Invasive Pneumococcal Disease Among Immunocompromised Persons: Implications for Vaccination Programs

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(See the Editorial Commentary by Luján and Gallego on pages 148–9.)

Background. In 2012/2013, a single dose of 13-valent pneumococcal conjugate vaccine (PCV13) was recommended for immunocompromised adults in the United States and Canada. To assess the potential benefits of this recommendation, we assessed the serotype-specific burden of invasive pneumococcal disease (IPD) among immunocompromised individuals.

Methods. From 1995 to 2012, population-based surveillance for IPD was conducted in Metropolitan Toronto and Peel Region, Canada. Disease incidence and case fatality were measured in immunocompromised populations over time, and the contribution of different serotypes determined.

Results. Overall, 2115/7604 (28%) episodes of IPD occurred in immunocompromised persons. IPD incidence was 12-fold higher (95% confidence interval [CI], 8.7–15) in immunocompromised compared to immunocompetent persons; the case fatality rate was elevated in both younger (odds ratio [OR] 1.8) and older (OR 1.3) adults. Use of immunsuppressive medications was associated with a 2.1–2.7 fold increase in the risk of IPD. Five years after PPV23 program implementation, IPD incidence had declined significantly in immunocompromised adults (IRR 0.57, 95% CI, .40–.82). Ten years after pediatric PCV7 authorization, IPD due to PCV7 serotypes had decreased by 90% (95% CI, 77%–96%) in immunocompromised persons of all ages. In 2011/2012, 37% of isolates causing IPD in immunocompromised persons were PCV13 serotypes and 27% were PPV23/not PCV13 serotypes.

Conclusions. Immunocompromised individuals comprised 28% of IPD. Both PPV23 and herd immunity from pediatric PCV7 were associated with reductions in IPD in immunocompromised populations. PCV13 vaccination of immunocompromised adults may substantially reduce the residual burden until herd immunity from pediatric PCV13 is fully established.

Keywords. IPD; immunocompromised; pneumococcal vaccine.

Streptococcus pneumoniae remains an important global cause of serious illness, and both pneumococcal infection incidence and mortality are significantly higher in immunocompromised persons compared to other individuals [1–8]. The 23-valent polysaccharide pneumococcal vaccine (PPV23) has been recommended for immunocompromised older children and adults in Canada since 1983 [9, 10]. In 2012 and 2013, respectively, the United States Advisory Committee on Immunization Practices [3], and the Canadian National Advisory Committee on Immunization [11] recommended that individuals with immunocompromising conditions also receive a dose of the 13-valent conjugate vaccine (PCV13).

Decisions to fund and implement vaccination recommendations require understanding the magnitude of pneumococcal disease burden and the sero-epidemiology of invasive disease among targeted populations [3]. In order to assess the potential benefit of the new vaccination recommendations for immunocompromised persons in our population, we used population-based surveillance for invasive pneumococcal disease (IPD) in Ontario to assess recent changes in the serotype-specific burden of IPD.

MATERIALS AND METHODS

Pneumococcal Immunization Programs

In Ontario, PPV23 was authorized for use in 1978 and has been recommended for adults over 65 years of age and persons aged 2–64 years with underlying illness predisposing to IPD [9]. A publicly funded PPV23 program for recommended recipients was implemented in October 1995. The 7-valent conjugate vaccine (PCV7) was authorized for use in children in Canada in June 2001, and a publicly funded routine infant vaccination
program was introduced in Ontario in January 2005. The 10-valent conjugate vaccine (PCV10) replaced PCV7 in this program in November 2009, and the 13-valent conjugate vaccine (PCV13) replaced PCV10 in November 2010.

**Population-based Surveillance**

Since 1 January 1995, the Toronto Invasive Bacterial Diseases Network (TIBDN) has performed active, population-based surveillance for IPD in metropolitan Toronto and the regional municipality of Peel (population in 2011, 4.1 million) [12, 13]. Residence in the population area is defined by postal code; homeless persons who visit hospitals within the population area are also considered residents. The laboratory-based surveillance involves all hospitals (N = 28) providing care to, and all laboratories (N = 25) processing sterile site cultures from, residents of the population area.

