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Vaccinations in the immunocompromised population

Paramount and paradox

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Publication date
2022

Citation for published version (APA):
Garcia Garrido, H. M. (2022). *Vaccinations in the immunocompromised population: Paramount and paradox*. [Thesis, fully internal, Universiteit van Amsterdam].

CHAPTER 3

3

Invasive pneumococcal disease among adults with haematological and solid organ malignancies: A population-based cohort study

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ABSTRACT

Objectives

To determine the risk of invasive pneumococcal disease (IPD) in adult cancer patients stratified by type of underlying malignancy, age, and capsular serotype and to assess herd effects of childhood pneumococcal vaccination.

Methods

All adult IPD cases reported to the Dutch pneumococcal surveillance system between 2004 and 2016 were included in this study. IPD incidence rates (IR) stratified by subtype of malignancy were calculated per 100 000 patient-years of follow-up. Incidence rate ratios (IRR) were calculated to compare IRs between groups.

Results

A total of 7167 IPD cases were included, of which 1453 were in patients with malignancies. For patients with hematological malignancies (HM) and solid organ malignancies (SOM), IRs were 482/100 000 and 79/100 000, respectively, compared with 15/100 000 in controls. The highest incidence was observed among patients with multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, pancreatic cancer, and lung cancer (3299/100 000, 2717/100 000, 538/100 000, 559/100 000, and 393/100 000, respectively), and in patients ≥50 years old. Among HM patients, the incidence of IPD declined significantly after the implementation of infant pneumococcal vaccination (IRR 0.65, 95% confidence interval 0.51–0.84); among SOM patients, the decline was not statistically significant (IRR 0.88, 95% confidence interval 0.72–1.07).

Conclusions

The IPD disease burden in cancer patients remains high. Large differences in IPD incidence between the different types of cancer demand tailored guidance regarding pneumococcal vaccination.

INTRODUCTION

Patients with hematological malignancies (HM) and solid organ malignancies (SOM) are at increased risk of invasive pneumococcal disease (IPD), either due to the malignancy itself or due to immunosuppressive antineoplastic treatment [1,2]. United States guidelines currently recommend vaccinating all cancer patients with the 13-valent pneumococcal conjugate vaccine (PCV13), followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23), but vaccination rates are disappointing [3, 4, 5]. In the Netherlands and several other European countries, vaccination of cancer patients is currently not recommended by national guidelines [6], despite epidemiological reports showing an increased IPD incidence for cancer patients compared to the general population.

Reported incidence rates (IR) of IPD in cancer patients in Scandinavian countries range between 380/100 000 and 415.4/100 000 for HM, and between 18/100 000 and 71/100 000 for SOM [1,2,7]. In the Netherlands, no prior studies on IPD in cancer patients have been conducted to date. In addition, most foreign studies investigating IPD incidence in cancer patients have described patient cohorts from before 2008 [2, 7, 8]. However, over the past decade, much has changed in the treatment of cancer patients, as well as in the epidemiology of pneumococcal infections.

The introduction of pneumococcal conjugate vaccination in national childhood immunization programs (NCIP) has led to a decreased burden of IPD in adults, and to a shift in serotype distribution [9,10]. In the Netherlands, PCV7 was introduced into the NCIP in 2006, and was replaced by PCV10 in 2011 [10]. It remains unclear how these changes may have affected the risk of pneumococcal infections in cancer patients in recent years [11, 12]. The only recent European study investigating IPD incidence in cancer patients was conducted in Denmark and reported a rate ratio (RR) of IPD of 9.53 (95% confidence interval (CI) 8.85–10.27) for HM and 1.78 (95% CI 1.70–1.87) for SOM compared to the general population. However, the study did not distinguish between the different types of SOM, precluding the development of tailored vaccination recommendations for SOM patients [1].

We hypothesized that the IPD disease burden has remained higher among adults with malignancies compared to those without a malignancy, despite the introduction of pneumococcal vaccination in the NCIP, and that factors such as age and the type of underlying malignancy greatly influence this risk of IPD.

The objectives of this study were (1) to determine the incidence of IPD in patients with SOM and HM stratified by the type of underlying malignancy, age group, and vaccine-targeted capsular serotype group; (2) to compare the incidence and clinical characteristics of IPD in cancer patients to those of the population without cancer; (3) to investigate herd effects associated with the introduction PCV in the NCIP in

3

the Netherlands (from 2006 onwards); and (4) to determine numbers-needed to vaccinate (NNV) for IPD in cancer patients.

METHODS

IPD case definition and identification

A population-based cohort study was performed including all adult IPD cases reported to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM). The definition of IPD was the isolation of Streptococcus pneumoniae from blood or cerebrospinal fluid. Nine Dutch sentinel laboratories, covering 25% of the Dutch population, routinely send all invasive pneumococcal isolates to the NRLBM as part of the Dutch pneumococcal surveillance system. The NRLBM uses co-agglutination and the Quellung method for pneumococcal serotyping [13]. Clinical information on adult IPD cases reported to the NRLBM during a 12-year period from June 2004 to June 2016 had previously been collected as part of another study. This information included the diagnosis of SOM/HM, without further specification of the type of malignancy [10].

