Vaccine 37 (2019) 510–515

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Long-term pneumococcal vaccine immunogenicity following allogeneic hematopoietic stem cell transplantation

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ARTICLE INFO

Article history:
Received 7 July 2018
Received in revised form 15 November 2018
Accepted 19 November 2018
Available online 27 November 2018

Keywords:
Hematopoietic stem cell transplantation
Allogeneic
Invasive pneumococcal disease
Pneumococcal vaccination
PCV13
PPSV23

ABSTRACT

Infection with *Streptococcus pneumoniae* is a life-threatening, but vaccine preventable complication in patients with allogeneic hematopoietic stem cell transplantation (allo-HSCT). The international consensus on post allo-HSCT immunization schedules, starting 3–6 months after HSCT, focuses on short-term immunogenicity while long-term immunogenicity is not well characterized. The current Dutch immunization schedule, which starts at 12 months post allo-HSCT, was developed as a result of concerns on the coverage of long-term immunogenicity in international guidelines. We recently encountered two cases of allo-HSCT recipients who developed invasive pneumococcal disease (IPD) despite adequate revaccinations, which led us to question the immunogenicity of pneumococcal vaccinations in this patient group, and whether the currently existing vaccination schedules are appropriate. We included allo-HSCT recipients, vaccinated from one year after transplantation, and tested antibody responses to pneumococcal vaccination. We also performed a systematic review. Antibody concentrations were measured in 42 of 103 (41%) patients, with a response rate of 85% to PCV13 and 62% to PPSV23-unique serotypes. In six relevant studies, protection rates varied between 64 and 98%. Antibody responses in early and late vaccination schedules were similar, but adequate antibody responses were maintained better after late vaccination. Therefore, we propose a vaccination schedule that combines the advantages of early and late vaccination. This new schedule has been introduced since March 2018 in the two academic hospitals in Amsterdam, The Netherlands.

1. Introduction

Streptococcus pneumoniae is the most important cause of community acquired bacteraemia, pneumonia and meningitis in the general population [1]. Due to being immunocompromised, particularly when graft-versus-host-disease (GvHD) is present, a condition that is both associated with hyposplenia and prolonged immunosuppressive treatment, allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients are at risk to develop invasive pneumococcal disease (IPD) [2–6]. Compared to the general population, studies have shown a 50-fold increased risk of contracting IPD in allo-HSCT recipients [7]. IPD is a serious cause of morbidity and mortality in these patients, affecting 4–20% during the first 100 days after transplantation, with a mortality rate of 25–30% [2,4,5,7,8].

An essential strategy to prevent IPD after allo-HSCT is vaccination. Vaccination is recommended for all allo-HSCT recipients by international guidelines, such as those of the Centers for Disease Control and Prevention (CDC) and the European Group for Blood and Marrow Transplantation (EBMT) (Table 1) [9]. The Academic Medical Center (AMC) mostly applies the consensus post allo-HSCT immunization schedule as proposed by the society of adult hematology-oncology in the Netherlands (HOVON). The consensus is largely based on international guidelines, but also on expert opinion (Table 1). To date, an international consensus exists on post allo-HSCT immunization schedules. However, this consensus primarily focuses on short-term and not on long-term immunogenicity. Immune reconstitution following allo-HSCT, in particular T-cell construction, is generally slow, and patients receive

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https://doi.org/10.1016/j.vaccine.2018.11.053
0264-410X/

Table 1
Pneumococcal immunization schedules.

	Time after allo-HSCT					
	First PCV13	*Second PCV13*	*Third PCV13*	*Fourth PCV13*	*PPSV23*	*Repeated PPSV23*
CDC and EBMT guideline	3–6 mo	4–7 mo	5–8 mo	n/a	≥12 mo[*]/[**]	n/a
AMC/VUmc guideline	12 mo	13 mo	14 mo	n/a	18 mo	Every 5 years
Recommended international guideline	4–6 mo[***]	5–7 mo	6–8 mo	12–14 mo	14–16 mo	n/a

Abbreviations: mo, months; n/a, not applicable.
[*] If there is no GvHD; if there is GvHD substitute PCV13 for PPSV23.
[**] If the patient is immunocompromised after five years, give an additional dose of PPSV23.
[***] If there is no use of immunosuppression for more than 1 month or a prednisolone doses <10 mg per day.

immunosuppressants to prevent GvHD over considerable time periods. Therefore, and in contrast to the CDC and EBMT guidelines, which recommend to start vaccinations 3–6 months post allo-HSCT, the Dutch immunization schedule advises not to start until 1 year after allo-HSCT (Table 1).

