Decreased Incidence of Respiratory Infections in Children After Vaccination with Ten-valent Pneumococcal Vaccine

Samuel Sigurdsson, BSc,* Karl G. Kristinsson, MD, PhD, FRCPath,† Helga Erlendsdóttir, MSc,*‡ Birgir Hrafnskellsson, PhD,‡ and Æsgeir Haraldsson, MD, PhD*§

Introduction: Respiratory tract infections (RTIs) and antibiotic usage are common in children, increasing the risk of antibacterial resistance. The introduction of protein-conjugated pneumococcal vaccines has led to reduction in pneumococcal infections. In 2011, pneumococcal protein-conjugated vaccine-10 was introduced into the national childhood vaccination in Iceland, a population not earlier vaccinated against pneumococcus, with 95% vaccine uptake in the first year. The aim of the study was to evaluate the number of children visiting the Children’s Hospital Iceland for RTIs before and after the introduction of the vaccine.

Methods: Admissions and visits to the Children’s Hospital because of RTIs were recorded, and children aged 3 months to 2 years in the nonvaccine eligible cohort (born 2008–2010) were compared with the vaccine eligible cohort (born in 2011). Statistical analysis was done using large sample Z test and incidence rate ratios (IRRs) were calculated.

Results: A significant reduction in incidence rate was found when comparing the nonvaccine eligible cohort with the vaccine eligible cohort, both for acute otitis media (AOM) (IRR: 0.76; 95% confidence interval: 0.67–0.87; P < 0.0001) and for pneumonia (IRR: 0.77; 95% confidence interval: 0.64–0.95; P < 0.01).

Conclusion: A significant reduction in hospital visits because of AOM and pneumonia in children vaccinated with pneumococcal protein-conjugated vaccine-10 was established. The abrupt and significant reduction of AOM is unusually clear. This reduction was noted very early after initiation of the vaccination.

Key Words: Respiratory infections, children, pneumococcal vaccination, Streptococcus pneumoniae, AOM, pneumonia

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espiratory tract infections (RTIs), in particular in the upper respiratory tract are common, with about 2 infections per year in adults and 6–8 per year in young children. RTIs, especially acute otitis media (AOM), are the most common indications for antibiotic prescriptions in children. The society’s health cost due to RTI is high.

AOM is the most common cause of health care visits in children and it is claimed that more than half of all children experience at least 1 episode during their first year of life and 60%–70% before 3 years of age. The most common bacteria are Streptococcus pneumonia (pneumococcus), nontypeable Haemophilus influenzae (H. influenzae) and Moraxella catarrhalis (M. catarrhalis). AOM is the most common cause of antibiotic usage in this age group, which consequently increases the risk of antibacterial resistance.

Lower respiratory tract infections (LRTIs) are also common, especially in young children and the elderly. Viral infections including the seasonal influenza virus are the most common cause of LRTI, sometimes followed by bacterial infections. Bronchiolitis may be the most common LRTI in children as the majority of children have had at least 1 episode of bronchiolitis before the age of 2, respiratory syncytial virus (RSV) being the most common cause. Worldwide, it is estimated that one fifth of under-5 mortality is caused by pneumonia, mainly in developing countries, pneumococcus being the most common organism in those cases.

Pneumococcus is often carried in the nasopharynx, especially in children and can cause various infections, especially in children and the elderly, including RTIs and severe invasive pneumococcal disease. Invasive pneumococcal disease in children younger than under 2 years before the start of pneumococcal vaccination was described in a European review to be as high as 27 per 100,000 children and even higher in US.

Pneumococcal infections is an important goal.

After introduction of the pneumococcal protein-conjugated vaccines (PCV), a reduction in the incidence of pneumococcal infections in children has been firmly established in various studies. Emerging results are also being published on the herd effect achieved by these immunizations.

In April 2011, a pneumococcal H. influenzae protein D conjugate vaccine (PHiD-CV10/PCV-10) was introduced into the national childhood vaccination program in Iceland, a population not earlier vaccinated against pneumococcus. Thus, all children born after January 1, 2011 were eligible for the vaccination. It is important to study the effect of this intervention on children and the whole population. The aim of this was to investigate the impact of PCV-10 on RTIs diagnosed in children younger than 18 years at the Children’s Hospital Iceland after the introduction of this immunization.

MATERIALS AND METHODS

A retrospective, epidemiologic survey was conducted, where all visits because of RTI for children younger than 18 years to the Children’s Hospital Iceland Landsdóttari University Hospital, in the period January 1, 2008 to December 31, 2013 were recorded including both those admitted to the hospital and those treated as outpatients.

