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MAJOR ARTICLE

Indirect Effects of Pneumococcal Childhood Vaccination in Individuals Treated With Immunosuppressive Drugs in Ambulatory Care: A Case-Cohort Study

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Background. The extent to which iatrogenically-immunosuppressed individuals benefit from indirect effects of childhood vaccination with pneumococcal conjugate vaccines (PCVs) is unknown. We determined how the sequential introduction of PCV7 (2006) and PCV13 (2011) in the Norwegian childhood vaccination program has affected the epidemiology of invasive pneumococcal disease (IPD) in individuals treated with immunosuppressants in ambulatory care.

Methods. We conducted a case-cohort study comprising 7926 IPD cases reported to the Norwegian Surveillance System for Communicable Diseases in 2005–2014 and 249 998 individuals randomly selected from the National Registry in 2012. We defined immunosuppressive treatment groups based on dispensed prescriptions retrieved from the Norwegian Prescription Database. Incidences and age-adjusted relative risks (RR) were estimated.

Results. IPD incidences decreased in all groups. The PCV13 incidence decreased by 5–12% across groups. The non-PCV13 incidence increased by 4–10%, mostly in individuals on chemotherapy (overlapping 95% confidence intervals). In the PCV13 era, the RR for IPD was highest (significant) and the percentage of cases caused by the polysaccharide vaccine PPV23 serotypes lowest (numerical) in individuals on chemotherapy (RR = 20.4, PPV23 = 52%), followed by individuals on corticosteroids (RR = 6.2, PPV23 = 64%), other immunosuppressants (RR = 5.6, PPV23 = 68%), and no immunosuppressants (RR = 1 [reference], PPV23 = 74%).

Conclusions. IPD incidences declined after PCV introduction in both immunocompetent and iatrogenically-immunosuppressed individuals, underscoring the benefit of childhood vaccination for the entire population. Still, individuals treated with immunosuppressants in ambulatory care are at increased risk of IPD caused by a more diverse group of serotypes.

Keywords. pneumococcal infections; pneumococcal vaccines; immunosuppressed host; case-cohort study; immunosuppressants.

Following the introduction of pneumococcal conjugate vaccines (PCVs) in childhood vaccination programs, the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes decreased substantially in all age groups [1]. The decrease was caused by indirect vaccine effects through shifts in circulating serotypes, and was followed by an increase in the incidence of disease caused by non-vaccine serotypes, termed serotype replacement [2]. The capacity to cause invasive disease differs between serotypes [3, 4], and several serotypes causing replacement disease have lower invasive capacities than those included in PCVs. In Norway, indirect effects were observed after introducing the 7-valent PCV (PCV7) in 2006 and after the switch to the 13-valent vaccine (PCV13) in 2011 [5]. Serotype replacement caused an increase in non–vaccine type IPD but, on a population level, the overall IPD incidence declined markedly.

Iatrogenic immunosuppression increases the risk of serious infections like IPD [6–9], due to factors such as underlying medical conditions, the use of different medications, and the dosages and durations of treatment. Individuals treated with immunosuppressive drugs may, therefore, be at a higher risk of IPD caused by serotypes with a low invasive capacity than healthy individuals, including serotypes that are not included in the currently-used PCV13 and the 23-valent pneumococcal polysaccharide vaccine (PPV23) [8]. Knowledge of the epidemiology of IPD in different immunosuppressive treatment groups is limited. Furthermore, it is unknown how the indirect effects of PCV childhood vaccination have influenced the incidence and serotype distribution in this iatrogenically-immunosuppressed group. An increased percentage of immunosuppressed individuals among IPD cases after PCV7 introduction has been reported [10, 11], but the results are contradictory [12].

In order to guide vaccine policy, it is essential to gain knowledge about the serotype-specific IPD epidemiology in individuals treated with immunosuppressive drugs. The aim of this

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study was to investigate the effects of the sequential introduction of PCV7 and PCV13 in children on the epidemiology of IPD in individuals treated with immunosuppressive drugs in ambulatory care.