Other data items collected included age, sex, clinical presentation (pneumonia, meningitis, bacteremia), comorbidities (asplenia, kidney failure, HIV, asthma, chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disease), immunosuppressive therapy in the month before the IPD diagnosis (steroids, chemotherapy, radiation, other), previous transplantation, smoking, IPD-related mortality, and hospital and intensive care unit admission.

Data linkage with the Netherlands Cancer Registration

The population-based Netherlands Cancer Registration (NKR) has registered all malignancies in the Netherlands since 1989, as described previously [14,15]. Information on the subtype of cancer in the included IPD cases was obtained through the linkage of personal data (sex, date of birth, initials, last name, address) between the NRLBM and the NKR. In addition, the NKR provided the total patient years of follow-up (PYFU) for each subtype of malignancy and the age group (18–49, 50–64, and >65 years) in the region corresponding to the NRLBM registration during the years of interest (2004–2016). IRs of IPD per 100 000 PYFU were calculated for each subtype of malignancy, age group (18–49, 50–64, and ≥65 years), and capsular serotype group: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV10/non-PCV7 serotypes (1, 5, and 7F), PCV13/non-PCV10 serotypes (3, 6A, and 19A), PPSV23/non-PCV types (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F), and non-vaccine serotypes.

Outcomes and data analysis

IRs of IPD for each type of malignancy were compared with the incidence in the population without malignancies in the same region, by calculating incidence rate ratios (IRRs) with 95% CI.

We compared IPD incidence and serotype distribution for different types of malignancies before the introduction of PCV7 in the NCIP (pre-PCV era; June 2004–May 2006), with the IPD incidence in the PCV7 era (June 2006–May 2011) and with the incidence in the PCV10 era (June 2011–May 2016).

Using multivariable regression analysis, adjusting for age and sex, baseline clinical characteristics of IPD patients with HM and SOM were compared to those of IPD patients without malignancies. List-wise deletion was applied in the case of missing clinical data. The characteristics of successfully versus unsuccessfully linked IPD cases were compared (univariable). The 0.05 alpha level was applied to indicate statistical significance. IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) was used for all analyses.

For patients with HM and SOM, as well as for patients with one of the malignancies with the highest incidence of IPD, the NNV to prevent one single case of IPD, using any vaccination schedule that included at least one dose of PPSV23, was calculated. Hypothetical vaccine efficacy values (Ve) of 40% and 60% were applied. The Ve values were based on several studies investigating the effectiveness and immunogenicity of pneumococcal vaccines [16,17,18,19]. NNV was calculated as follows:

$$NNV = \frac{1}{Absolute\ risk\ reduction\ (ARR)}$$

$ARR = IR\ PCV10\ era - ((1 - (Ve *$
$proportion\ IPD\ cases\ caused\ by\ vaccine\ serotypes\ 2014 - 2016) * IR\ PCV10\ era)$

RESULTS

Study population

During the study period, 7167 IPD cases were reported to the NRLBM, of which 1453 (20%) occurred in patients with a malignancy. Of these, 478 (33%) occurred in HM patients, 917 (63%) in SOM patients, and 58 (4%) in patients diagnosed with both HM/SOM. The malignancy subtype was identified by data linkage in 1279 of 1453 IPD cases (88%). Data linkage was unsuccessful in 174/1453 (12%) IPD cases. These cases were in general older, and were less often treated with immunosuppressive treatment (Supplementary material Table S1).

IPD incidence rates

The IR of IPD was 482/100 000 in HM patients and 79/100 000 in SOM patients, compared with 15/100 000 in adults without a malignancy. The highest IRs were found among patients with multiple myeloma (MM), non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), pancreatic cancer, and lung cancer (Table 1). The IPD incidence differed considerably between age groups, with the highest IRs in individuals older than 65 years of age (Figure 1).

Compared with the population without malignancy, IPD incidence was significantly higher for all subtypes of malignancy, with the exception of patients with skin cancer and bone or soft tissue cancer. IRRs of IPD of cancer patients versus the general population ranged between 1.07 and 218 (Table 1).

Over the entire study period (pre-PCV era versus PCV10 era), IPD IRs declined significantly among HM patients (IRR 0.65, 95% CI 0.51–0.84); among SOM patients, the decline was not statistically significant (IRR 0.88, 95% CI 0.72–1.07). After the introduction of PCV10 (2011–2016), the incidence of IPD declined significantly for individuals ≥50 years of age for both categories of malignancies, while IPD incidence remained stable in younger adults (Figure 1).

In the first years after the introduction of PCV7 (2006–2011), there was no statistically significant decline in IPD incidence among HM patients, except patients with MM. In addition, there was an increase in overall IPD incidence among patients with SOM (IRR 1.33, 95% CI 1.10–1.62) (Supplementary material Table S2), which was caused in particular by an increased incidence of PPSV23/non-PCV serotypes in this group (IRR 1.92, 95% CI 1.25–2.94). The decline in IPD incidence during the PCV10 era (2011–2016) among patients with either HM or SOM, was caused by a decreased incidence of both PCV7 and PCV10/non-PCV7 serotypes, with limited serotype replacement (Figure 2A, B).