Existing data on the immunogenicity and efficacy of pneumococcal vaccines in this patient group, especially on longer term, are very limited. The currently available vaccines against IPD are the conjugate vaccines (PCV7, 10 and 13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23). PCV13 covers the 13 most prevalent serotypes that cause IPD and elicits a strong T-cell dependent immune response resulting in long-lasting memory [10–13]. By contrast, PPSV23, covering 23 serotypes, induces a T-cell independent immune response without the development of long-lasting memory [14,15]. Sequential vaccination of PCV13, followed by PPSV23, increases the response rate to PCV13 serotypes and broadens the narrow spectrum of PCV13 [14]. In the current Dutch immunization schedule total of three doses of PCV13 followed by a single vaccination with PPSV23 is recommended (Table 1).

We recently encountered two cases of IPD after allo-HSCT, despite adequate revaccinations; one of whom nearly died as a result of severe pneumococcal meningitis (Supplementary File 1). These cases prompted us to re-evaluate the level of long-term immunogenicity of pneumococcal vaccinations in this patient group. In addition, we investigated whether better guidance is needed regarding the measurement of post-vaccination antibody responses and which scientific data underlie various immunization schedules. The main aims of our study were to define the optimal timing of post allo-HSCT pneumococcal revaccinations, and to assess the need for post-vaccination antibody measurements, based on analysis of our own data and on existing literature.

2. Methods

2.1. Study setting and definition of IPD

All patients who received post allo-HSCT immunizations at the AMC between January 2009–2017 were included in this study. Under the existing immunization schedule (Table 1), it is advised to start vaccinations in allo-HSCT recipients 1 year after transplantation, on the condition that patients are not treated with immunosuppressive medication other than prednisolone in a dose lower than 10 mg/day at the moment of vaccination. During the first year after transplantation and until the completion of vaccinations, patients routinely receive trimethoprim/sulfamethoxazole as antimicrobial prophylaxis against IPD. The reason for choosing this prophylaxis is that resistance against trimethoprim/sulfamethoxazole is very low in the Netherlands. Therefore, trimethoprim/sulfamethoxazole is used as prophylaxis for both pneumococcal infection and pneumocystis pneumonia. IPD was defined as an infection confirmed by isolation of *S. pneumoniae* from a normally sterile site. Early IPD was defined as any episode <1 year and late IPD as ≥1 year post allo-HSCT.

2.2. Data collection

An electronic hospital database was used to obtain demographic and clinical information. Data were collected on underlying medical conditions, transplant type, post-transplant care, occurrence of GvHD, pneumococcal vaccinations, and post-vaccination antibody concentration measurements.

2.3. Immunogenicity assessment

Post-vaccination concentrations were measured 4–6 weeks after the final (PPSV23) vaccination. Serotype-specific antibody concentrations were determined using Luminex 23-plex technology (Luminex Corporation, USA), in which responses to all serotypes of PCV13 and PPSV23 were evaluated separately [16]. The used standard was calibrated against the 007sp reference serum (NIBSC). An insufficient post immunization antibody response was defined as a concentration of <0.35 μg/mL; a sufficient response was defined as concentration between 0.35 and 1.3 μg/mL. A good response was defined as a concentration of ≥1.35 μg/mL. The 0.35 μg/mL cut-off was based on the internationally accepted minimal threshold for vaccination response, [17] and the 1.3 μg/mL cut-off was based on a commonly applied threshold defining an immune response as adequate [18].

2.4. Literature review

We performed a literature search in PubMed and Cochrane database on December 1, 2017 (Supplementary File 2). ACL and MvA independently screened articles retrieved from the above databases. Studies were included if they met the following inclusion criteria: (1) The study included adult subjects after allo-HSCT; (2) Patients received pneumococcal vaccines; (3) Immunogenicity was measured as outcome of interest. No language restrictions were applied. We excluded paediatric studies and studies on autologous HSCT.