MATERIAL AND METHODS

Study Design, Study Population, and Data Sources

We performed a case-cohort study, including all IPD cases reported to the Norwegian Surveillance System for Communicable Diseases in 2005–2014 as cases. The cohort comprised 250 000 individuals randomly selected from the National Registry. To be eligible for inclusion in the cohort, individuals had to be registered as a Norwegian inhabitant on 31 December 2012. To increase the precision of estimates for younger and older age groups, we oversampled these age groups compared to the 45–64 year age group.

For both cases and the cohort, we retrieved information about dispensed prescriptions from the Norwegian Prescription Database (NorPD [13]) for the years 2004–2014. NorPD contains information about all dispensed prescriptions from pharmacies for patients in ambulatory care. Drugs dispensed in hospitals and nursing homes are not recorded in the register. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [14]. The data were linked using the personal identification number, and were de-identified by an external partner before the researchers were given access to the data.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Norwegian Data Protection Authority, the Regional Committee for Medical Research Ethics, South Eastern Norway, and the owners of the registers (the Norwegian Tax Administration and Norwegian Institute of Public Health).

Definition Of Immunosuppressive Treatment Groups

To define immunosuppressive treatment groups, we used prescriptions dispensed up to 1 year before the index month. The index month was defined as the month and year of the IPD laboratory diagnosis for the cases and as December 2012 for the cohort. We categorized the use of immunosuppressive drugs into 3 immunosuppressive treatment groups: chemotherapy (ATC code L01), long-term systemic corticosteroids (ATC codes H02A and H02B), and other immunosuppressants (ATC code L04A). The immunosuppressive treatment groups were not mutually exclusive. Individuals with no dispensed immunosuppressants in the year before the index month were defined as the no-immunosuppressants group. We defined long-term use of systemic corticosteroids as having been prescribed, on average, more than 1.5 defined daily doses for more than 1 month in the year before the index month and having at least 1 dispensed prescription of a corticosteroid during the 6 months prior to the index month.

Serotype Categorization

In Norway, it is obligatory to notify the Norwegian Surveillance System for Communicable Diseases of all individuals diagnosed with IPD (ie, isolation of *Streptococcus pneumoniae* from a normally sterile site). Furthermore, all IPD isolates are sent to the reference laboratory for serotyping by the Quellung reaction. We categorized the isolates by serotype into vaccine-types: PCV7, PCV13 but not PCV7 (PCV13-7), PCV13, PPV23 and non-vaccine-type (NVT) serotypes; see the legend of Figure 1 for the serotypes.

There were 6 isolates in the serogroups 7, 11, 18, and 22 that had not been factor-typed. As ≥98% of isolates within these serogroups had the same serotype, we imputed that serotype for these 6 isolates. To calculate the number of cases per vaccine-type and the vaccine-type–specific incidence rates and relative risks (RR), we imputed missing data by assuming a similar distribution by vaccine-type for cases with or without serotype information.

Data Analysis

We calculated the annual incidence rate using the number of cases per treatment group per year, divided by the estimated number of Norwegian inhabitants per treatment group per year. We estimated the denominator by multiplying the following 3 components:

1. The proportion of individuals in the cohort treated with the different immunosuppressive drugs in 2012. The proportion was determined using a weighted analysis with population size (N)/sample size (n) as weighting factor per age group, thereby correcting for the sample distribution.
2. The yearly change in the number of users with dispensed prescriptions for immunosuppressive drugs/1000 inhabitants, registered in NorPD for the years 2005–2011, 2013, and 2014 compared to 2012 [15] (Supplementary Figure 1).
3. The number of Norwegian inhabitants on 1 January of the corresponding year.