Address for correspondence: Æsgeir Haraldsson, MD, PhD, Children’s Hospital Iceland Landsdóttari University Hospital, 101 Reykjavik, Iceland. E-mail: ae@sh.is.

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From the †Faculty of Medicine, University of Iceland, Reykjavik, Iceland; ‡Department of Clinical Microbiology, Landsdóttari University Hospital, Reykjavik, Iceland; §Department of Mathematics, University of Iceland, Reykjavik, Iceland; and ¶Children’s Hospital Iceland, University Hospital – Landsdóttari, Reykjavik, Iceland.

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Address for correspondence: Æsgeir Haraldsson, MD, PhD, Children’s Hospital Iceland Landsdóttari University Hospital, 101 Reykjavik, Iceland. E-mail: ae@sh.is.

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information were collected from all children in the study. This approach detected all emergency ward visits and hospital admissions for RTI. When a patient’s chart contained more than 1 ICD-10 diagnosis, an algorithm was created to reliably identify the most relevant diagnoses for the study (in this order: (1) pneumonia or AOM, (2) complications of pneumonia or AOM and (3) other RTI). Only one diagnosis was used for each visit. For recurrent visits of the same patient, a new case was defined if the patient had previously been discharged. The patients were stratified according to age group, sex and diagnosis. The age stratification were <1, 1 to <2, 2 to <3, 3 to <7 and 7 to <18 years.

The mean incidence rate (IR) in a 3-year period before the immunization (2008–2010) was compared with the mean IR in a 3-year period after the initiation of the vaccination (2011–2013). IR was calculated as number of cases per 10,000 children each year in the area using population data from Statistics Iceland (www.statice.is). Each group was studied separately, and age matched comparison made.

To better evaluate the vaccination effect, children born in 2011 (vaccine eligible cohort, VEC) were compared with children born 2008–2010 (nonvaccine eligible cohort, NVEC). Follow-up was from 3 months of age (first primary vaccination) until 2 years of age.

To evaluate the possible impact of misdiagnosis of pneumonia as acute bronchiolitis, the yearly incidence of both diagnoses was calculated separately and the trends analyzed. Acute bronchiolitis diagnosis was analyzed independently, for example, an algorithm was created to search for all visits where acute bronchiolitis was noted on the patients chart.

The possible impact of annual influenza was evaluated by calculating the incidence of RTI with and without influenza cases as primary diagnosis. The diagnostic and admission practices at the hospital did not change during the study period.

Statistical analysis was done in R. Difference between IRs of 2 populations was tested using a large sample Z test. Asymptotic confidence intervals (CIs) for IR and incidence rate ratio were constructed using large sample theory.

The study was approved by The National Bioethics Committee (VSNb2013010015/03.07), The National Data Protection Authority (2013010100VEL/--) and the University Hospital director. The study is a part of a larger study on vaccinations in Iceland (The Vîce study).

RESULTS

The number of hospital visits for RTI during the study period was 11,752, by 7,158 patients, thereof 643 admissions. Less than 15% of the patients had more than 2 visits because of RTI during the 6-year study period. The median age was 1.5 years, and males were 56%. Seasonal variation revealed the highest incidence of RTI during the winter months. The quarterly IR of RTI per 10,000 children during the study period is given in Figure 1.

Changes in Incidence Rate

IR for all-cause RTI before and after the commencement of the vaccination was highest in children 1–2 years of age, for whom the IR...
declined 15% (95% CI: 8%–22%, \( P < 0.0005 \)) from 2322 to 1967 per 10,000 children-years in the period (Table 2; Fig. 2). A 15% reduction (95% CI: 0%–28%, \( P < 0.05 \)) was also noted for children 7–18 years of age (Table 2). For children in their first year, a 13% increase (95% CI: 2%–24%, \( P < 0.05 \)) was seen in overall IR for all-cause RTI. The IR was unchanged in other age groups (Table 2; Fig. 2).