3. Results

3.1. Study subjects

A total of 103 patients were included in the study (52 males and 51 females) with a median age at the time of allo-HSCT of 49 (16–68) years. Patient characteristics are given in Table 2. In 74 patients (72%), acute leukemia (AML/ALL) had been the primary diagnosis. GvHD had been diagnosed in 70 (68%) patients. All these patients suffered from chronic GvHD. The median time period between allo-HSCT and pneumococcal vaccination was 609 days (range 365–4932 days); 9/75 (12%) patients were vaccinated exactly

Table 2
Allo-HSCT patient characteristics.

Variables	Cases (*n = 103*)
Age at transplantation (range)	
Mean age in years	50 (16–68)
Sex (%)	
Male	52/103 (50)
Female	51/103 (50)
Underlying condition (%)	
Acute leukemia	74/103 (72)
Other	29/103 (28)
HSCT donor[a] (%)	
MUD	49/103 (48)
SIB	44/103 (43)
CB	8/103 (8)
Comorbidities (%)	
GvHD	70/103 (68)
Post-transplant care (%)	
Prednison[b]	15/103 (15)
Antibiotics	38/103 (37)
Antibody concentration measurements (%)	
No	61/103 (59)
Yes	42/103 (41)

Abbreviations: MUD, match unrelated donor; SIB, sibling; CB, cord blood.
[a] Both myeloablative (MA) and non-myeloablative (RIST). In one patient, the transplant type was not described in the dossier.
[b] More than 10 mg a day or more than 700 mg in 2 weeks.

1 year after allo-HSCT. Ninety-two of 103 (89%) allo-HSCT recipients were fully vaccinated according to the MATCH protocol. Of the other eleven patients, seven had an unknown vaccination schedule, one had received an abbreviated schedule, and three had not yet received their vaccinations. Data on time intervals to revaccination were lacking for 28/103 (27%) patients. Among the remaining 75 (73%) patients, the median time period to pneumococcal vaccination for patients suffering from GvHD (n = 54; 72%) was 731 days, as compared to 426 days for patients without GvHD (n = 21; 28%). Post HSCT pneumococcal concentration was not correlated with the presence of GvHD before vaccination (r = -0.034, p = 0.83). In addition, 15 (15%) patients were using prednisone and 38 (37%) patients were using antibiotics at the time of vaccination, but none of them developed a pneumococcal infection.

3.2. Serotype-specific antibody assessment

Blood samples for measurement of antibody concentrations were collected in 39/103 (38%) patients. PCV13 serotype specific antibody responses were measured in 39 (38%) patients, while PPSV23 serotype specific antibody responses, measured one year after the PCV13 responses, were available for 30 (29%) patients. Good antibody responses against PCV13 serotypes varied from a minimum of 30/39 (77%) for serotype 5 to a maximum of 37/39 (95%) for serotype 19F (Fig. 1). Across all PCV13 serotypes, sufficient seroprotection as defined earlier was demonstrated in 33/39 (85%) patients.

Fig. 2 shows the results obtained for the 10 additional PPSV23 serotypes that are not covered by PCV13. The response to several of these PPSV23 serotypes was found to be lower compared to serotypes included in PCV13. The lowest responses were observed for serotypes 11 (12/30, 60%) and 12F (7/30, 23%), respectively.

3.3. IPD episodes

Of 103 included patients, seven (7%) developed microbiologically confirmed IPD, of whom three (43%) had early IPD and four (57%) had late IPD. The median time to the occurrence of early

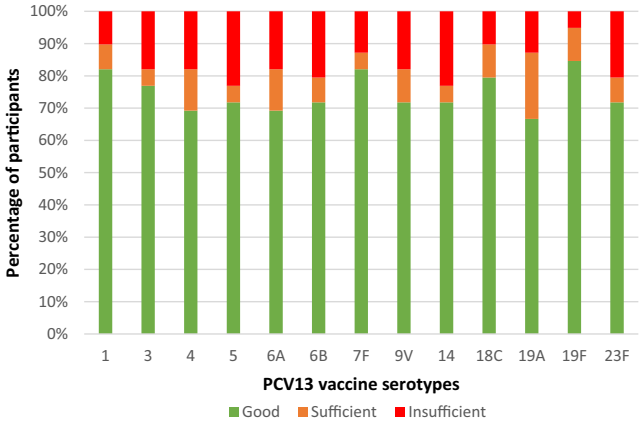

Fig. 1. Protection against PCV13 serotypes (n = 39) following the MATCH protocol. Post-vaccination antibody concentrations were measured 4–6 weeks after the final (PPSV23) vaccination.

