To fully elucidate the effect the conjugate vaccine may have on pneumococcal disease in children, and the incidence would be particularly reduced in those children aged 1 year. Additional benefits may be gained in adults through herd protection. Continued surveillance of IPD is required before, during, and after the introduction of PCV7.

**Streptococcus pneumoniae** (the pneumococcus) remains a major cause of otitis media, pneumonia, septicemia, and meningitis (18, 29). It causes substantial morbidity and mortality, especially in the young and old. The pneumococcus is classified into more than 90 pneumococcal serotypes in 46 serogroups (23). However, the majority of invasive and noninvasive diseases are associated with a much smaller number of serotypes. The surveillance of invasive pneumococcal disease (IPD) has improved substantially throughout the United Kingdom in recent years due to interest in the potential for new pneumococcal vaccines (10, 16, 24, 25, 30). There remains a considerable burden of IPD in the United Kingdom, particularly during the winter months, despite the availability of antibiotics and pneumococcal polysaccharide vaccines (PPVs) (16, 24). The recent implementation of PPV for the elderly and the potential introduction of pneumococcal conjugate vaccines (PCVs) for young children mean that there is now excellent pneumococcal serotype data available for IPD in the United Kingdom, as well as some molecular characterization data (24, 30). In England and Wales, the overall incidence of IPD is 8.6 per 100,000 population (16), with the highest burden among the very young and elderly, an excess of 30 per 100,000 (16, 32, 37). In Scotland, the overall incidence of IPD is 11 cases per 100,000 population, although the incidence rises to 51 cases per 100,000 in those aged 1 year and 45 cases per 100,000 in those aged over 65 years (24). The 10 most common pneumococcal serogroups associated with IPD in England and Wales are 14, 9, 6, 19, 23, 8, 1, 4, 18, and 7 (16), while the most common serotypes in Scotland are 14, 8, 9V, 1, 3, 22F, 23F, 6B, 18C, and 19F (30).

The prevention of IPD by immunization is an attractive proposition. PCVs have a good record of eradicating carriage as well as protecting against invasive disease (22, 26, 28). PCVs evoke a T-cell-dependent response and are efficacious in children less than 2 years of age. Importantly, the licensed PCV7 provides a moderate amount of protection against ear infections in children under 3 1/2 years of age (15) and significantly reduces the risk of pneumonia, particularly in those aged less than 1 year (6). PCV7 contains the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to a nontoxic variant of diphtheria toxin (CRM197). In 2000, PCV7 was licensed for use in infants and young children in the United States (1, 2, 34). It was licensed across Europe in 2001 for use in children under 2 years of age, and this license was recently extended to include infants and children up to 5 years of age (35, 36). Initial studies have been carried out to compare the molecular epidemiology of the pneumococcus in the United States prior to vaccine administration (17, 39) with that immediately following vaccine administration (7, 39). These studies reveal that the use of PCV7 has significantly reduced the burden of pneumococcal disease in young children (5, 6, 8, 39).

The implementation of PCV-7 in Scotland, or elsewhere, will likely have a dramatic effect on the population of pneumococci being carried and on that causing disease. To fully elucidate the effect the conjugate vaccine may have on pneumococcal disease, an understanding of the population at risk...
and the likely efficacy of the vaccine is required. This aim of this study was therefore to determine the potential impact of PCV7 on the incidence of IPD among children in Scotland.

MATERIALS AND METHODS

Incidence of invasive pneumococcal disease. The incidence of IPD in Scotland was determined using data from the enhanced pneumococcal surveillance program, which is a partnership between the Scottish Meningococcus and Pneumococcus Reference Laboratory (SMPRL) and Health Protection Scotland (previously the Scottish Centre for Infection and Environmental Health) (24). All cases of IPD from all National Health Service Board areas of Scotland between 2000 and 2004 were included in the study. The actual incidence of IPD in children less than 5 years of age was calculated from this data set using the date of birth compared to the date of disease onset or, if not available, the date the pneumococcal isolate was taken. Age breakdowns of <2 months, 2 to 5 months, 6 to 11 months, 1 year, and 2 to 4 years of age were also used, and the incidence of IPD in each was determined. Age-specific population rates (per 100,000) were calculated using the population for each age group gained from the General Register Office for Scotland for 30 June 2003 (http://www.gro-scotland.gov.uk).