Laboratory personnel telephone the study office whenever *S. pneumoniae* is isolated from a normally sterile site [13]. After obtaining patient consent, study personnel collect detailed information by chart review and patient and physician interview. Standardized questionnaires are used to collect demographic and medical information. Laboratories are audited annually to ensure completeness of reporting. The study is approved by the research ethics boards of all participating institutions.

**Laboratory Procedures**

Participating laboratories submit isolates to the TIBDN laboratory at Mount Sinai Hospital in Toronto, where they are confirmed as *S. pneumoniae* using standard methodology [14]. Isolates are serotyped at the TIBDN laboratory, the Canadian National Centre for Streptococcus, Alberta Provincial Public Health Laboratory, Edmonton, Alberta, or the National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, by latex agglutination using commercial antisera (Statens Serum Institut, Denmark) and Quellung reaction as appropriate [15, 16].

**Definitions**

IPD is defined as an illness occurring in association with the isolation of *S. pneumoniae* from a normally sterile body fluid. Clinical diagnosis is based on documentation from attending physicians. Death attributable to IPD is defined as that occurring during the hospitalization in which disease was diagnosed and within 30 days of the positive culture.

Underlying chronic medical conditions predisposing to pneumococcal disease [10] are identified from patients’ medical records or interview. For this analysis, immunocompromising conditions were defined as: human immunodeficiency virus (HIV) infection, previous solid organ or bone marrow/stem cell transplantation, asplenia, sickle cell disease or other hematologic disorders, systemic lupus erythematosus, hematologic malignancy, hepatic cirrhosis, chronic renal failure (creatinine >200 mg/dL or requiring chronic renal dialysis), primary immunodeficiency, or chronic receipt of immunosuppressive therapy. Immunosuppressive therapy was defined as chronic daily receipt of oral corticosteroids, current chemotherapy for cancer treatment, or other immunosuppressive medications used for chronic management of inflammatory/rheumatologic conditions (eg, methotrexate, azathioprine, recombinant human immune mediators) prior to the episode of IPD. Pneumococcal vaccination history was recorded based on immunization records provided by patients and/or physicians.

**Population Prevalence of Immunocompromising Conditions**

Age-specific population estimates were obtained from Statistics Canada [12]. We obtained population prevalence estimates for the years 1995–2011 for cancer from Cancer Care Ontario; for HIV infection from the Ontario HIV Epidemiologic Monitoring Unit at the University of Toronto; for solid organ and stem cell transplantation from the Institute for Clinical Evaluative Sciences; for sickle cell disease from the Global Sickle Cell Disease Network and The Hospital for Sick Children, Toronto; for chronic renal failure requiring dialysis from a 2011 annual report on the treatment of end-stage organ failure in Canada [17], and for systemic autoimmune diseases from Broten et al [18].

We obtained data on the prevalence of asthma from the Ontario Asthma Surveillance Information System; and data on the prevalence of rheumatoid arthritis and chronic obstructive pulmonary disease from the Institute for Clinical Evaluative Sciences. Estimates of the prevalence of chronic oral corticosteroid use among persons with these conditions were obtained from North American patient cohorts [18–22, unpublished information, Dr Claire Bombardier].

**Data Management/Statistical Analysis**

Data were entered in duplicate and cleaned using SAS version 9.3 (SAS Institute, Cary, North Carolina), which was also used for all analyses. The annual incidence of IPD among different populations was calculated by dividing the annual number of cases of IPD with the condition of interest by the annual population prevalence estimates for the condition. The incidence in the immunocompetent population was calculated by including immunocompetent cases in the numerator and removing the estimated immunocompromised population number from the population denominator. Serotype-specific incidence was calculated assuming that the distribution of serotypes for cases with available and missing serotype data were the same. Disease incidence in different population subgroups was compared using Poisson regression to calculate incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Confidence limits for differences in IRRs were estimated using the method of Zhou and Donner [23].