Table 1. Comparison of incidence rates of invasive pneumococcal disease for several types of malignancies versus the general Dutch population with no malignancy.[a]

Period June 2004–May 2016

	Number of cases	Patient years of follow-up	IR/100 000	IRR	95% lower	95% upper
No malignancy	5714	37 831 731	15	NA	NA	NA
Any malignancy	1453	1 352 129	107	**7.12**	**6.72**	**7.54**
Hematological	536	111 097	482	**31.9**	**29.2**	**34.9**
Acute myeloid leukemia	16	4661	343	**22.7**	**13.9**	**37.1**
Acute lymphoblastic leukemia	2	1136	176	**11.7**	**2.91**	**46.6**
Chronic lymphocytic leukemia	78	14 493	538	**35.6**	**28.5**	**44.6**
Chronic myeloid leukemia	5	2979	168	**11.1**	**4.62**	**26.7**
Hodgkin lymphoma	14	12 712	110	**7.29**	**4.32**	**12.3**
Non-Hodgkin lymphoma	117	4306	2717	**180**	**150**	**216**
Multiple myeloma	235	7124	3299	**218**	**192**	**249**
Other	19	63 586	30	**1.98**	**1.26**	**3.10**
Solid organ malignancies	975	1 241 032	79	**5.20**	**4.86**	**5.57**
Head and neck cancer	41	33 089	124	**8.20**	**6.03**	**11.2**
Esophageal cancer	29	10 365	280	**18.5**	**12.9**	**26.7**
Gastric cancer	22	12 847	171	**11.3**	**7.46**	**17.2**
Colon cancer	103	170 581	60	**4.00**	**3.29**	**4.86**
Pancreatic cancer	43	7689	559	**37.0**	**27.4**	**50.0**
Liver cancer	7	2034	344	**22.8**	**10.9**	**47.8**
Lung cancer	234	59 536	393	**26.0**	**22.8**	**29.7**
Skin cancer	32	186 274	17	1.14	0.80	1.61
Bone and soft tissue cancer	3	18 483	16	1.07	0.35	3.33
Breast cancer	85	346 690	25	**1.62**	**1.31**	**2.01**
Female reproductive organ cancer	31	87 929	35	**2.33**	**1.64**	**3.32**
Prostate cancer	78	162 881	48	**3.17**	**2.54**	**3.96**
Kidney cancer	18	31 978	56	**3.73**	**2.35**	**5.92**
Bladder cancer	20	29 152	69	**4.54**	**2.93**	**7.05**
Endocrine gland cancer	11	13 908	79	**5.24**	**2.90**	**9.46**
Central nervous system cancer	9	5929	152	**10.1**	**5.23**	**19.3**
Other solid tumors	27	61 667	44	**2.90**	**1.99**	**4.23**

IR, incidence rate; IRR, incidence rate ratio; NA, not applicable.
[a]Bold highlights significant difference, P < 0.05

A. Incidence rate per 100.000 PYFU - Hematological malignancies

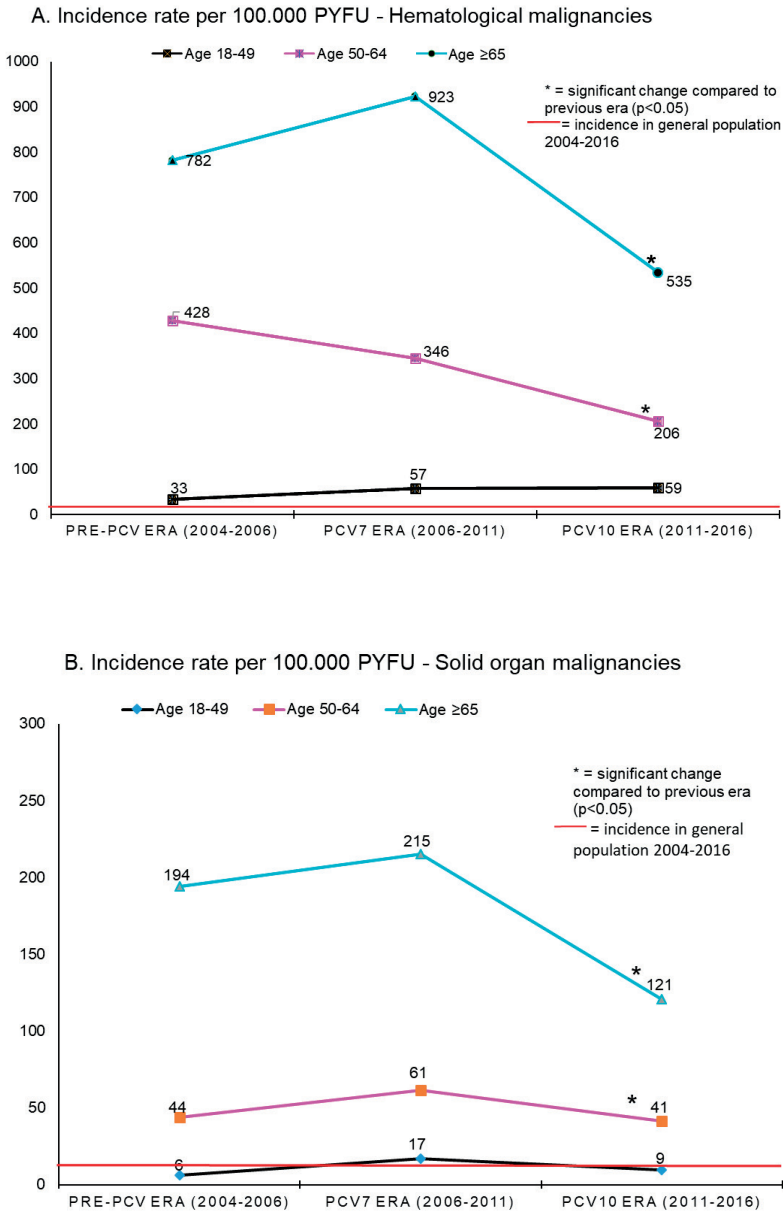B. Incidence rate per 100.000 PYFU - Solid organ malignancies