As a relative measure of the indirect effects of vaccination, we used the average annual change in incidence rates from the time of vaccine introduction onwards (ie, the average gradient in the incidence rate over time plot; incidence rate ratios; IRRs). As PCV7 was introduced in 2006, we included the years 2006–2014 for all IPD independent of serotype, PCV7-type IPD, or non-PCV13-type IPD. As PCV13 was introduced in 2011, we included the years 2011–2014 for PCV13-7–type IPD. The IRRs and 95% confidence intervals (CIs) were determined by Poisson regression. Because of the known increased risk for IPD at older compared to younger ages and because PPV23 is recommended in Norway to those aged 65 years and older, we checked for potential effect modifications by age by including the interaction term year*aged ≥65. As this was not significant in any of the groups, we present only the crude results.

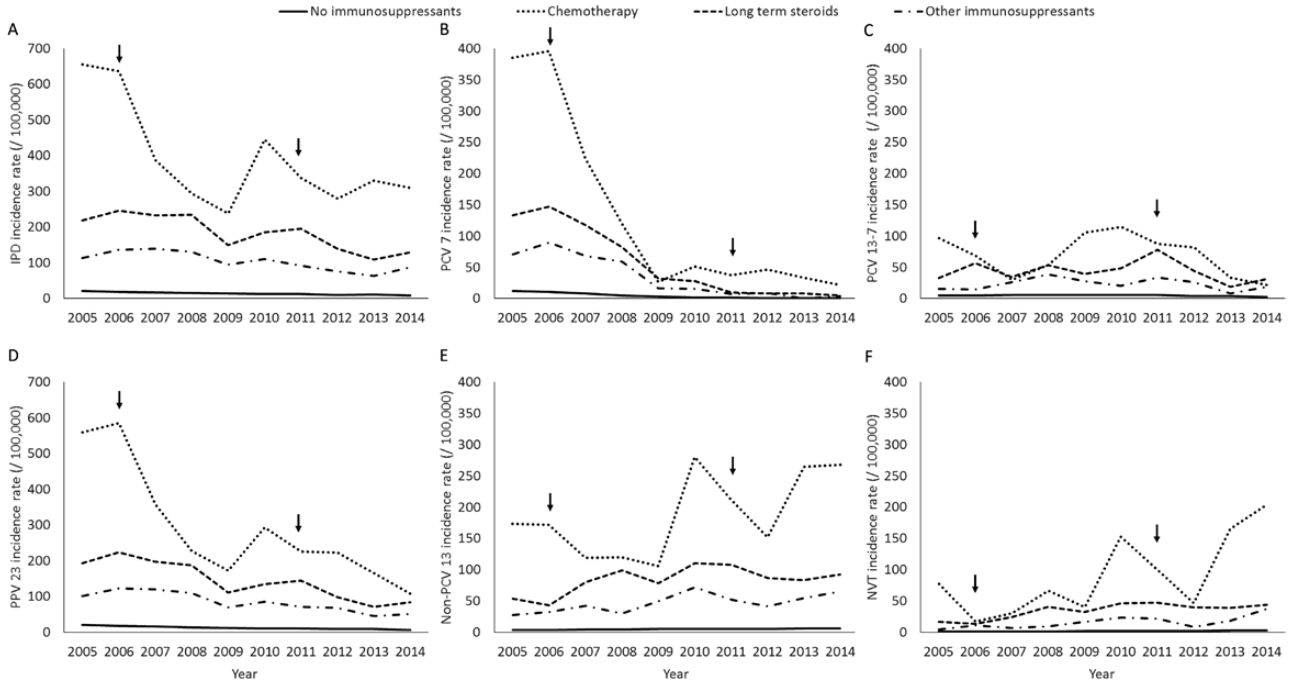

Figure 1. IPD incidence over time by treatment group. A, All IPD. B, PCV7-type IPD. C, PCV13-7–type IPD. D, PPV23-type IPD. E, Non–PCV13-type IPD. F, NVT IPD. Arrows indicate the years of vaccine introduction (2006: PCV7; 2011: PCV13). Note the difference in resolution of the Y-axes on the left compared to the middle and right side of the figure. The figure presents data of all ages together. The immunosuppressive treatment groups are not mutually exclusive, but the no-immunosuppressants group is. The PCV7 serotypes are 4, 6B, 9V, 14, 18C, 19F, and 23F. The PCV13-7 serotypes are serotypes that are included in PCV13, but not in PCV7: 1, 3, 5, 6A, 7F, and 19A. The PPV23 serotypes are all PCV13 serotypes except serotype 6A and serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F. The number of IPD cases included in the chemotherapy group, long-term corticosteroids group, other immunosuppressants group and no-immunosuppressants group infected by PCV7-serotypes are n = 80, n = 255, n = 97, and n = 1885, with PCV13-7 serotypes n = 48, n = 227, n = 83, and n = 2158, with PPV23 serotypes n = 189, n = 719, n = 284, and n = 5350, with non-PCV13 serotypes n = 141, n = 460, n = 183, and n = 2252, and with NVT serotypes n = 73, n = 194, n = 65, and n = 782, respectively. Abbreviations: IPD, invasive pneumococcal disease; NVT, non-vaccine type; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