For all-cause AOM, a 26% reduction in IR (95% CI: 17%–34% \( P < 0.001 \)) from 1426 to 1058 per 10,000 children-years for Table 2. Yearly Incidence of RTI Per 10,000 Children in Each Age Group

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age Group (yr)</th>
<th>PrV IRR (n)</th>
<th>PoV IRR (n)</th>
<th>Children-years At Risk</th>
<th>IRR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All RTI</td>
<td>&lt;1</td>
<td>1724 (1642)</td>
<td>1948 (1779)</td>
<td>9522/9134</td>
<td>1.13 (1.02–1.24)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>1 to &lt;2</td>
<td>2322 (2103)</td>
<td>1967 (1844)</td>
<td>9049/9027</td>
<td>0.85 (0.78–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;3</td>
<td>707 (692)</td>
<td>919 (876)</td>
<td>8688/9526</td>
<td>1.01 (0.90–1.15)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;7</td>
<td>229 (744)</td>
<td>204 (715)</td>
<td>32,478/34,982</td>
<td>0.80 (0.75–1.06)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>7 to &lt;18</td>
<td>78 (689)</td>
<td>66 (574)</td>
<td>88,677/87,153</td>
<td>0.80 (0.72–1.00)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>All RTI excluding influenza</td>
<td>&lt;1</td>
<td>1671 (1592)</td>
<td>1935 (1768)</td>
<td>9522/9134</td>
<td>1.16 (1.05–1.27)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>1 to &lt;2</td>
<td>2284 (2067)</td>
<td>1939 (1819)</td>
<td>9049/9027</td>
<td>0.85 (0.77–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;3</td>
<td>826 (749)</td>
<td>926 (868)</td>
<td>8688/9526</td>
<td>1.12 (0.99–1.27)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;7</td>
<td>192 (672)</td>
<td>192 (670)</td>
<td>32,478/34,982</td>
<td>1.00 (0.85–1.16)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>7 to &lt;18</td>
<td>49 (591)</td>
<td>43 (524)</td>
<td>88,677/87,153</td>
<td>0.88 (0.74–1.05)</td>
<td>NS</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>&lt;1</td>
<td>245 (233)</td>
<td>172 (157)</td>
<td>9522/9134</td>
<td>0.70 (0.55–0.89)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>1 to &lt;2</td>
<td>596 (539)</td>
<td>460 (431)</td>
<td>9049/9027</td>
<td>0.77 (0.66–0.90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;3</td>
<td>358 (311)</td>
<td>388 (370)</td>
<td>8688/9028</td>
<td>1.00 (0.89–1.12)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;7</td>
<td>93 (346)</td>
<td>91 (319)</td>
<td>32,478/34,982</td>
<td>0.98 (0.79–1.23)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>7 to &lt;18</td>
<td>39 (348)</td>
<td>32 (275)</td>
<td>88,677/87,153</td>
<td>0.80 (0.64–1.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Acute bronchiolitis</td>
<td>&lt;1</td>
<td>423 (403)</td>
<td>637 (582)</td>
<td>9522/9134</td>
<td>1.51 (1.28–1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1 to &lt;2</td>
<td>149 (135)</td>
<td>292 (274)</td>
<td>9049/9027</td>
<td>1.96 (1.56–2.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;3</td>
<td>54 (47)</td>
<td>105 (100)</td>
<td>8688/9028</td>
<td>1.94 (1.60–2.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;7</td>
<td>8 (25)</td>
<td>9 (31)</td>
<td>32,478/34,982</td>
<td>1.15 (0.66–2.00)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>7 to &lt;18</td>
<td>0 (3)</td>
<td>1 (13)</td>
<td>88,677/87,153</td>
<td>4.41 (1.23–15.75)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>AOM</td>
<td>&lt;1</td>
<td>910 (867)</td>
<td>980 (895)</td>
<td>9522/9134</td>
<td>1.06 (0.94–1.23)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1 to &lt;2</td>
<td>1426 (1290)</td>
<td>1058 (992)</td>
<td>9049/9027</td>
<td>0.74 (0.66–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>2 to &lt;3</td>
<td>371 (322)</td>
<td>315 (300)</td>
<td>8688/9028</td>
<td>0.85 (0.70–1.03)</td>
<td>&lt;0.1 (NS)</td>
</tr>
<tr>
<td></td>
<td>3 to &lt;7</td>
<td>60 (194)</td>
<td>63 (221)</td>
<td>32,478/34,982</td>
<td>1.06 (0.83–1.34)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>7 to &lt;18</td>
<td>8 (74)</td>
<td>10 (87)</td>
<td>88,677/87,153</td>
<td>1.19 (0.86–1.67)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Influenza cases are included. PrV indicates prevaccination, 2008–2010; PoV, postvaccination, 2011–2013; NS, nonsignificant; IRR, incidence rate ratio.