Pneumococcal isolates. All pneumococci isolated from blood and cerebrospinal fluid in those children less than 5 years of age identified above were used. Pneumococci were isolated in Scottish diagnostic microbiology laboratories and sent to the SMPRL as part of the enhanced pneumococcal surveillance program in Scotland (24). They were then characterized at the SMPRL by serotyping, which was performed by coagglutination using reagents from the Statens Serum Institut, Denmark, as previously described (38).

Calculation of serotype coverage of PCV7. The proportion (percentage) of serotypes covered by PCV7 was calculated by analyzing the serotypes of those pneumococci in the isolate collection in relation to the serotypes contained in PCV7, namely, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Overall serotype coverage was calculated as well as that for each age group that was less than 5 years old, namely, children aged less than 2 months, those aged 2 to 5 months, those aged 6 to 11 months, those aged 1 year, and those aged 2 to 4 years. In addition, as PCV7 would be given to those aged over 2 months of age, if introduced into the childhood immunization schedule, data for children aged less than 2 months were removed from the data set, and the serotype coverage was recalculated for those aged between 2 months and 4 years. For completeness, due to the potential for vaccine-related serotypes to provide cross-protection, the proportion (percentage) of serogroups covered by PCV7 was calculated by analyzing the serotype data from above in relation to the vaccine-related serotypes for PCV7, namely, 6A, 9N, 18B, 18F, and 19A.

Estimate of vaccine efficacy and uptake. The efficacy of PCV7 was gained from published data (5, 31). Vaccine uptake was determined using available data from Scotland on the uptake of the Haemophilus influenzae type b conjugate vaccine and Neisseria meningitidis serogroup C conjugate vaccine (data available at http://www.isdscotland.org/Child_Immunisations).

Potential impact of PCV7 on IPD in children. The potential impact of PCV7 in children less than 5 years of age in Scotland was estimated for the 5-year period and also as an average per year over the 5-year period. The number of preventable cases was determined by multiplying the number of incident cases of IPD by the estimated vaccine efficacy and by the estimated vaccine uptake. To gain the average per year over the 5-year period, the figure was divided by 5. The assumption was made that vaccine efficacies were identical for all pneumococcal serotypes contained within PCV7 and for all age groups within the study. In addition, as PCV7 serotype coverage was calculated for those aged between 2 months and 4 years, the potential impact in this age group was also determined. The methods of calculation were identical apart from the fact that data for those aged less than 2 months were removed. The same assumptions regarding vaccine efficacy for each serotype and for each age group were made.

RESULTS

Pediatric invasive pneumococcal disease. There were a total of 238 pneumococci from cases of IPD in children less than 5 years of age in Scotland between January 2000 and August 2004. Serotyping of these pneumococcal isolates indicated that 21 were nontypeable. For the purposes of this study, these isolates were excluded from further analysis. A total of 217 pneumococci were therefore available for the study. One hundred ninety-five were isolated from blood, and 22 were from cerebrospinal fluid; although this is unlikely to be reflective of the relative incidence of septicemia and meningitis among the study population, no further analyses were performed in this respect.

It was not possible to gain population breakdowns for each age group by coagglutination using reagents from the Statens Serum Institut, Denmark, as previously described (38).

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It was not possible to gain population breakdowns for each age group by the National Health Service Board. However, the population for each age group was available from the General Register Office for Scotland, although the age splits did not exactly follow those in this study. For children aged less than 1 year, the incidence rate was 30.9 per 100,000; for those aged 1 year, it was 38.7 per 100,000; and for those aged 2 to 4 years, it was 4.7 per 100,000.

Pneumococcal serotypes. All 217 isolates were successfully serotyped into 22 different serogroups/types. In rank order, the 10 most common serotypes among all children aged less than 5 years were 14 (36.9%), 19F (10.1%), 6B (10.1%), 18C (6.0%), 23F (5.1%), 9V (4.6%), 4 (3.7%), 1 (3.7%), 19A (3.7%), and 6A (3.2%). These accounted for 189 (87.1%) of all isolates in this study.