For the PCV13 era (ie, the complete years with PCV13: 2012–2014), we determined the RR of IPD and its 95% CI as the ratio between the risk in the immunosuppressive treatment groups and the no-immunosuppressants group. We adjusted for confounding by age using the Cochran-Mantel-Haenszel estimate calculator for cohort studies (cs command) in Stata using age strata of <65 and ≥65 years [16]. Furthermore, we tested the number and percentage of cases infected with vaccine serotypes in the immunosuppressive treatment groups versus the no-immunosuppressants group with chi-squared tests. The serotype diversity was determined using the Simpson's index of diversity [17] (method as previously described [5]; 1-D). Its 95% CI was calculated using bootstrap (5000x).

Data were analyzed in Stata 15.0.

RESULTS

Characteristics of the Study Population

We included 7926 cases and 249 998 cohort individuals in the analyses: 95% of the cases had serotype information available (Table 1). The median age of the cases was 65 years (inter-quartile range: 49–78). Of the cases, 16% were treated with immunosuppressive drugs in ambulatory care within 1 year before the index month: 4% with chemotherapy only, 13% with long-term corticosteroids only, and 5% with an other immunosuppressant, while 28% of the cases on immunosuppressants were treated with multiple kinds of immunosuppressants. The median age of the cohort was 38 years (95% CI 20–56 years); cohort individuals in the immunosuppressive treatment groups were generally older (median age between 54 and 66) than in the no-immunosuppressants group (38 years; see Supplementary Table 1 for inter-quartile ranges). Only 2% (95% CI 1.9–2.1%) of the cohort was treated with immunosuppressive drugs in ambulatory care, of which 16.9% (95% CI 15.6–18.3%) was treated with multiple immunosuppressants (see Supplementary Table 2 for the combinations of multiple immunosuppressants).

Changes in Invasive Pneumococcal Disease Epidemiology After Introduction of Pneumococcal Conjugate Vaccines

Both overall and vaccine-type–specific IPD incidence rates were considerably higher in the immunosuppressive treatment groups than in the no-immunosuppressants group, but the time trends were quite similar (Figure 1). The overall IPD incidence rate decreased in all groups. The incidence rate of PCV7-type IPD decreased directly after PCV7 introduction. The PCV13-7 incidence rate increased after PCV7 introduction, but decreased