**FIGURE 2.** A comparison of annual incidence per 10,000 children before and after the initiation of the vaccination. Prevaccination, 2008–2010; postvaccination, 2011–2013; +, significant. X-axis indicates changes in incidence rate ratio (IRR).
was noted for children 1–2 years of age. In other age groups, no significant change was noted (Table 2; Fig. 2). For all-cause pneumonia, a 30% reduction in IR (95% CI: 11%–45%, \( P < 0.01 \)) from 245 to 172 per 10,000 children-years in children younger than 1 year, a 23% reduction in IR (95% CI: 10%–34%, \( P < 0.01 \)) from 596 to 460 for children 1–2 years of age. In other age groups, no significant change was noted (Table 2; Fig. 2). For all-cause acute bronchiolitis, a 51% increase in IR (95% CI: 33%–85%, \( P < 0.001 \)) from 423 to 637 per 10,000 children-years in children younger than 1 year was noted, a 96% increase in IR (95% CI: 46%–240%, \( P < 0.001 \)) from 149 to 292 for children 1–2 years of age and a 94% increase in IR (95% CI: 46%–240%, \( P < 0.001 \)) from 54 to 105 for children 2–3 years of age. In other age groups, no significant change was noted (Table 2; Fig. 2).

Comparison of Vaccine Eligible and Nonvaccine Eligible Cohorts

When comparing the IR of children born in 2011 (VEC) with children born 2008–2010 (NVEC), a 24% reduction (95% CI: 13%–33%, \( P < 0.0001 \)) for all-cause AOM was found from 1198 to 915 per 10,000 children-years. A 23% reduction (95% CI: 5%–36%, \( P < 0.01 \)) for all-cause pneumonia was established and a 53% increase in all-cause acute bronchiolitis (95% CI: 24%–90%, \( P < 0.0005 \)) from 223 to 342 (Fig. 3).

Lower Respiratory Infection IR, Influenza and Other Hospital Visits

For children <18 years of age, the incidence for bronchiolitis was 187, 425, 624, 671, 685 and 642 and for pneumonia 1218, 1160, 1214, 1205, 1041 and 855 for the years 2008–2013, respectively, per 100,000 children-years.

Incidence of influenza during each winter period was low for all the years except the winter of 2009–2010 during the H1N1 influenza epidemic. Excluding patient visits whose primary diagnosis was associated with influenza did only have a minor effect on the evaluation of RTI (Table 2).

The total number of visits to the emergency ward at the Children’s Hospital increased significantly during the study period from 12,229 in 2008 to 13,525 in 2013.

DISCUSSION

A statistically significant reduction in the incidence of AOM (1 to <2 years of age) and pneumonia (<2 years of age) was found in children visiting the Children’s Hospital Iceland after the introduction of the PCV-10 vaccine. This is in context with earlier reports.25–28 However, this early effect of an abrupt and significant reduction of AOM is noteworthy.

The primary vaccinations with PCV-10 are given at age 3 and 5 months in Iceland, with an impressive >95% vaccination coverage in the first year of the vaccination (www.landlaeknir.is/english). One can expect the antipneumococcal antibodies to become protective after the primary vaccinations. We compared RTI in children in the VEC with RTI in children in NVEC with a follow-up time from 3 months to 2 years of age and found a significant difference in IR of AOM and pneumonia. The only major difference between the groups was the vaccination. We, therefore, assume that the main factor in the noted reduction in AOM and pneumonia is the impact of the vaccination.

In this context, it is important to compare these changes with the incidence of other infections. One RTI that should not be affected by the immunization is acute bronchiolitis,16–18 often caused by RSV causing yearly epidemics varying in severity.19,30,31 The annual bronchiolitis epidemics were unusually strong in Iceland in the postvaccination era (2011–2013) with a significant increase in the number of children infected. These severe epidemics were also observed in Ireland, where a 100% increase in bronchiolitis hospitalization was noted in 2011 and 2012 compared with the previous 4 years,31 perhaps fueled by a novel RSV-A strain first detected in Canada in December 2010 and had become prevalent in Europe in 2011–2012 epidemic season.32 Several studies have shown an increase in bacterial adherence on respiratory tract
epithelium, especially in the URT, after respiratory tract viral infections, including RSV infections. Recent viral infection has also been shown to have a small but significant impact on incidence of AOM and pneumonia. Therefore, one would expect an increase in the incidence of AOM and pneumonia after this increase in bronchiolitis. In fact, the opposite was found.

