820 in low-risk and 386 to 449 in high-risk adults (range depends on waning scenario). Assuming a VE of 65% for PPV-23 in asthmatics, the NNV would be 581 to 677 in low-risk and 355 to 1,532 in high-risk adults.

CONCLUSION: The NNV with both PCV-13 and PPV-23 in asthmatic children and adults is comparable with that of other high-risk conditions such as age 65 years. Therefore, the addition of asthma to the list of high-risk conditions for pneumococcal vaccination is warranted.

Key Words: Asthma; Pneumococcal; Vaccine

Invasive pneumococcal disease (IPD) is defined as the isolation of Streptococcus pneumoniae from a normally sterile site. Several conditions have been recognized to increase the risk of IPD: sickle cell disease or other hemoglobinopathy; functional or anatomical asplenia; immunocompromising conditions (eg, primary immunodeficiencies, HIV, malignancies, induced immunosuppression for organ transplant or post-transplantation, long-term systemic corticosteroids); chronic medical conditions (cerebrospinal fluid leaks, chronic cardiac and pulmonary disease, diabetes mellitus, chronic renal disease, dialysis, cirrhosis); cochlear implants; smoking; alcoholism; age 65 years; and residence in a long-term care facility (1,2). Furthermore, homeless individuals and individuals who use illicit drugs may also be at increased risk (3). In Canada, children between two months and 18 years of age who belong to high-risk groups should receive a pneumococcal conjugate vaccine (PCV), followed by the 23-valent pneumococcal polysaccharide vaccine (PPV-23) if ≥2 years of age. The recommendation for adults in these high-risk groups is a dose of PPV-23 (1).

In early 2012, both Health Canada and the United States Food and Drug Administration approved the use of the 13-valent PCV (PCV-13)
IPD surveillance system
IPD is a reportable disease in Quebec. Quebec has a laboratory surveillance system that is enhanced and complete for all pneumococcal isolates from sterile body fluids from children ≥5 years of age. Isolates from older children and adults are sent on a voluntary basis through a sentinel laboratory surveillance network (n=21 hospital laboratories). All IPD isolates are sent to the Quebec Public Health Laboratory for serotyping and antimicrobial susceptibility testing. In 2011, the sentinel network only contributed 328 (24%) of the 1358 isolates that were part of the surveillance program; most of the pneumococcal isolates from sterile sites were, thus, sent through voluntary participation (17). IPD isolates are categorized according to age groups (0 to 11 months, 12 to 23 months, 24 to 35 months, 36 to 59 months, five to 11 years, 12 to 17 years, 18 to 49 years, 50 to 64 years and ≥65 years of age). Serotype data are available for each age group. The study population was children five to 17 years of age and adults 18 to 50 years of age.

Study design
Because the incidence of IPD among asthmatics in Quebec is unknown, published incidence data for unvaccinated subjects available in the literature were used (14): 4.2 episodes per 10,000 individuals with high-risk asthma, 2.3 episodes per 10,000 individuals with low-risk asthma and 1.2 episode per 10,000 individuals without asthma. In the cited study, high-risk asthma was defined as asthma requiring hospital admission or an emergency department visit, use of a course of corticosteroids as rescue therapy, long-term use of oral corticosteroids (≥120 days) or dispensing of ≥3 prescriptions for β-agonists within the previous year.

The NNV was calculated as the inverse of the absolute risk reduction, which was, in turn, divided by the estimated length of vaccine protection (VP). The absolute risk reduction was calculated as the difference in disease incidence between unvaccinated and vaccinated subjects. The NNV and incidence in vaccinated subjects were derived as follows:

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NNV = \frac{1}{VP \text{ length} \times (1/(\text{incidence unvaccinated} - \text{incidence vaccinated}))}
\]

\[
\text{Incidence in vaccinated} = \frac{\text{incidence unvaccinated} \times (1 - (VE \times \% serotype coverage))}{\text{VP}}
\]

Variables
Based on the literature cited in the introduction, the published estimates of VE are highly variable. For simplicity, the VE in healthy children and adults was estimated to be 80% for both PCV-13 and PPV-23. However, a sensitivity analysis was performed using a worst-case scenario of 60% VE and a best-case scenario of 97% VE. Because the VE in asthmatics is not known but is assumed to be inferior, the VE in this population was arbitrarily decreased to 65% for PCV-13 and PPV-23. A sensitivity analysis was performed, varying the VE between 45% and 80% and, for both PCV-23, between 60% and 95%, based on the known Canadian epidemiology (18).

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The possibility of waning VE was accounted for using four scenarios. The first assumed no waning VE. The second scenario assumed a steady VE for five years followed by a decline of 1% per year thereafter. The third scenario assumed a steady VE for 10 years followed by a decline of 2% per year thereafter. The fourth scenario assumed a steady VE for five years, then a decline of 2.5% per year for the next 10 years, a decline of 1.67% per year for the next 15 years and 1.25% per year for the next 20 years after vaccination. A static model that did not take into account herd immunity or serotype replacement was used.
Asthma and invasive pneumococcal disease

TABLE 1
Percent of invasive pneumococcal disease isolates from 2009 to 2012 in Quebec covered by pneumococcal conjugate vaccine (PCV)-13 and pneumococcal polysaccharide vaccine (PPV)-23 according to age group.