Table 1. Characteristics of the Study Population

	Percentage in the Cohort (95% CI or as Indicated)	Percentage of Cases Included in the Analysis (Number of Cases)
Individuals sampled from the National Registry/notified to MSIS	100 (n = 250 000)	100 (n = 7994)
Missing/wrong personal identification number[a]	<1 (n = 2)	<1 (n = 68)
Number of individuals/IPD episodes included in the analysis (% of MSIS)	100 (n = 249 998)	99.1 (n = 7926)
Sampling fraction[b]	5.0	3.5
Available serotype	NA	94.7 (n = 7505)
Male sex	49.9 (49.6–50.1)	50.2 (n = 3981)
Immunosuppressive treatment groups[c]		
No immunosuppressants	98.0 (97.9–98.1)	83.9 (n = 6653)
Chemotherapy[d]	0.2 (0.1–0.2)	3.6 (n = 282)
Long-term corticosteroids[e]	1.3 (1.2–1.3)	12.7 (n = 1004)
Other immunosuppressants[f]	0.9 (0.9–1.0)	4.8 (n = 383)

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; MSIS, Norwegian Surveillance System for Communicable Diseases; NA, not applicable.

[a]Excluded.

[b]The sampling fraction for the cohort is the percentage of the Norwegian population that was sampled in the cohort; for the cases, it is the percentage of cases that was sampled in the cohort.

[c]The immunosuppressive treatment groups are not mutually exclusive, but the no-immunosuppressants group is.

[d]Chemotherapy (L01) includes L01A (Alkylating agents), L01B (Antimetabolites), L01D (Cytotoxic antibiotics and related substances), and L01X (other antineoplastic agents).

[e]Long-term corticosteroids includes H02A (corticosteroids for systemic use, plain) and H02B (corticosteroids for systemic use, combinations) at a dose of >1.5 defined daily doses for a period of >1 month.

[f]Other immunosuppressants (L04A) includes L04AA (Selective immunosuppressants), L04AB (tumor necrosis factor alpha inhibitors), L04AC (interleukin inhibitors), L04AD (calcineurin inhibitors), and L04AX (other immunosuppressants).

after the switch to PCV13. The incidence rate of PPV23-type IPD decreased during the 3 years after PCV7 introduction, but subsequently increased until PCV13 was introduced; thereafter, the PPV23 incidence rate decreased. The incidence rate of non-PCV13 and NVT-IPD increased from the time of PCV7 introduction onwards. Together, Figure 1B and C represent the absolute size of the assumed indirect protection through vaccination. Figure 1E presents the absolute size of the assumed serotype replacement.

Figure 2 shows the average change in incidence rate after PCV introduction. For all groups, the decrease in the overall IPD incidence rate was statistically significant and reflected a large decrease in PCV7-type IPD and a decrease in PCV13-7–type IPD. Non–PCV13-type IPD increased significantly for all groups, which was most pronounced in individuals on chemotherapy (IRR 1.10, 95% CI 1.02–1.17; overlapping 95% CIs between groups).