Figure 1. Incidence rate of invasive pneumococcal disease stratified by age for patients with (A) hematological malignancies, and (B) solid organ malignancies.

PYFU = patients years of follow-up; PCV = pneumococcal conjugate vaccine.

Figure 2. Incidence rate of invasive pneumococcal disease stratified by serotype group and period for patients with (A) hematological malignancies, and (B) solid organ malignancies.

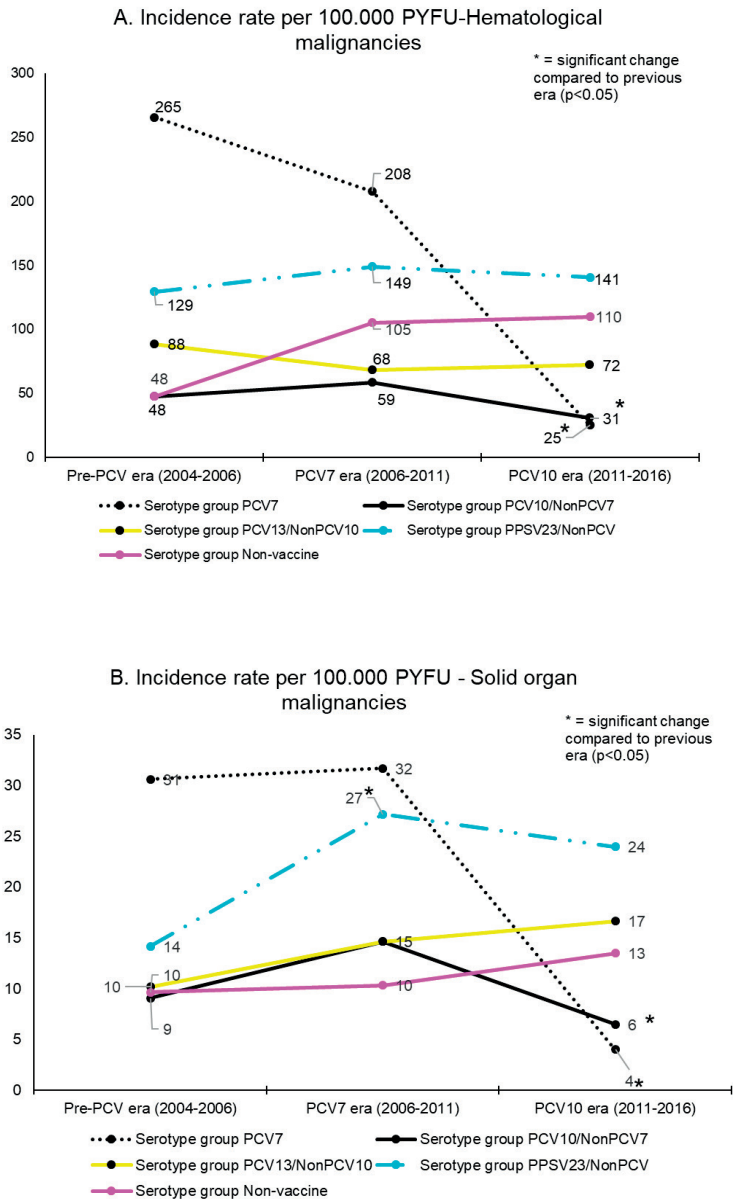PYFU = patients years of follow-up; PCV = pneumococcal conjugate vaccine; PSV23 = 23-valent pneumococcal polysaccharide vaccine.

Clinical characteristics

Baseline clinical characteristics of IPD cases with and without malignancies can be found in Table 2. Of all HM patients, 15.3% had undergone a previous transplantation, most likely a stem cell transplantation, although this was not specified during the initial data collection (Table 2).

With respect to the clinical presentation of IPD, pneumonia was less common in HM patients, whereas pneumococcal meningitis was less common in SOM patients (Table 2). Overall, bacteremia without focus was more common in patients with both types of malignancies.