We defined 3 time periods: pre-PPV23 (1995 and 1996, prior to the introduction of the publicly funded PPV23 program), post-PPV23/pre-PCV7 (1997 to 2001, after PPV23 implementation but before authorization of PCV7), and post-PCV7 (2002 and later). To assess the impact of PPV23, we compared the incidence in population subgroups in the 2 years before the program was...
introduced (1995/1996) to that in the year before and year of PCV7 authorization (2000/2001); to assess PCV7 impact, we compared the incidence in 2000 and 2001 to that in 2010 and 2011, the years for which most recent data were available for population prevalence estimates. Changes in incidence were reported as percentage changes ([IRR-1] × 100%) with 95% CIs.

Logistic regression adjusted for age, presence of comorbidity, gender, and year of study was used to compare case fatality rates in immunocompromised and immunocompetent patients. Proportions were compared using χ² or Fisher exact tests. In all statistical tests, P-values <.05 were considered significant.

RESULTS

Characteristics of the Study Cohort

Of 7902 episodes of IPD identified between 1995 and 2012, clinical information was available for 7604 (96.2%), and 6981 (91.8%) isolates were available for serotyping. Overall, 2115 of 7604 (27.8%) episodes occurred in patients immunocompromised by underlying disease or medical treatment (Table 1); 2815 (37.0%) had at least one underlying comorbidity but were not immunocompromised; and 2674 (35.2%) had no underlying conditions. The proportion of immunocompromised patients was 9.3% (137/1469) among children, 34.5% (1080/3128) among younger adults (aged 15–64 years), and 29.9% (898/3007) among older adults (≥65 years).

The distribution of immunocompromising conditions differed between children and adults (Table 1). The most frequent conditions among children (n = 137) were acute leukemia (n = 56, 40.9%), sickle cell disease (n = 24, 17.5%), and organ/bone marrow transplant (n = 19, 13.9%). Among younger adults (n = 1080), the most common conditions included HIV...
infection (n = 274, 25.4%), hepatic cirrhosis (n = 206, 19.1%), and organ/bone marrow transplantation (n = 106, 9.8%). The most common conditions among older adults (n = 898) were chronic renal failure (n = 216, 24.1%), multiple myeloma (n = 128, 14.3%), leukemia (n = 96, 10.7%), and lymphoma (n = 93, 10.4%). Overall, 452 of 2115 (21.4%) immunocompromised patients were immunocompromised due to therapy rather than due to underlying disease.

Vaccination status for PPV23 was available for 1521 of 1978 (77%) immunocompromised adults. Of these, 35.0% (n = 532) had received at least one dose of PPV23 from 2 weeks to 27 years prior to their disease episode, including 28.5% (234/821) of younger and 47.0% (329/700) of older adults.

Overall Disease Incidence in Immunocompromised Populations
During the 5-year post-PPV23/pre-PCV7 period, the incidence of IPD did not change among children irrespective of immunocompromise (Figure 1A and 1C) but declined significantly among both immunocompetent (IRR 0.70; 95% CI, .57–.84) (Figure 1B) and immunocompromised adults (IRR 0.54; 95% CI, .39–.74) (Figure 1D).

During the 10 years after PCV7 authorization, the incidence of IPD decreased from 14.1 to 4.9 per 100 000 (IRR 0.35; 95% CI, .23–.52) among immunocompetent children (Figure 1A), whereas the rate in immunocompromised children did not change significantly (112 and 199 per 100 000, respectively; IRR 1.78; 95% CI, .53–5.98) (Figure 1C). Disease incidence decreased in both immunocompetent (IRR 0.75; 95% CI, .61–.93) and immunocompromised adult populations (IRR 0.57; 95% CI, .40–.82) (Figure 1B and 1D).

The incidence of IPD was significantly higher in immunocompromised compared to immunocompetent persons, with an IRR of 15.7 (95% CI, 12.5–19.7) in 1995/1996, 11.3 (95% CI, 8.7–14.7) in 2000/2001, and 11.5 (95% CI, 8.7–15.3) in 2010/2011 (Table 2). There was no significant change in the IRR for immunocompromised compared to immunocompetent children over time. In HIV-infected adults, the IRR declined significantly from 29.7 (95% CI, 19.3–45.5) in 1995/1996, to 26.0 (95% CI, 16.0–42.2) in 2000/2001 and to 11.1 (95% CI, 5.8–21.0) in 2010/2011. In other immunocompromised adults, the IRR declined from 16.5 (95% CI, 12.6–21.6) in 1995/6 to 12.5 (95% CI, 9.1–17.3) in 2000/2001 and 11.2 (95% CI, 8.0–15.6) in 2010/2011.