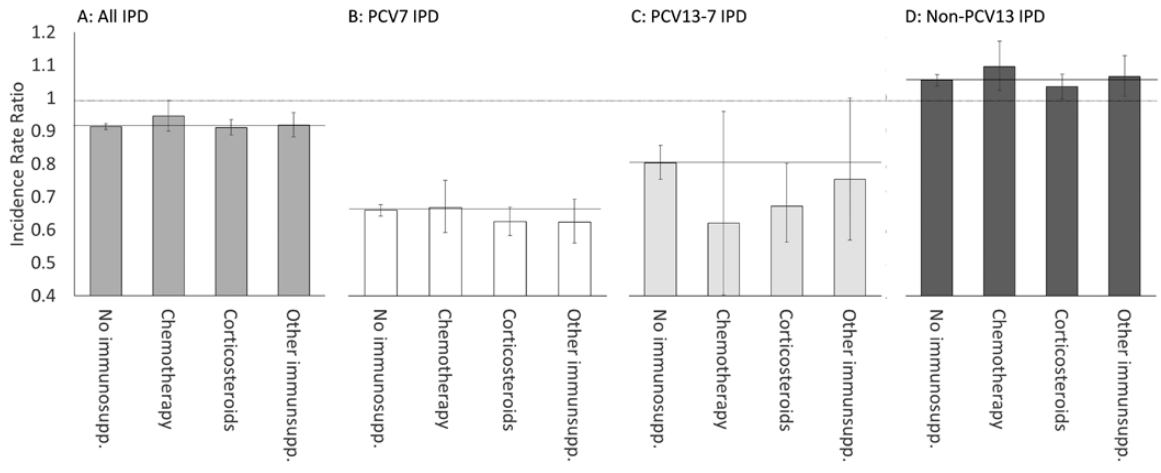

Figure 2. Average annual incidence rate ratios (IRR) after introduction of PCV by treatment group. The immunosuppressive treatment groups are not mutually exclusive, but the no-immunosuppressants group is. The years that are included in the Poisson regression analysis are 2006–2014, except for PCV13-7, which covered 2011–2014. The dotted horizontal line indicates an IRR of 1 (ie, unchanged incidence rate during the study period). The straight, horizontal black lines indicate the IRR in the no-immunosuppressants group. The thin, vertical lines indicate the 95% confidence interval. Note that the IRRs can be interpreted as the average gradients of the lines presented in Figure 1. Abbreviations: IPD, invasive pneumococcal disease; IRR, incidence rate ratios; PCV, pneumococcal conjugate vaccines.

Invasive Pneumococcal Disease Epidemiology in the 13-Valent Pneumococcal Conjugate Vaccine Era (2012–2014)

The proportion of IPD cases infected with PCV13-type IPD serotypes was lower in the immunosuppressive treatment groups (25–30%) than in the no-immunosuppressants group (42%; Table 2). Similarly, PPV23-type IPD was less common in the immunosuppressive treatment groups (53–71%) than in the no-immunosuppressants group (76%). In other words, the proportion of cases infected with NVT serotypes was higher in the groups treated with immunosuppressive drugs and highest in the chemotherapy group (numerical; not tested, as the immunosuppressive treatment groups are not mutually exclusive).

The overall serotype diversity was significantly higher in the immunosuppressive treatment groups (particularly in the chemotherapy group) than in the no-immunosuppressants group (Table 2). The frequency ranking of the serotypes was similar between groups, except for in the chemotherapy group, although the numbers were small (Supplementary Table 3). The most common serotype in all groups in the PCV13 era was 22F, a serotype found in PPV23 but not in PCV13. PCV13-7 serotypes 7F, 19A, and 3 were common (ie, ≥5%) in all groups except for the chemotherapy group (≤1%). NVT serotypes 35C, 21, 7C, and 29 and PCV7 serotype 6B were common in the chemotherapy group, but comprised <1% in the other groups. Other PCV7 serotypes were uncommon (≤2%) in all groups, as expected 6 to 8 years after PCV7 introduction.

The adjusted RR for IPD was 20.4 (95% CI 16.3–25.4) in the group treated with chemotherapy, 6.2 (95% CI 5.4–7.1) in the long-term corticosteroids group, and 5.6 (95% CI 4.6–6.8) in the other immunosuppressants group (Table 3). The adjusted RR for NVT IPD was significantly higher than for PCV13- and PPV23-type IPD in the chemotherapy group; for the long-term corticosteroids and other immunosuppressants groups this trend was non-significant. This difference between the RRs for PCV13 and NVT IPD was more pronounced in the PCV13 era than before the introduction of PCVs (2005; data not shown).