The IPD-related case fatality rate (CFR) was higher in SOM patients compared to patients without malignancies (adjusted odds ratio (OR) 1.60, 95% CI 1.34–1.91). A similar trend was observed for HM patients (adjusted OR 1.16, 95% CI 0.91–1.48). Among HM patients, the IPD-related CFR increased significantly with age, whereas this effect was less pronounced among SOM patients (Figure 3).

Among HM patients, IPD occurred significantly later after the cancer diagnosis compared to SOM patients (median interval 3 years (interquartile range (IQR) 1–6 years) versus 1 year (IQR 0–4 years); P < 0.001). For the malignancies with the highest IPD incidence, the median time between cancer diagnosis and IPD was 2 years (IQR 0–4.5 years) for MM, 3 years (IQR 1–5 years) for NHL, 5 years (IQR 1.5–8.5 years) for CLL, 0 years (IQR 0–1 years) for pancreatic cancer, and 1 year (IQR 0–2 years) for lung cancer.

Serotype distribution

Serotypes included in PCV7 and PCV10 became less common after the introduction of PCV7 and PCV10 in the national immunization program (Figure 2). During the last 2 years of the study period, 30% of all IPD cases in cancer patients were caused by serotypes present in PCV13, while 74% of all cases were caused by serotypes present in PPSV23 (Figure 4). Data on the prevalence of individual capsular serotypes rather than vaccine-targeted groups can be found in Supplementary material Table S3.

Table 2. Baseline clinical characteristics of invasive pneumococcal disease in patients with hematological malignancies and solid organ malignancies compared with the population without malignancy.[a]

	IPD population without malignancy n = 5718	IPD hematological malignancies n = 536	P-value versus no malignancy[b]	IPD solid organ malignancies n = 975	P-value versus no malignancy[b]
Age (years), mean ± SD	65.0 (16.7)	68.0 (11.9)	0.001	70.5 (10.7)	<0.001
Age (years) n/N (%)					
18–49	1067/5718 (18.7)	38/536 (7.1)		32/975 (3.3)	
50–64	1428/5718 (25.0)	150/536 (28.0)	<0.001	232/975 (23.6)	<0.001
>65	3223/5718 (56.4)	348/536 (64.9)		711/975 (72.9)	
Sex n/N (%)					
Female	2842/5611 (50.7)	196/527 (37.2)		422/956 (44.1)	
Male	2769/5611 (49.3)	331/527 (62.8)	<0.001	534/956 (55.9)	0.001
Comorbidities n/N (%)					
Diabetes	1003/4513 (22.2)	60/425 (14.1)	<0.001	216/812 (26.6)	0.098
Pulmonary disease	1615/5406 (29.9)	78/534 (14.6)	<0.001	297/974 (30.5)	0.47
Cardiovascular	2776/4786 (58.0)	269/468 (57.5)	0.69	579/905 (64.0)	0.28
HIV	51/5244 (1.0)	3/536 (0.6)	0.84	2/975 (0.2)	0.37
Liver disease	170/5224 (3.3)	6/534 (1.1)	0.005	48/974 (4.9)	<0.001
Asplenia	59/5224 (1.1)	31/534 (3.9)	<0.001	8/974 (0.8)	0.91
Kidney disease	138/5224 (2.6)	14/536 (2.6)	0.77	20/975 (2.1)	0.039
Neurotrauma/CSF leakage	32/5415 (0.6)	1/536 (0.2)	0.32	4/975 (0.4)	0.95
Primary immune disorder	18/4340 (0.4)	2/414 (0.5)	0.44	0/762 (0)	0.99
IV drug abuse n/N (%)	32/5235 (0.6)	1/534 (0.2)	0.37	2/974 (0.2)	0.74
Smoking n/N (%)	1211/3236 (37.4)	16/288 (21.2)	<0.001	157/546 (28.8)	0.81
Alcohol abuse n/N (%)	328/5224 (6.3)	7/534 (1.3)	<0.001	63/974 (6.5)	0.87
Transplantation n/N (%)	20/4338 (0.5)	65/425 (15.3)	<0.001	2/763 (0.3)	0.013
Immunosuppressive treatment n/N (%)	437/4410 (9.9)	217/461 (47.1)	<0.001	291/829 (35.1)	<0.001
Clinical syndrome n/N (%)					
Meningitis	524/5405 (9.7)	30/534 (5.6)	0.06	49/974 (5.0)	0.003
Pneumonia	4290/5405 (79.4)	370/534 (69.3)	<0.001	753/974 (77.3)	0.32
Bacteremia without focus	339/5405 (6.3)	97/534 (18.2)	<0.001	127/974 (13.0)	<0.001

3

Table 2. Baseline clinical characteristics of invasive pneumococcal disease in patients with hematological malignancies and solid organ malignancies compared with the population without malignancy.[a]