The highest disease incidence was observed among individuals with multiple myeloma (IRR 176; Table 2). The incidence of IPD among patients with other hematological malignancies and solid organ/bone marrow transplantation was about 50-fold higher, and that among individuals with systemic autoimmune conditions was 3–4-fold higher, than in the general population. The estimated IRR in persons chronically

![Figure 1. Annual incidence of invasive pneumococcal disease (IPD) among children and adults by presence of immunocompromise and by vaccine-covered serotype groups, Toronto Invasive Bacterial Diseases Network, 1996/1997–2010/2011. A, Immunocompetent children (<15 years); B, Immunocompetent adults; C, Immunocompromised children; D, Immunocompromised adults. The solid line = the overall IPD incidence; the grey shaded area, pneumococcal conjugate vaccine (PCV7) = disease incidence due to serotypes included in the 7-valent pneumococcal vaccine (serotypes 4,6B,9V,14,18C,19F,23F); hatched bars, PCV13 not PCV7 = disease incidence due to serotypes included in the 13-valent but not the 7-valent conjugate vaccine (serotypes 1,3,5,6A,7F,19A); open bars, polysaccharide pneumococcal vaccine (PPV23) not PCV7 = disease incidence due to serotypes included in the 23-valent polysaccharide vaccine but not conjugate vaccines (2,8,9N,10A,11A,12F,15B,17F,20,22F,33F); black bars, NVT (nonvaccine type) = disease incidence due to serotypes not included in any vaccine.]
receiving immunosuppressive medication compared to those not receiving such medication was 2.1 (95% CI, 1.1–4.0) for persons with rheumatoid arthritis, 2.0 (95% CI, 1.5–2.6) for persons with chronic obstructive pulmonary disease, and 2.7 (95% CI, 1.6–4.4) for persons with asthma.

Changes in Disease Incidence by Vaccine-covered Serotype Groups

The introduction of routine infant PCV7 programs resulted in dramatic decreases in disease due to PCV7 serotypes in all population subgroups (Figure 1A–D). Concurrently, disease incidence due to non-PCV7 serotypes increased significantly among immunocompetent children (IRR 2.46; 95% CI, 1.27–4.73) and adults (IRR 1.78; 95% CI, 1.34–2.37) but did not change among immunocompromised adults (IRR 1.31; 95% CI, 0.81–2.12). Although disease incidence due to non-PCV7 serotypes among immunocompromised children appeared to increase (IRR 6.64), the increase was not statistically significant (95% CI, 0.82–53.92).

Changes in disease incidence due to non-PCV7 serotypes were similar among immunocompromised and immunocompetent populations, with the possible exception of increased incidence due to serotypes included in PCV13 but not PCV7 in immunocompetent (IRR 2.33; 95% CI, 1.58–3.43) but not immunocompromised (IRR 0.93; 95% CI, 0.43–2.00) persons. The incidence of disease due to serotypes included in PPV23 but not conjugate vaccines did not change significantly in any age or risk groups. That due to serotypes not included in any vaccine increased among both immunocompetent (IRR 2.26; 95% CI, 1.27–4.03) and immunocompromised (IRR 2.37; 95% CI, 1.02–5.54) populations.

Serotype Distribution

From 1996 to 2005, there were no differences in the distribution of serotypes in immunocompromised and immunocompetent individuals (data not shown). By 2011/2012, nonvaccine serotypes had become significantly more common among the immunocompromised (36.0% vs 22.8% in immunocompetent, \( P = .0003 \)), whereas serotypes included in PCV13 were less common (37.0% vs 54.5%, \( P < .0001 \)) (Figure 2). In the most recent 2 years of surveillance (2011 and 2012), the 6 most common serotypes were 19A, 22F, 7F, 23A, 6C, and 3, comprising 50% of isolates from immunocompromised persons and 62% of isolates from immunocompetent persons.