DISCUSSION

Our results indicate that the use of PCVs in the Norwegian childhood vaccination program has provided indirect protection against IPD in the entire population, including in individuals treated with immunosuppressive drugs in ambulatory care. The decrease in PCV-type IPD in individuals treated with immunosuppressive drugs was at least of the same magnitude as in those not receiving immunosuppressive treatment. An increase in non–PCV13-type IPD was seen in all groups, and was most pronounced in individuals treated with chemotherapy (not significant). The adjusted RR of IPD (particularly for NVT IPD), the serotype diversity, and the percentage of IPD caused by NVT serotypes were highest in the chemotherapy group, followed by the groups on long-term corticosteroids, other immunosuppressants, and no immunosuppressants. This indicates that iatrogenically-immunosuppressed individuals have an increased susceptibility to IPD, caused by a more diverse group of serotypes that have lower invasive capacities compared to immunocompetent individuals. The increased susceptibility to IPD caused by NVT serotypes in immunosuppressed individuals has also been shown after the introduction of PCV7 [8]. We do not know whether the severity of IPD has changed after the introduction of PCV, but it is known that the clinical presentation differs between serotypes, with several vaccine serotypes causing more severe disease than NVT serotypes [18, 19]. After the introduction of PCV13 in the childhood vaccination program, circulation of less-invasive NVT serotypes has become more prevalent [4, 20].

Although the incidence rate of vaccine-type IPD decreased and the corresponding percentage of the cases was lower in the immunosuppressive treatment groups than the no-immunosuppressants group, the RR and absolute number of vaccine-type IPD cases among the groups treated with immunosuppressive drugs in ambulatory care are still substantial. Therefore, increasing the PPV23 coverage in these risk groups may provide further protection, particularly if vaccination is provided prior to the initiation of immunosuppressive treatment [21]. The low

Table 2. Number and Percentage of IPD Cases According to Vaccine-Type and Serotype Diversity During the PCV13 Era (2012–2014) by Treatment Group

Immunosuppressive Treatment Groups[a]	Number of IPD Cases (100%)	Number of PCV13-Type Cases (%)	*P*-Value[b]	Number of PPV23-Type Cases (%)	*P*-Value[b]	Number of NVT Cases (%)	*P*-Value[b]	Simpson's Index of Diversity[c] (95% CI)
No immunosuppressants	1483	625 (42)	Reference	1130 (76)	Reference	353 (24)	Reference	0.926 (0.919–0.932)
Chemotherapy	83	21 (25)	.002	44 (53)	<.001	38 (46)	<.001	0.954 (0.939–0.964)
Long-term corticosteroids	244	73 (30)	<.001	162 (66)	.001	80 (33)	.003	0.949 (0.941–0.956)
Other immunosuppressants	113	32 (28)	.004	80 (71)	.196	33 (29)	.196	0.942 (0.922–0.954)

Serotype diversity was determined by Simpson's Index of Diversity.

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; NVT, non-vaccine type; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

[a]The immunosuppressive treatment groups are not mutually exclusive, but the no-immunosuppressants group is.

[b]The *P*-values reflect the comparison of the immunosuppressive treatment groups with the no-immunosuppressants group (= reference category).

[c]The higher the Simpson's index of diversity, the more diverse the serotype distribution. Note that for the Simpson's index, 54 of 1801 cases (3%) could not be included because of a missing serotype or factor type.

Table 3. Age-adjusted RRs for IPD According to Vaccine-Type During the PCV13 Era (2012–2014) in the Immunosuppressive Treatment Groups Compared to the No-Immunosuppressants Group

Immunosuppressive Treatment Groups[a]	Adjusted RR for all IPD (95% CI)	Adjusted RR for PCV13-Type IPD (95% CI)	Adjusted RR for PPV23-Type IPD (95% CI)	Adjusted RR for NVT IPD (95% CI)
No immunosuppressants	Reference	Reference	Reference	Reference
Chemotherapy	20.4 (16.3–25.4)	13.4 (8.6–20.6)	14.7 (10.9–19.9)	35.4 (25.4–49.4)
Long-term corticosteroids	6.2 (5.4–7.1)	5.0 (3.9–6.4)	5.7 (4.8–6.7)	7.3 (5.7–9.3)
Other immunosuppressants	5.6 (4.6–6.8)	4.0 (2.8–5.7)	5.3 (4.3–6.7)	6.4 (4.5–9.2)

RRs calculated by the Cochran-Mantel-Haenszel method and adjusted for the age strata <65 years and ≥65 years.