	IPD population without malignancy n = 5718	IPD hematological malignancies		IPD solid organ malignancies	
		n = 536	P-value versus no malignancy[b]	n = 975	P-value versus no malignancy[b]
Bacteremia other focus	252/5405 (4.7)	37/534 (6.9)	0.003	45/974 (4.6)	0.55
Case fatality rate n/N (%)	688/5358 (12.8)	89/524 (16.9)	0.23	210/963 (21.8)	<0.001
ICU admission n/N (%)	1278/5334 (24.0)	79/524 (15.1)	<0.001	191/952 (20.1)	0.048
Duration of hospital admission in days, median (IQR)	10 (6–17)	9 (5–16)	0.086	10 (6–17)	0.293
Serotype distribution					
PCV7	1258/5718 (22.0)	138/536 (25.7)	0.13	225/975 (23.1)	0.76
PCV10/non-PCV7	1289/5718 (22.5)	48/536 (9.0)	<0.001	123/975 (12.6)	<0.001
PCV13/non-PCV10	883/5718 (15.4)	81/536 (15.1)	0.38	186/975 (19.1)	0.032
PPSV23/non-PCV	1833/5718 (32.1)	158/536 (29.5)	0.20	295/975 (30.3)	0.13
Non-vaccine	455/5718 (8.0)	111/537 (20.7)	<0.001	146/975 (15.0)	<0.001

CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; ICU, intensive care unit; IPD, invasive pneumococcal disease; IQR, interquartile range; IV, intravenous; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; SD, standard deviation.

[a] Bold highlights significant difference, P < 0.05.

[b] P-values were adjusted for age and sex in a multivariable regression analysis, except duration of hospital admission (Mann–Whitney U-test). The variable age was adjusted for sex only. The variable sex was adjusted for age only.
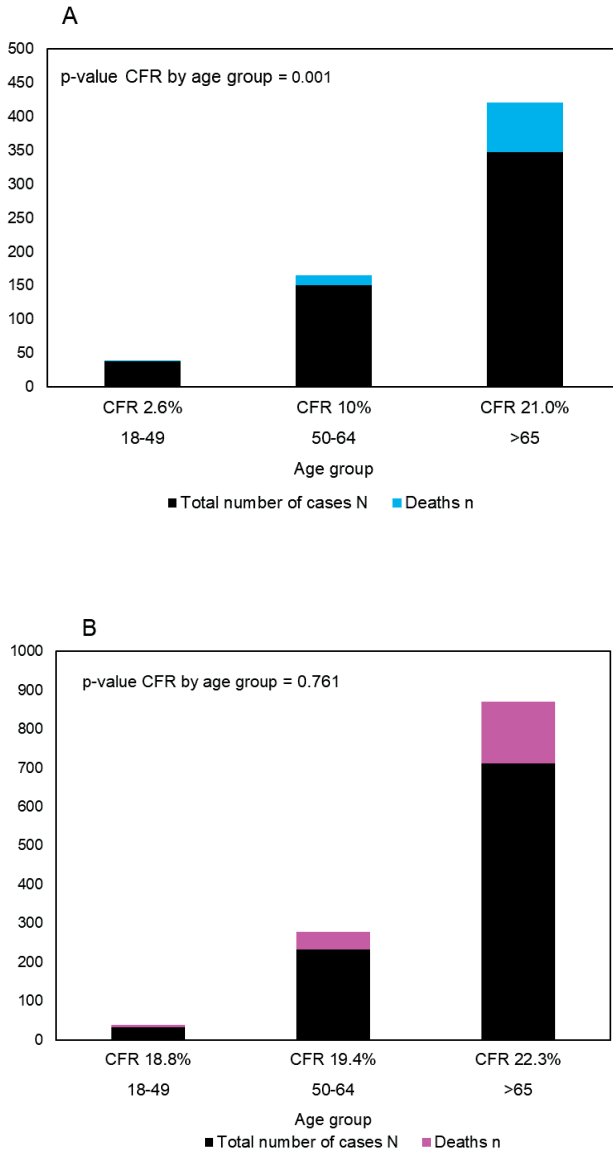
A

p-value CFR by age group = 0.001

CFR 2.6% CFR 10% CFR 21.0%
18-49   50-64   >65
Age group

■ Total number of cases N   ■ Deaths n

B

p-value CFR by age group = 0.761

CFR 18.8% CFR 19.4% CFR 22.3%
18-49   50-64   >65
Age group

■ Total number of cases N   ■ Deaths n

Figure 3. Number of cases of invasive pneumococcal disease and number of deaths stratified by age group for patients with (A) hematological malignancies, and (B) solid organ malignancies.

CFR = case fatality rate.

IPD SEROTYPE DISTRIBUTION IN CANCER PATIENTS JUNE 2014-MAY 2016 (TOTAL NUMBER OF CASES 245)

* highlights significant change
compared to period june 2011- may

PCV7
6%

PCV10/nonPCV7
7%

Non-vaccine
26%

PCV13-
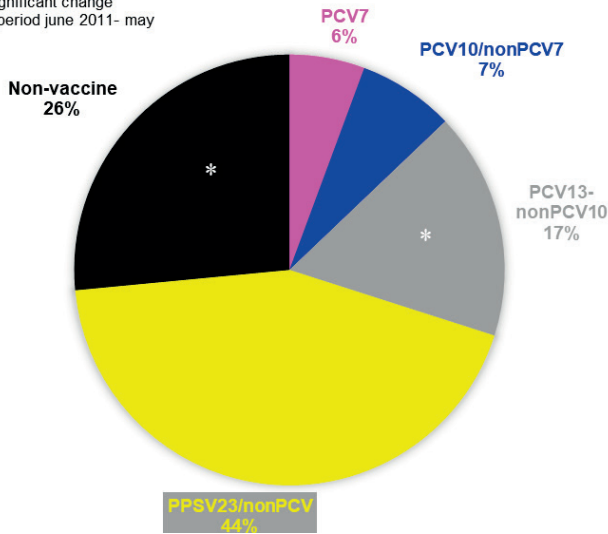nonPCV10
17%

PPSV23/nonPCV
44%

Figure 4. Pneumococcal capsular serotype distribution during the last 2 years of the study period.