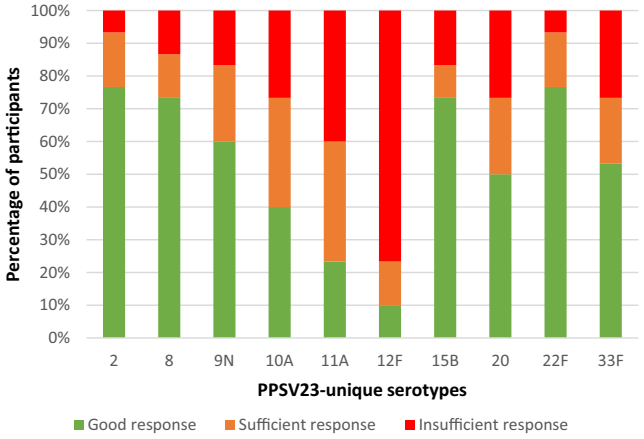

Fig. 2. Protection against PPSV23 serotypes not included in PCV13 (n = 30) following the MATCH protocol. Post-vaccination antibody concentrations were measured 4–6 weeks after the final (PPSV23) vaccination.

IPD was 6 (range 4–8) months and of late IPD 56 (range 12–91) months post allo-HSCT. All pneumococcal infections within the first year occurred despite antimicrobial prophylaxis during this period. In addition to these 7 patients with confirmed IPD, 14/103 (14%) patients were diagnosed with pneumonia without microbial testing results, some of which probably also caused by *S. pneumoniae* as this is the most common cause of community-acquired pneumonia. Taken together, an estimated 7–21/103 (7–20%) of patients developed IPD.

3.4. Literature review

We performed a literature search, initially yielding 100 articles, narrowed down to six relevant studies after exclusion criteria were applied (Table 3). Among the included studies, four described the serologic response to pneumococcal vaccinations in allo-HSCT recipients, and two studies investigated the immunogenicity of early versus late vaccination after allo-HSCT.

Among the four studies on post allo-HSCT serologic response rates, protection varied from 64 to 99%, depending on the vaccine types, time intervals between allo-HSCT and revaccination, and the used definition of the correlate of protection [12,15,19]. Two studies assessed the effect of early versus late post allo-HSCT vaccination. Both found similar antibody responses after early (3 months)

Table 3
Literature overview on immunogenicity in allo-HSCT recipients.

Study	Year	Design	Study Participants, No.		Vaccine Regimen	Immunization schedule after HSCT	Vaccine-Antibody Measurement Interval	Primary Outcome	Protection Rate, %	Cut-off Values, μg/mL
			Patients	Controls						
Molrine et al. [13]	2003	Randomized controlled trial	30	35	PCV7	3x PCV7 at 3, 6 and 12 mo	4 wk	Seroprotection	64	PVL ≥ 0.50
Meerveld-Eggink et al. [21]	2009	Clinical trial	26	n/a	PCV7 PPSV23	2x PCV13 (1 yr + 2 wk and + 8 wk)1x PPSV23 (+ 26 wk)	NR	Seroprotection	85	Protection against ≥ 3 serotypes
Cordonnier et al. [22]	2009	Randomized clinical trial (multicenter)	158	n/a	PCV7 PPSV23	3x PCV7 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Early vs. late post allo-HSCT immunization	*1.* 79 (PCV7) *2.* 82 (PCV7)	PVL ≥ 0.15
Cordonnier et al.[a] [15]	2010	Randomized clinical trial (multicenter)	101	n/a	PCV7 PPSV23	3x PCV7 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Early vs. late post allo-HSCT immunization	*1.* 88 (PPSV23) *2.* 69 (PPSV23)	PVL ≥ 0.15
Cordonnier et al.[a] [23]	2015	Randomized prospective trial (multicenter)	30	n/a	PCV7 PPSV23	3x PCV7 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Seroprotection	66	PVL ≥ 0.15
Cordonnier et al. [6]	2015	Open-label clinical trial (multicenter)	251	n/a	PCV13 PPSV23	3x PCV13 (3 or 6 mo) 1x PPSV23 (12 or 18 mo)	1 mo	Seroprotection	After dose 3: 89–98 After dose 4: 83–99	PVL ≥ 0.35