Diagnosis of pneumonia in children can be difficult. In our study, we used all pneumonias, physician diagnosed as well as X-ray confirmed, and all possible complications thereof in a single centre. Mild pneumonias can be misdiagnosed as bronchiolitis. As all clinical diagnoses of pneumonias were included in this study, this represents a possible confounder. During the study period, no change in the diagnostic and admission practices at the hospital took place. It is, therefore, unlikely that changes in the incidence of pneumonias or bronchiolitis are caused by misdiagnosis of these diseases. Moreover, the incidence of bronchiolitis was initially low, increased in period before the vaccination and plateaued in the postvaccination period. The incidence of pneumonia on the other hand was relatively stable in the prevaccination period but decreased after the initiation of the vaccine. This indicates that the decrease in pneumonia incidence is independent of the increase in bronchiolitis.

As the majority of RTI infections are of viral origin and only a proportion are caused by bacteria whereof some only are caused by pneumococcus, the significant reduction in the total number of children with pneumonia is noteworthy. There are some possible explanations in addition to the direct vaccination impact, for this very clear decrease in the incidence of AOM and pneumonia. The most virulent bacteria in AOM are the pneumococci often resulting in recurrent AOM. Recurrent AOM are often the result of disrupted epithelium in the middle ear, mucosal damage and impaired clearing of mucus following bacterial otitis, paving the way for recurrent infections, often with other microbes such as nontypeable H. influenzae and M. catarrhalis. Preventing this first episode can interrupt this process. In addition, formations of biofilms may play a role in recurrent infections. In some studies, biofilms account for a considerable part of culture negative AOM. Although one Israeli study has shown reduction of 85% in vaccine-type AOM, others have only shown a 0%-7% reduction of all cause AOM. However, these studies used the PCV-7 vaccine, whereas in this study, the vaccinations were done with the PCV-10 vaccine. The more serotypes included in that vaccine may be important, but the protein D conjugate from H. influenzae may have added to this effect. Reports on the PCV-10 vaccine impact on H. influenzae have been conflicting; a prelicensure study of a 11 valent pneumococcal H. influenzae protein D vaccine showed up to 34% reduction in AOM caused by H. influenzae. A result that has not been replicated in later studies for the 10 valent vaccine, which studied vaccine efficacy for carriage of nontypeable H. influenza rather than vaccine efficacy against AOM. This warrants further attention. A large NI11 influenza epidemic was established in Iceland in the fall and winter of 2009 as opposed to mild influenza outbreaks the other years; this could be viewed as a possible confounder. However, excluding visits contributed by influenza did not change the results.

The study shows a clear reduction in hospital visits because of AOM and pneumonia in the VEC. This significant and early effect described is encouraging.

REFERENCES

Large Outbreak of Botulism Associated With a Church Potluck Meal, Ohio, 2015


On April 21, 2015, the Fairfield Medical Center and Fairfield Department of Health contacted the Ohio Department of Health about a patient suspected of having botulism in Fairfield County, Ohio. Within 2 hours of health department notification, 4 more patients with similar clinical features arrived at Fairfield Medical Center’s emergency department. Later that afternoon, 1 patient died of respiratory failure shortly after arriving at the emergency department. All affected persons had eaten at the same widely advertised potluck meal at a church on April 19, 2015. Centers for Disease Control and Prevention Strategic National Stockpile sent 50 doses of botulinum antitoxin to Ohio.

Among 77 persons who consumed potluck food, 25 (33%) met the confirmed case definition, and 4 (5%) met the probable case definition. The median age of patients was 64 years (range: 9–87 years); 17 (59%) were female. Among 26 (90%) patients who reported onset dates, illness began a median of 2 days after the potluck (range: 1–6 days). Among 19 cases that were laboratory confirmed, serum and stool specimens were positive for botulinum neurotoxin type A or Clostridium botulinum type A.

Interviews were conducted with 75 of 77 persons who ate any of the 52 potluck foods. Consumption of any potato salad (homemade or commercial) yielded the highest association with probable or confirmed case status [risk ratio: 13.9; 95% confidence interval: 4.6–41.8], followed by homemade potato salad (risk ratio: 9.1; confidence interval: 3.9–21.2). Of 12 food specimens collected from the church dumpster, 6 were positive for botulinum neurotoxin type A; 5 contained potato salad. The attendee who prepared the potato salad with home-canned potatoes reported using a boiling water canner, which does not kill Clostridium botulinum spores, rather than a pressure canner, which does eliminate spores.

Comment: Botulism is a severe, potentially fatal neuroparalytic illness. A single case is a public health emergency, because it can signal an outbreak. This was the largest botulism outbreak in the United States in nearly 40 years. Early recognition of the outbreak by an astute clinician and a rapid, coordinated response likely reduced illness severity and facilitated early hospital discharge. Close adherence to established home-canning guidelines can prevent botulism and enable safe sharing of home-canned produce.