<table>
<thead>
<tr>
<th>Group</th>
<th>PCV-13</th>
<th>PPV-23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 5 to 17 years of age</td>
<td>63.3</td>
<td>76.7</td>
</tr>
<tr>
<td>Adults 18 to 50 years of age</td>
<td>58.8</td>
<td>85.1</td>
</tr>
<tr>
<td>Adults ≥65 years of age</td>
<td>46.6</td>
<td>64.5</td>
</tr>
</tbody>
</table>

Data presented as %

RESULTS

Serotype data
The proportion of isolates that were vaccine serotypes in Quebec from 2009 to 2012 are presented in Table 1. PCV-13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) comprised 63.3% of the IPD strains in children five to 17 years of age, 58.8% of the strains in adults 18 to 50 years of age, and 46.6% of the strains in adults ≥65 years of age.

NNV
Depending on the waning scenario used, the NNV using PCV-13 varied from 1097 to 1239 for healthy children five to 17 years of age, 704 to 820 for low-risk and 386 to 449 for high-risk asthmatic children five to 17 years of age (Table 2). For adults, the NNV using PCV-13 was between 554 to 1502 for healthy adults 18 to 50 years of age, 355 to 1532 for low-risk and 195 to 839 for high-risk asthmatic adults 18 to 50 years of age (Table 3).

Depending on the waning scenario used, the NNV using PPV-23 varied from 905 to 1023 for healthy children, 581 to 677 for low-risk and 318 to 371 for high-risk asthmatic children (Table 2). For adults, the NNV using PPV-23 was between 690 to 1023 for healthy adults, 470 to 581 for low-risk and 398 to 449 for high-risk asthmatic adults (Table 3).

Sensitivity analysis
Tables 2 and 3 also present the best- and worst-case scenarios for various age groups, using different waning scenarios for both vaccines. Overall, the NNV for children with low-risk asthma could be as high as 1798 (PCV-13) and 1348 (PPV-23), compared with a worst-case scenario of 984 (PCV-13) and 738 (PPV-23) in children with high-risk asthma. For adults, the NNV for low-risk asthma could be as high as 8783 (PCV-13) or 6588 (PPV-23) for low-risk asthma, or 4810 (PCV-13) or 3608 (PPV-23) for high-risk asthma.

DISCUSSION
Current Canadian vaccination guidelines do not include asthma as a high-risk condition warranting pneumococcal vaccination. However, based on our calculations, not taking into account herd immunity and previous vaccination with PCV, the NNV to prevent one case of IPD is low. In fact, the NNV to prevent one case of IPD with both PCV-13 and PPV-23 is lower than in the high-risk groups that are routinely vaccinated. For example, the NNV with PPV-23 in adults ≥65 years of age has been calculated at 3333 in one study and 5206 in another.

High-risk groups in Canada are currently vaccinated with PPV-23, although the calculated NNV to prevent one case of IPD with PPV-23 and PCV-13 appear to be similar. Due to the immunogenicity advantage of conjugate vaccines and because of its expanded serotype coverage compared with PCV-7, PCV-13 should be further explored as an alternative to PPV-23 in high-risk groups, particularly in immunocompromised populations. However, although there may be an immunogenicity advantage, correlates of protection and the actual efficacy of PCV-13 in adults is yet to be determined. On the other hand, the introduction of PCV-13 vaccination in children may lead to serotype replacement and herd immunity, which may limit the benefit for adults in the future. For example, with the introduction of routine infant vaccination programs with PCV-7 in Canada in 2002, there has been near eradication of IPD caused by PCV-7-serotype strains in both children and adults (19). A surveillance study from Calgary (Alberta) comparing incidence of IPD from 1998 to 2001 (prevaccine period) with 2007 showed a 94% decline in the incidence of PCV-7-serotype IPD in children <2 years of age. They also found a 92% decline in PCV-7-serotype IPD among adults 65 to 84 years of age and a 29% decline in overall IPD (20). This is likely due to reduced nasopharyngeal colonization in infants and young children, which may have reduced transmission to adults.

Similar results were observed in the United States; from 1998-1999 to 2008, overall rates of IPD decreased by 34% in individuals 18 to 49 years of age, 14% in those 50 to 64 years of age and 37% in those...
7. Kelly H et al. The number needed to vaccinate (NNV) and population studies would be to vaccinate adult asthmatics in Canada with PPV-23. PCV-13, and the lower cost of PPV-23, the best strategy pending further analyses are needed to evaluate the cost effectiveness of vaccination in conditions warranting pneumococcal vaccination in Canada. Further studies would be to vaccinate adult asthmatics in Canada with PPV-23.

CONCLUSIONS
The NNV with both PCV-13 and PPV-23 in asthmatic children and adults is comparable with, if not lower than, the NNV to prevent one case of IPD in individuals with high-risk conditions such as age ≥65 years. Therefore, asthma should be added to the list of high-risk conditions warranting pneumococcal vaccination in Canada. Further analyses are needed to evaluate the cost effectiveness of vaccination in this risk group. Given the similar calculated NNVs, the limited data on this risk group. Our study is limited by the fact that the efficacy and effectiveness of PCV-13 is not yet known in the adult population; therefore, number are extrapolated from studies of PCV-7 involving children. Moreover, the efficacy of PPV-23 could have been overestimated due to the fact that some children and young adults have previously received one or more pneumococcal conjugate vaccines, which would lessen the added benefit of PPV-23. The waning scenario may be overestimating the PPV-23 VE. However, current Canadian guidelines only recommend one dose of PPV-23 without a booster in individuals who have a chronic condition, but who are not otherwise considered immunocompromised. Furthermore, the potential for serotype replacement with the introduction of vaccination in asthmatics was not taken into account, nor was the possibility of herd immunity.

REFERENCES