Abbreviations: NR, not reported; PVL, post-vaccination level; mo, months, wk, weeks; yr, years; n/a, not applicable.
[a] Surviving patients of the cohort of Cordonnier et al (2009).

and late (9 months) vaccination. These responses were however not maintained: two years after allo-HSCT, 26/44 (59%) early vaccinated patients still had adequate antibody concentrations compared to 35/42 (84%) later vaccinated patients ($p = 0.013$) [14,20]. Two studies by Cordonnier [14,20], derived from the same patient cohort, assessed the effect of early versus late post allo-HSCT vaccination. Both found similar results.

4. Discussion

4.1. Summary of main findings

Allo-HSCT recipients mounted sufficient immune responses to PCV13 vaccination, with an overall protection rate of 85%; provided that these patients were vaccinated >1 year after allo-HSCT and were not treated with immunosuppressive medication at the time of vaccination. These results were comparable to the results obtained from our literature search. The finding that 15% of allo-HSCT recipients did not develop adequate antibody responses underscores the importance of routine post-vaccination antibody measurements, to identify patients without protection by vaccination. In addition, regular follow-up concentration measurements are important, because immunity can disappear more quickly than in the healthy population. It should be noted that vaccination confers protection against the 23 most prevalent serotypes of around 90 distinct pneumococcal serotypes that have been identified to date. As a consequence, even in the presence of adequate post-vaccination immunity, patients could still develop IPD caused by a non-vaccine serotype. Furthermore, since the measurement of antibodies is a derivative of protection; theoretically, IPD by a vaccine strain could still occur. The clinical vignette illustrates that both unrecognised antibody decline and vulnerability to non-vaccine strain pneumococcal serotypes pose a real and possibly mortal risk to this group of patients. Based on the literature, antibody decline seems to occur at a faster pace when patients are vaccinated relatively early (3 months) after allo-HSCT. Because the initial antibody response to vaccination was similar in early vs. late vaccinated patients, early vaccination followed by a booster vaccination strategy from 1 year post allo-HSCT may therefore be an attractive option. The efficacy and safety of such an approach does however require confirmation through prospective studies.

4.2. Early vs. late vaccination

The optimal time-interval between allo-HSCT and the start of routine vaccinations with PCV13 is controversial. Early immunization offers an earlier protection and may avoid life-threatening IPD shortly after allo-HSCT, but is also associated with a lower antibody response and faster decline of antibody concentrations during the second year after transplantation. By contrast, late immunization offers better chances of achieving adequate antibody concentrations and a better long-lasting immunity, but the price is inadequate protection in the vulnerable time period early after transplantation [14]. The high clinical impact of IPD is emphasized by our finding of a 7% rate of confirmed IPD, possibly increasing to 20% when unconfirmed cases were included, reflecting a considerable underestimation in clinical practice.

The estimated incidence of IPD in allo-HSCT recipients is 347 infections per 100,000, compared to an incidence of 7 per 100,000 persons in the general population [21]. Almost half of the IPD cases occurred during the first year after transplantation, despite the fact that patients still used antimicrobial prophylaxis, which underscores the importance of optimal protection in this time period [4,22,23]. The clinical impact of early IPD is high: one study reported a mortality of 2/7 (29%) in patients with early

IPD, versus 8/44 (18%) in patients with late IPD [2]. These findings suggest that the best vaccination strategy would be to start earlier rather than later after allo-HSCT. Therefore, we propose a vaccination schedule that combines the advantages of early and late vaccination, in which the first PCV13 is administered 4–6 months post allo-HSCT, followed by two PCV13 booster vaccinations with a 1-month interval, then a fourth PCV13 vaccination 6 months after the previous PCV13 dose, and subsequently one PPSV23 vaccination 2 months later (Table 1). The theoretical groundwork for this schedule is supported by the recent study of Cordonnier et al. that provides evidence of a higher antibody response after the administration of an additional fourth PCV13 vaccination [15]. Based on the results of our serological data in combination with the findings from the literature review, we hypothesize that this fourth vaccination would be most effective when administered ≥6 months after the previous PCV13 vaccination. The postponed timing of this last PCV13 vaccination will elicit a late booster response, when immune reconstitution has evolved further, leading to a stronger and longer-lasting immune response. However, this regimen needs to be evaluated in clinical practice.