Case Fatality

Among immunocompromised individuals, the case fatality was 1.5% (2/137) among children, 16.2% (175/1080) in younger adults, and 29.5% (265/898) in older adults (Table 3). Case fatality rates in immunocompromised children were not higher than in immunocompetent children (OR 0.8; 95% CI, 0.2–3.8). Among adults, case fatality rates among the immunocompromised were higher than among the immunocompetent in both younger (OR 1.8; 95% CI, 1.4–2.3) and older (OR 1.3; 95% CI, 1.1–1.6) adults.
DISCUSSION

In 18 years of surveillance, the percentage of IPD occurring in immunocompromised individuals remained stable at just under 30%, somewhat higher than the 17% identified in Finland [7], but lower than the 36% and 37% reported from Spain and the United Kingdom, respectively [8, 24]; differences that arise in part because of different definitions of immunocompromise. The difficulty in defining immunocompromise simply and consistently and the large number of underlying immunosuppressive conditions that contribute to the burden of IPD makes the effective delivery of public health pneumococcal vaccination programs to immunosuppressed populations particularly challenging.

Although the incidence of disease in immunocompromised individuals remains more than 10-fold higher than that in immunocompetent individuals, the relative risk of disease in immunocompromised adults decreased over the study period. This decrease may in part be due to the introduction of PPV23 programs. It is also likely due to more effective management of some conditions. The greatest decrease in relative risk of disease over time was seen in those with HIV infection, where combination antiretroviral therapy is effective in immune reconstitution for many patients [25, 26]. However, natural changes in the epidemiology of pneumococcal disease [13, 27] or improved diagnosis of immunocompromising conditions resulting in the identification of less severely compromised cases may also have played a role.

Rates of disease due to conjugate vaccine serotypes decreased at about the same rate in immunocompetent and immunocompromised children and adults, and parallel increases in nonvaccine
type strains occurred across all subpopulations. Herd immunity appears to protect immunocompromised persons as well as those who are immunocompetent. If herd immunity against the 6 additional serotypes included in PCV13 is as effective as that against the serotypes included in PCV7, disease due to these serotypes can be expected to decrease rapidly in all subpopulations over the next 5 years. There is already evidence that this is occurring [28–30]. Despite these anticipated benefits, rates of IPD in excess of 20–30 per 100 000 per year will persist in many immunocompromised populations.

Similar to other studies, we found the highest rates of invasive disease occurred among persons with hematological malignancy, particularly multiple myeloma and acute leukemia [4,7,31]. Our available population data allowed us to estimate disease incidence in systemic autoimmune disease, validating risks estimated from studies of administrative databases [32,33], and to estimate the increased risk of IPD associated with receipt of immunosuppressive therapy for patients with asthma, chronic obstructive lung disease, and rheumatoid arthritis. Our estimate of the risk associated with receipt of immunosuppressive medication is similar to estimates from studies of different design in patients with rheumatoid arthritis [34].

Our finding that serotypes not included in any pneumococcal vaccine were more common in isolates from immunocompromised IPD cases as compared to immunocompetent cases is similar to results from Lujan et al, although there are substantial differences between serotype distributions in the 2 studies, and we were unable to confirm the associations they identified between specific serotypes and individual underlying conditions [24]. These findings highlight the importance of monitoring the serotype distribution of disease among immunocompromised populations. Serotypes differ in their ability to colonize and cause invasive disease [24,34–38], and some less virulent serotypes that rarely cause invasive disease in the general population may consistently cause invasive disease among persons with serious underlying comorbidities [24,38,39].

Our analysis suggests that both PCV13 and PPV23 are of benefit for immunocompromised adults. The CAPITA trial did not identify an effect of the PCV13 on pneumococcal pneumonia in immunocompromised adults [40]. However, the study was underpowered for this secondary endpoint. Many studies suggest that PPV23 can prevent invasive disease and reduce severity of illness in populations with underlying disease including immunocompromise [3,7,13,41–43], and both US and Canadian expert bodies consider the evidence sufficient to recommend both PCV13 and PPV23 for immunocompromised persons [3,11]. Systematic and individual efforts to improve pneumococcal vaccine usage in immunosuppressed populations are clearly warranted, as is ongoing evaluation of their impact.