The number of different serotypes in each age group varied. The greatest number, 16, was seen in those aged 6 to 11 months, indicating greater heterogeneity of pneumococci in this age group. Serotype 14 remained the most common serotype in all age groups, except in those aged less than 2 months (Table 1). In those aged between 2 and 4 years, there were 11 (28.9%); in those aged 1 year, there were 44 (44.4%); in those aged 6 to 11 months, there were 15 (34%); and in those aged 2 to 4 months, there were 10 (45.5%). Interestingly, there were no serotype 14 pneumococci in those aged less than 2 months, although the total number of pneumococci in this age group was only 15. Serotypes 6B, 14, 18C, 19F, and 23F were com-
Haemophilus influenzae likely 95%, based on previous experiences in Scotland with a booster at 12 to 15 months. The vaccine coverage is United States is 97.4%, based on a 2-, 4-, and 6-month schedule.

The reported efficacy of PCV7 from trials and actual use in the United Kingdom is of great interest and importance. Recent studies in the United Kingdom have characterized collections of pneumococci in an attempt to better understand their clonal distribution, population biology, and invasive disease potential. However, no recent study in the United Kingdom has yet looked in detail at the potential impact of PCV7 on the incidence of IPD in children less than 5 years of age using actual serotype data. By serotyping a large collection of pneumococci from IPD in children less than 5 years of age, an insight can be gained into the epidemiology of IPD. Furthermore, if this collection is representative of pneumococci currently circulating in a given population, then certain inferences can be made if the vaccine efficacy and vaccine uptake are known.

In the present study, of a collection of 217 pneumococci, the incidence rate of IPD among children less than 5 years of age was in agreement with that reported for England and Wales between 1996 and 1998 (32). The results of this study should therefore be generalizable to the whole of the United Kingdom. However, the incidence rate in those aged 1 year was lower than that previously reported in Scotland (24). The serotypes commonly associated with the pneumococci causing IPD were also similar to those seen in a previous study, although the rank order of these was different, probably due to the larger data set used (217 isolates compared to 51) (30). Regardless, serotype 14 was the most common in this study.

**TABLE 2. Potential impact of PCV7 on IPD in children more than 2 months but less than 5 years of age in Scotland (by serotype)**

<table>
<thead>
<tr>
<th>Pneumococcal serotype</th>
<th>No. of serotypes</th>
<th>% of IPD before vaccine</th>
<th>% of IPD after vaccine</th>
<th>No. of preventable cases</th>
<th>Avg no. of preventable cases per yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 158</td>
<td>72.8</td>
<td>5.4</td>
<td>146</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>2.8</td>
<td>0.2</td>
<td>6</td>
<td>1.1</td>
</tr>
<tr>
<td>6B</td>
<td>22</td>
<td>10.1</td>
<td>0.8</td>
<td>20</td>
<td>4.1</td>
</tr>
<tr>
<td>9V</td>
<td>9</td>
<td>4.1</td>
<td>0.3</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td>14</td>
<td>80</td>
<td>36.9</td>
<td>2.8</td>
<td>74</td>
<td>14.8</td>
</tr>
<tr>
<td>18C</td>
<td>11</td>
<td>5.1</td>
<td>0.4</td>
<td>10</td>
<td>2.0</td>
</tr>
<tr>
<td>19F</td>
<td>20</td>
<td>9.2</td>
<td>0.7</td>
<td>19</td>
<td>3.7</td>
</tr>
<tr>
<td>23F</td>
<td>10</td>
<td>4.6</td>
<td>0.3</td>
<td>9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**TABLE 3. Potential impact of PCV7 on IPD in children less than 5 years of age in Scotland (by age)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>IPD incidence (no. of pneumococci)</th>
<th>% Serotype coverage</th>
<th>% of IPD after vaccine</th>
<th>No. of preventable cases</th>
<th>Avg no. of preventable cases per yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 217</td>
<td>76.5</td>
<td>5.7</td>
<td>154</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>&lt;2 mo</td>
<td>14</td>
<td>57.1</td>
<td>4.3</td>
<td>7</td>
<td>1.5</td>
</tr>
<tr>
<td>2-5 mo</td>
<td>22</td>
<td>59.1</td>
<td>4.4</td>
<td>12</td>
<td>2.4</td>
</tr>
<tr>
<td>6–11 mo</td>
<td>44</td>
<td>68.2</td>
<td>5.1</td>
<td>28</td>
<td>5.6</td>
</tr>
<tr>
<td>1 yr</td>
<td>99</td>
<td>88.9</td>
<td>6.6</td>
<td>81</td>
<td>16.3</td>
</tr>
<tr>
<td>2–4 yr</td>
<td>38</td>
<td>71</td>
<td>5.4</td>
<td>25</td>
<td>5.0</td>
</tr>
</tbody>
</table>