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; NVT, non-vaccine type; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; RR, risk ratio.

[a]The immunosuppressive treatment groups are not mutually exclusive, but the no-immunosuppressants group is. The no-immunosuppresants group was used as reference category in the analysis.

percentage of PCV13-type IPD in the PCV13 era indicates that PCV13 has limited potential for additional prevention of IPD and, if the observed trend continues, this may decrease even further [22]. We did not collect information on vaccination history for the cases and the cohort. PPV23 has been recommended for medical risk groups and those aged 65 years and older since 1996, but sales statistics indicate a low but stable vaccine uptake (23 000–29 000 doses per year in a total Norwegian population of 5 million) [23]. Since 2013, PCV13 has only been recommended outside the childhood vaccination program for selected medical risk groups at very high risk of IPD [24].

A strength of this study is its large size, with inclusion of 5% of the Norwegian population and 99% of all IPD cases notified in the study period. Furthermore, we were able to define immunosuppressive treatment groups based on registered dispensed prescriptions, although we were unable to ascertain whether individuals used the drugs. The study also has limitations. Data on drugs administered to individuals in hospitals or nursing homes are not available in the NorPD on the individual level, and are therefore not included in this study. According to data from 2012 from Norwegian Drug Wholesales and NorPD, approximately 70% of chemotherapy and 83% of other immunosuppressants were dispensed to individuals in ambulatory care (Solveig Sakshaug, personal communication with A. Steens, 26 February 2018). We may, therefore, have misclassified individuals in nursing homes and individuals that exclusively were treated in hospitals, such as cancer patients on chemotherapy, as not being treated with immunosuppressive drugs. Such misclassification may have diluted our results. In a sensitivity analysis using hospital discharge data from the Norwegian Patient Registry, we found that if all cancer patients (International Classification of Diseases, Tenth Revision [ICD-10] codes C00-C96) were excluded from the no-immunosuppressants group, the IPD incidence rate over the period of 2009–2014 was reduced from 11.5/100 000 to 10.3/100 000 for this group. However, it is well known that only a minority of cancer patients are treated with chemotherapy, and many would therefore not be misclassified. The potential effect of such misclassification is, therefore, smaller than indicated by the sensitivity analysis. Another limitation to our study was that we had to base the annual denominators on cohort data from December 2012, while data from NorPD show that the proportion of the population treated with immunosuppressive drugs in ambulatory care changed during the study period. Although we tried to correct for this increase, incorrect estimates of the denominator would affect the incidence rate, IRR, and RR, but not the serotype diversity and the percentage of vaccine-type cases.

Selection bias is a potential limitation in all register studies. Access to drugs was unlikely to have been different between the immunosuppressive treatment groups and the no-immunosuppressants group, as 96.1% (95% CI 96.0–96.2) of the no-immunosuppressants group had at least 1 dispensed prescription registered in NorPD, compared to 100% of the immunosuppressive treatment groups. The fact that individuals in the immunosuppressive treatment groups were older than the no-immunosuppressants group may have increased the observed differences in incidence rates and percentages of cases by vaccine-type between groups, but not the IRRs, which were determined within each group. The RRs for (vaccine-type) IPD were adjusted for confounding by age.

CONCLUSIONS

The observed decline in IPD incidence rates in both immunocompetent and iatrogenically-immunosuppressed individuals underscores the benefit of PCV childhood vaccination for the entire population. Although a high proportion of cases are now caused by NVT serotypes, there is a continued need to provide effective protection against IPD, both by effective vaccines and by adherence to recommendations. New strategies and vaccines are needed to improve the protection of medical risk groups against IPD, including vaccines targeting additional serotypes, conjugated vaccines targeting non-PCV13 serotypes for use in risk groups, or universal pneumococcal vaccines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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