Late IPD was often associated with GvHD [2,24]. It is important to note that vaccinations are often delayed when allo-HSCT recipients develop GvHD, firstly because this complication is treated with immunosuppressive medication and secondly because of fear that vaccinations may trigger or aggravate GvHD. The immunosuppressed state associated with GvHD renders patients exceptionally vulnerable to IPD, which makes adequate protection all the more important. In our study, 70 (68%) patients were diagnosed with GvHD, with a median time of around 2 years between transplantation and pneumococcal vaccination. Another study reported a median time of 1.3 years, in which only 35% of patients had started the vaccination schedule at 1 year after allo-HSCT, for similar reasons as in our study [19]. In this context, we advise to vaccinate patients with GvHD. Furthermore, it has been suggested that hyporesponsiveness to PPSV23 can occur after repeated vaccinations at short time intervals [25]. Therefore, more research is required to determine dynamics and protective levels of anti-serotype antibodies at regular time-intervals in this patient population.

4.3. PCV13 vs. PPSV23

We found lower protection rates against PPSV23 serotypes compared to PCV13 serotypes, with very low protection against PPSV23 serotype 12F. Although this finding may be an intrinsic flaw in the diagnostic panel, a more logical explanation is that PPSV23 is indeed less immunogenic compared to PCV13, which is supported by previous studies [12–15,26]. We hypothesize that in a setting of nascent immunity after allo-HSCT, T-cell independent vaccines such as PPSV23 do not work that well in this patient population, similar to the situation in small children [11]. The main advantages of PPSV23 vaccination are that more serotypes are included than in PCV13, and that this vaccination is thought to act as a booster of the immune response to the PCV13 serotypes [27].

4.4. Antibody measurements

In our study, antibody concentration measurements were only performed in 39/103 (38%) patients. Reasons for this rate of attrition are unknown. Assuming that this is rule rather than exception in clinical practice, increased awareness among health care providers about the risks of insufficient or fading protection is needed, which was also emphasized in recent work of Cordonnier et al., who stressed the importance of routine individual assessments of vaccine serotype antibodies to identify and possibly revaccinate non-responders [28]. We have therefore included specific time intervals for antibody measurements in our new guideline.

4.5. Correlates of protection

In the international literature, there is no consensus on the exact correlates of protection, nor on the required number of reactive serotypes in response to vaccination. For allo-HSCT recipients, reported cut-off concentrations differ between an absolute increase to ≥0.15–1.3 μg/mL or a ≥2–4-fold increase in antibody concentrations [12,14,15,19,20,29–31]. The definition of the required number of reactive serotypes varies between five and eight [32]. Internationally accepted reference intervals would therefore be very useful to identify and compare patients with inadequate post-vaccination pneumococcal antibody responses.

5. Conclusion

In conclusion, although few studies have been performed in which the optimal time intervals of pneumococcal immunizations are determined, we propose a uniform immunization schedule for allo-HSCT recipients, which combines the advantages of early and late vaccination (Table 1). We recommend starting the immunization schedule 4–6 months following allo-HSCT with three early PCV13 vaccinations, followed by a late PCV13 booster vaccination and a vaccination with PPSV23. The evidence base of our vaccination recommendation is weak at best. However, this also applies to the currently accepted guidelines [33]. Clearly, more research on this topic is needed. That none withstanding, we feel that this recommendation is a more logical extrapolation from the limited evidence to date. We have introduced this vaccination schedule in two academic hospitals in Amsterdam, The Netherlands, and we will evaluate the immunogenicity of this schedule prospectively.

Acknowledgments

We thank our patients who visited the AMC Travel Clinic for their pneumococcal vaccinations between 2009 and 2017.

Author contributions

ACL and AG conceived the paper. ACL performed the data extraction. ACL and MvA performed the literature search. ACL drafted the first version of the manuscript. ACL, AG, BM, EMMvL, MDH, MvA, MPG, and SZ contributed to various aspects of data collection, data analysis, writing, and endorsed the final version of the manuscript.

Potential conflict of interests

None of the authors has any conflicts to report.

Funding

No funding received.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.053.

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