DISCUSSION

The extent to which PCV7 will have an impact on IPD in the United Kingdom is of great interest and importance. Recent studies in the United Kingdom have characterized collections of pneumococci in an attempt to better understand their clonal distribution, population biology, and invasive disease potential. However, no recent study in the United Kingdom has yet looked in detail at the potential impact of PCV7 on the incidence of IPD in children less than 5 years of age using actual serotype data. By serotyping a large collection of pneumococci from IPD in children less than 5 years of age, an insight can be gained into the epidemiology of IPD. Furthermore, if this collection is representative of pneumococci currently circulating in a given population, then certain inferences can be made if the vaccine efficacy and vaccine uptake are known.

In the present study, of a collection of 217 pneumococci, the incidence rate of IPD among children less than 5 years of age was in agreement with that reported for England and Wales between 1996 and 1998 (32). The results of this study should therefore be generalizable to the whole of the United Kingdom. However, the incidence rate in those aged 1 year was lower than that previously reported in Scotland (24). The serotypes commonly associated with the pneumococci causing IPD were also similar to those seen in a previous study, although the rank order of these was different, probably due to the larger data set used (217 isolates compared to 51) (30). Regardless, serotype 14 was the most common in this study.
Importantly, the seven most common serotypes found in this study are included in PCV7.

Serotype coverage of PCV7 for those aged under 5 years was found to be higher than that previously reported in the United Kingdom (11, 30, 32). It is likely that children less than 6 months of age will not be fully protected by PCVs (4), and hence, the low serotype coverage of 57.1% in this age group is of less concern. However, if those aged more than 2 months but less than 5 years, the ages at which PCV7 immunization is likely, are included in serotype analysis, the serotype coverage is 72.8%. If the efficacy of PCV7 is mirrored in the United Kingdom and the success in vaccine uptake from the implementation of previous conjugate vaccines is achieved, then the joint vaccine efficacy and uptake will be high. This study estimates an overall reduction of 70.8% of all IPD cases, with at least 31 preventable cases of IPD each year in Scotland alone.

Around 11% of all pneumococci are resistant to macrolides in Scotland (12, 14), while 60% of serotype 14 pneumococci are macrolide resistant (13). If PCV7 were routinely introduced in the United Kingdom, it is likely that the incidence of antibiotic resistance among pneumococci would fall, simply because the majority of resistant pneumococci are covered by PCV7. Such a drop in antibiotic resistance has been seen in the United States (39).

As PCV7 includes serotypes 6B, 9V, 19F, 18C, and 23F, it is possible that cross-protection may be afforded to vaccine-related serotypes; it is thought that while this is variable, it may be substantial (27, 33). The vaccine-related serotypes for PCV7 are 6A, 9N, 18B, 18F, and 19A (19, 20), although only 6A, 9N, and 19A were found in this study. If so, the serotype coverage of PCV7 would increase proportionately, as found in this study, depending on the efficacy of cross-protection for each related serotype. In two independent studies in the United Kingdom (16, 24), it was reported that serogroup coverage for PCV7 was around 86% in children less than 5 years of age. In the present study, a serogroup coverage of 85.2% for PCV7 was consistent with that of previous studies. However, this and previous studies make the assumption that all serotypes within the serogroups in PCV7 possess complete and equal immune cross-protection. It is likely, in reality, that cross-protection is less than 100% for each vaccine-related serotype and that it also varies depending on the serotype. It is clear, however, that a better understanding of cross-protection from vaccine-related serotypes is needed. New PCVs are also undergoing development, including 10- and 13-valent options, which may improve the cross-protection effects. In addition, data are required on the incidence of noninvasive pneumococcal disease in children so that the burden of otitis media and pneumonia can be determined prior to and after the introduction of PCV7 in the United Kingdom. Nevertheless, this study provides a detailed insight into the incidence and serotypes of pneumococci causing IPD in children less than 5 years of age in Scotland. It provides the baseline for continued surveillance after the introduction of PCV7 so that the incidence of IPD and the potential for serotype replacement can be monitored. It also indicates the potential for the partial control of IPD.

ACKNOWLEDGMENTS

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