In Ontario, immunization coverage data for PPV23 in children with underlying medication conditions is not available. The fact that more than one-third of episodes of IPD in immunosuppressed children were due to PPV23, non-PCV13 serotypes, and the suggestion in our data that disease due to these serotypes

Table 3. Case Fatality Ratio and Adjusted Odds Ratio for Death Among Patients With Invasive Pneumococcal Disease and Underlying Immunocompromising Conditions Compared to Immunocompetent Persons, Toronto Invasive Bacterial Diseases Network, 1995–2012

<table>
<thead>
<tr>
<th>Age Group</th>
<th>15–64 y</th>
<th>≥65 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFR (95% CI)</td>
<td>OR (95% CI)*</td>
</tr>
<tr>
<td>Immunocompetent</td>
<td>8.9% (7.7%–10.2%)</td>
<td>Ref</td>
</tr>
<tr>
<td>Immunocompromised (all)</td>
<td>16.3% (14.1%–18.5%)</td>
<td>1.8 (1.4–2.3)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>16.7% (8.4%–24.9%)</td>
<td>1.5 (1.2–1.8)</td>
</tr>
<tr>
<td>HIV infected</td>
<td>9.2% (5.7%–12.6%)</td>
<td>1.2 (1.7–1.8)</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>29.6% (23.4%–35.9%)</td>
<td>2.8 (1.9–4.1)</td>
</tr>
<tr>
<td>Hematological malignancy</td>
<td>11.8% (7.5%–16.1%)</td>
<td>1.6 (1.0–2.6)</td>
</tr>
<tr>
<td>Solid organ/bone marrow transplant</td>
<td>10.4% (6.5%–16.2%)</td>
<td>0.9 (1.4–1.7)</td>
</tr>
<tr>
<td>Asplenia</td>
<td>20.0% (11.0%–29.1%)</td>
<td>2.4 (1.3–4.6)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>0</td>
<td>21.4% (0.0%–42.9%)</td>
</tr>
<tr>
<td>Other*</td>
<td>8.0% (5.5%–15.5%)</td>
<td>1.1 (1.4–3.3)</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid organ cancer*</td>
<td>38.5% (28.5%–48.5%)</td>
<td>1.8 (1.0–3.2)</td>
</tr>
<tr>
<td>Other*</td>
<td>9.3% (3.2%–15.4%)</td>
<td>1.2 (1.0–2.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CFR, case fatality ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; Ref, reference.

* OR, adjusted odds ratio; adjusted for age (in years), presence of concurrent nonimmunocompromising chronic conditions predisposing to invasive pneumococcal disease (10), the year of study and gender.

† Other includes sickle cell disease, other hematologic disorders or primary immunodeficiency.

‡ Cases on immunosuppressive therapy for treatment of solid cancer.

§ Other on immunosuppressive therapy includes cases receiving immunosuppressive therapy for condition that are not themselves immunosuppressive, including COPD, asthma, inflammatory and/or rheumatologic conditions.
may be increasing, emphasizes the need to reassess the use and effectiveness of PPV23 in immunosuppressed children over 2 years of age [44].

Our study has limitations. It describes disease in one geographic area. Our definition of chronic underlying conditions is based primarily on chart review, and we relied on a variety of different data sources to estimate the population prevalence of immunocompromising conditions. Although all our sources are validated, they use different methods of data collection, and their definitions of underlying illness may not match that described by chart review. We could not obtain prevalence data for several important medical conditions (eg, hepatic cirrhosis, asplenia) or for potential occupational risks (eg, welding) [45] and were thus unable to estimate incidence for populations with these conditions. We could not obtain population prevalence estimates for persons with combinations of underlying conditions, so we are unable to assess the increased risk for persons with multiple comorbidities [46].

In summary, our findings document the evidence for ongoing substantial incidence of IPD and elevated case fatality among immunocompromised populations, despite the benefits of pneumococcal vaccines. They highlight the importance and complexity of vaccination programs for immunosuppressed persons, the need for continued surveillance to assess their impact, and the need for continued development of pneumococcal vaccines.

Notes

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APPENDIX

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