PCV = pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

Number needed to vaccinate (NNV)

At the lowest hypothetical vaccine efficacy of 40%, the NNV to prevent one single IPD case would range between 145 and 1248 for the malignancies with the highest IPD incidence. At a hypothetical vaccine efficacy of 60%, NNV would range between 75 and 646 for the malignancies with the highest IPD incidence (Table 3).

Table 3. Number needed to vaccinate (NNV) to prevent one case of invasive pneumococcal disease (IPD) for the malignancies with the highest IPD incidence.

Vaccine efficacy 40%

Disease	NNV
Any hematological malignancy	912
Acute myeloid leukemia	1034
Chronic lymphocytic leukemia	896
Multiple myeloma	152
Non-Hodgkin lymphoma	145
Any solid organ malignancy	5263
Liver cancer	1248
Lung cancer	858
Pancreatic cancer	424

Vaccine efficacy 60%

Disease	NNV
Any hematological malignancy	604
Acute myeloid leukemia	539
Chronic lymphocytic leukemia	466
Multiple myeloma	79
Non-Hodgkin lymphoma	75
Any solid organ malignancy	2740
Liver cancer	646
Lung cancer	439
Pancreatic cancer	264

DISCUSSION

Dutch epidemiological data from 2004 to 2016 show an increased incidence of IPD in patients with HM (IRR 32.8) and SOM (IRR 5.34) compared with the general population. Increased IPD incidence rates in cancer patients have been reported previously in Denmark, Sweden, Canada, and the United States [1, 2, 8, 11].

The IPD incidence varied greatly across the different age groups and subtypes of malignancies. In line with the general Dutch population and previous studies in cancer patients, elderly cancer patients were at higher risk of IPD compared with younger patients [2, 10, 11]. With respect to HM, patients with MM, NHL, and CLL were at the highest risk of developing IPD. Previous reports from other countries have already identified MM and CLL as conditions with a high risk of IPD [8]. However, we report a much higher incidence in NHL patients compared with

previous studies [1, 8]. This could be attributed to changes in treatment protocols for NHL over time, such as an increased use of B cell depleting regimens for indolent lymphomas [20].

Regarding SOM, the present study identified pancreatic cancer, lung cancer, and liver cancer as malignancies with the highest IPD risk. While lung cancer has previously been identified as an important risk factor for IPD [8,11], we found no previous studies that reported the incidence of IPD in patients with pancreatic cancer and liver cancer. In addition to immunosuppressive chemotherapy, functional hyposplenism associated with these underlying malignancies could contribute to the observed increased IPD incidence [21].

After the implementation of immunization with PCV7 (2006) and PCV10 (2011) in the national immunization program, a significant 35% decline in IPD incidence in HM patients was observed, especially in older adults (≥50 years), which could be fully attributed to an overall decline in incidence of PCV7 and PCV10/non-PCV7 serotypes. The observed decline can be explained by indirect herd effects generated by the introduction of PCV in the NCIP, in combination with limited serotype replacement. Similar herd effects were not found in younger adults, which may be due to the lower incidence in younger adults limiting the observation of a significant impact in this age group.

A decline in IPD incidence after childhood vaccination has also been observed among elderly individuals in the general Dutch population, as well as in other European countries and in the United States, although less pronounced [9, 10]. Herd effects through reduced carriage might be greater in immunocompromised cancer patients because of a higher rate of pneumococcal invasion once colonized [22].

Pneumococcal vaccination strategies for cancer patients

Randomized controlled trials showing the clinical efficacy of pneumococcal vaccines against IPD in cancer patients are lacking and may never be conducted given the large number of individuals required to demonstrate clinical efficacy [22]. If we continue to demand scientific proof on the level of such trials before accepting the potential clinical benefit of pneumococcal vaccination, we may never arrive at broadly accepted vaccination guidelines. Therefore, vaccination recommendations in cancer patients need to be based on studies showing a high disease burden of IPD – such as the present study – combined with evidence of acceptable vaccine immunogenicity and evidence from observational studies suggesting a clinical benefit of vaccination.

In most European countries, pneumococcal vaccination of patients with malignancies is currently not recommended, with low vaccine uptake as a consequence [1, 6, 23]. In the United States, the Infectious Diseases Society of America (IDSA) and the Centers for Disease Control and Prevention (CDC)

recommend pneumococcal vaccination for all cancer patients [3, 4]. However, despite these recommendations, pneumococcal vaccination rates remain low, especially in the age group 18–64 years (5%) [5]. Importantly, the IDSA and CDC recommendations do not distinguish between the types of malignancy, which, as is clearly shown in the present study, is an important variable in the estimation of IPD risk. The study data suggest that pneumococcal vaccination should be prioritized in patients with pancreatic cancer and lung cancer. Such a tailored approach would likely improve the cost-effectiveness and feasibility of pneumococcal vaccination, potentially increasing vaccine uptake.

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Regarding pneumococcal vaccine effectiveness in cancer patients, an observational Australian study recently reported an 89% reduction in IPD incidence for both allogeneic and autologous hematopoietic stem cell transplantation (HSCT) after the implementation of post-HSCT vaccination [24]. For SOM patients, before the initiation of anti-cancer treatment, the effectiveness of pneumococcal vaccines is not likely to be impaired. An observational study in lung cancer patients showed that PPSV23 alone had an effectiveness of 30% against community-acquired pneumonia (CAP) hospitalization [16]. This is comparable to vaccine efficacy of one single dose of PPSV23 (vaccine efficacy 27%) or PCV13 (vaccine efficacy 31%) against pneumococcal CAP in healthy elderly persons [22, 25]. Immunogenicity studies report serological response rates of >50% for MM, CLL, gastric cancer, and colon cancer, and post HSCT [17, 26, 18,19].

Recent Dutch recommendations to vaccinate all persons ≥60 years old with PPSV23 were based on a NNV of 3333 (assuming a vaccine efficacy of PPSV23 against IPD of 64% and a prevalence of 12% non-vaccine serotypes in the healthy elderly population) [27]. The NNV values that we provide for patients with the most high-risk HM and SOM are much lower, suggesting that tailored vaccination strategies have the potential to reduce the burden of IPD at an acceptable cost. In addition, cost-effectiveness could be improved by targeting patients aged ≥50 years. Regarding the timing of vaccination, we argue that patients with SOM are best vaccinated immediately after diagnosis, before starting anti-neoplastic treatment, as most IPD cases occur early after diagnosis (median 1 year). For HM, IPD occurs later after diagnosis (median 3 years), and guidelines recommend vaccination before treatment initiation, or 3–6 months after stem cell transplantation [28,29].

Similar to the general population, serotype distribution in cancer patients has shifted since the introduction of PCV in the NCIP, with a significant decline in IPD caused by PCV10 serotypes [10]. In the most recent years of the study period (2014–2016), 30% of all IPD cases was caused by PCV serotypes, whereas PPSV23 still covered 74% of isolated IPD serotypes, emphasizing that PPSV23 should be part of any vaccination strategy until higher-valent pneumococcal conjugate vaccines become available [30].

Strengths and limitations

The findings reported here shed new light on the disease burden of IPD in patients with both HM and SOM since the implementation of PCV in the NCIP. The population-based nature of the study with a high case load allowed for a detailed stratification of disease burden by malignancy subtype, which could be of use for policy-makers and clinicians caring for cancer patients.

A limitation of this study was that data on pneumococcal vaccine uptake were not available. We estimate that vaccine uptake was very low, because no national pneumococcal vaccination recommendations existed during the study period. In addition, pharmacy prescription data show that <1% of the Dutch elderly population ≥65 years old had received PPSV23 during the study period [31, 32] studies among other high-risk patient cohorts in the Netherlands have reported low pneumococcal vaccine uptake [33]. A second limitation was that the subtype of malignancy could not be identified for all IPD cases. The NKR database was only complete after 1989, precluding the linkage of IPD cases with a malignancy diagnosed earlier. As a consequence, IPD IRs stratified by subtype of malignancy may be an underestimation of the actual incidence.

In conclusion, the disease burden of IPD among cancer patients remains high, despite the indirect effects of childhood pneumococcal vaccination. In addition, there are large differences in IPD incidence between the different cancer types. This study indicates the need to prioritize vaccination for cancer patients over 50 years of age with certain hematological malignancies (MM, NHL, CLL), pancreatic cancer, lung cancer, and liver cancer.

Funding

Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethical considerations

For this study, a waiver for medical ethical approval was granted by the Medical Ethics Committee of the Amsterdam UMC–Location AMC (reference number: W19_467#19.540).

Conflict of interest

None of the authors report a conflict of interest.

Author contributions

HMGG, JH, and AG conceived the study. HMGG, MK, JH, NS, and AG contributed to the study protocol. LS and MK performed and coordinated the data collection. HMGG and MK performed the data analysis. HMGG and AG wrote the first version of the manuscript. MK, LS, NS, MPG, AG, EAMS, HJK, and JH contributed to the data interpretation, reviewed the manuscript, and contributed to the writing of the final manuscript. All authors approved of the final version of the manuscript.

3

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SUPPLEMENTARY MATERIALS

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.072.

The supplementary materials not printed here include:

Table S1. Characteristic of cases in which data linkage failed compared with successfully linked cases

Table S2. Incidence rates of invasive pneumococcal disease per 100,000 patient years of follow-up (PYFU) in cancer patients stratified to type of malignancy between June 2004 and May 2016.*

Table S3. Number of IPD cases per pneumococcal capsular serotype

STROBE Statement—Checklist of items that should be included in reports of cohort studies

3