1.1. Overview of reports of Adverse Events after Prevenar13® administered to a selected population of elderly

Introduction

In the period September 8, 2014 and November 1, 2014 Lareb received 140 reports, with a total of 214 possible AEFIs after vaccination with Prevenar13®. A report may contain multiple AEFIs. Of these reports, we noted a large number of reports of injection site inflammation with an unexpected long latency (time to onset). Lareb reported this signal to the Medicines Evaluation Board (MEB) [1]. These reports came from a selected group of elderly who participated in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA).

In the autumn of 2008 CAPiTA was initiated [2,3]. It was a double-blind, randomized, placebo-controlled vaccine efficacy trial using Prevenar13®. Placebo consisted of the vaccine minus pneumococcal antigens, and was basically an adjuvant containing salt solution. The study population was 84,496 persons aged 65 and above. The study showed that vaccination with Prevenar13® protected the vaccinees against pneumonia and that the safety was acceptable [4]. Because of these results, it was decided that placebo recipients (42,000) would be offered the active vaccine. These placebo recipients were invited for a vaccination. Through attrition (7.1% 3,500 deaths), other loss to follow-up (5.5%) and refusal of the vaccination, 21,000 people aged 70 and above were vaccinated between September 2014 and February 2015. A single batch of Prevenar13® was used (batch number unknown) in this catch-up campaign.

As the vaccine is now registered for vaccination in the elderly, Adverse Events Following Immunisation (AEFI) from the vaccine administered, were collected through spontaneous reporting. Vaccinees were encouraged to report possible AEFIs to the Netherlands Pharmacovigilance Centre Lareb. After vaccination they received a leaflet with information about the importance of reporting AEFIs as well as the website and telephone number where to report.

This overview gives a complete overview of the reports Lareb received in the period September 2014 and February 2015.

Reports

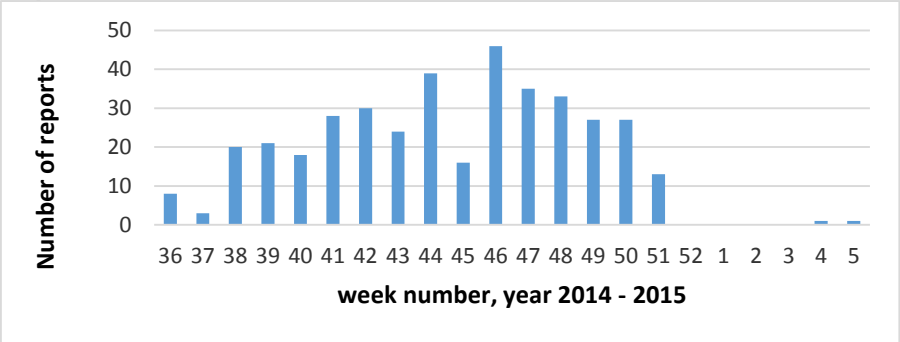

Figure 1 Numbers of reports per vaccination week

In the period September 2014 and February 2015 Lareb received in 390 spontaneous reports (1.3% of the vaccinees), with a total of 616 possible AEFI's. Lareb received most reports after vaccinations administered in week 38 until week 51, see figure 1.

Most reports of possible AEFIs are of vaccinees in the age group 71 - 79 years. Also vaccinees above 80 years of age or their relatives reported possible AEFI's after Prevenar13® to Lareb. More than 70% of the reports were of AEFI's of females (70.7%).

More than 71% of the reports were recorded by telephone by an assessor of Lareb. The remainders used the reporting form on the Lareb website. Lareb received 97% of the reports of vaccinees themselves or their relatives, only 3% were reports of health care professionals.

Serious Reports

Table 1 Serious reports

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 183143, F, 76 year, Pharmacist	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Prevenar13®), prophylaxis	barnidipine, bisoprolol, acetylsalicylic acid, simvastatine met ezetimib, perindopril;	cerebral haemorrhage	6 days not applicable death
B 186843, F, 75 year, Consumer	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Prevenar13®), prophylaxis		cardiac arrhythmia	19hours not applicable recovered
C 186913, F 70 year, specialist doctor	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Prevenar13®) prophylaxis		decreased oxygen saturation	5 day, not applicable, recovered
D 187057, M 72 year, Consumer	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Prevenar13®) prophylaxis	rosuvastatin, acetylsalicylic acid;	Myocarditis/pericarditis;	7 days, not applicable, not recovered
E 189064, F 73 year, Consumer	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Prevenar13®) prophylaxis	tiotropium bromiden;	myocardial infarct; injection site inflammation	7 hours not applicable recovering

According to the international CIOMS criteria 5 reports were serious (1.3%), see table 1.

Patient A: A female of 76 years of age developed 6 days after Prevenar13®-vaccination a cerebral haemorrhage. In the evening, during playing bridge, suddenly, totally unexpected she became unwell and was brought to the hospital by ambulance. She was admitted to the hospital. On the CT scan there was a large cerebral haemorrhage. During the night the patient had several cerebral bleedings. The patient died next day. The medical history of the patient is unknown.

Patient B: A female of 75 years of age developed 19 hours after Prevenar13®-vaccination cardiac arrhythmia and was admitted to the hospital. The symptoms were treated with medication not further specified. She recovered and could leave the hospital the same day. The medical history indicates that the patient had cardiac arrhythmia in 2011, which is treated with medication. Since 2011 the patient

had no episodes of cardiac arrhythmia. Concomitant medication was medication for cardiac arrhythmia.

Patient C: A female of 70 years of age, started 1 day after Prevenar13®-vaccination with coughing. Five days after the vaccination she had dyspnea. She was admitted to the hospital. In the hospital she had low oxygen saturation and increased CRP. On the chest X-ray were no abnormalities. The patient was treated with antibiotics and could leave the hospital after 4 days. She recovered after an unknown period. The medical history indicates that the patient has idiopathic pulmonary arterial hypertension and diastolic heart failure

Patient D: A male of 72 years of age, with a pacemaker insertion and coronary stent insertion, developed 7 days after Prevenar13®-vaccination myocarditis/pericarditis and cardiac failure. An echo scan suggested that the patient had a myocarditis/pericarditis. The patient stayed 4 weeks in the hospital. On the day of reporting, the patient was not recovered.

Patient E: A female of 73 years of age developed 7 hours after Prevenar13®-vaccination injection site inflammation and a myocardial infarct. She was vaccinated in the morning, and after about 7 hours (at dinner time) she suddenly fell away. Ambulance took her to the hospital where a myocardial infarct was diagnosed. During the day also injection site inflammation developed (pain, redness 3x3 cm). The patient recovered. She recovered after a not further specified period. Concomitant medication was tiotropium bromide. The medical history indicates that the patient had COPD.

A report can contain multiple AEFI's. 309 Reports of Prevenar13® contain a total of 616 AEFI's (1.6 AEFI per report). AEFI's are coded according to the Medical Dictionary for Regulatory Activities (MEDRA) and classified by System Organ Class (SOC), see table 2. Almost 50% of the AEFI's are General disorders (administration site conditions), local reaction at the injection site. Other frequently reported AEFI's are Systemic General disorders (pyrexia 44x, malaise 8x, fatigue 8x) , Gastro-intestinal disorders (diarrhoea 12x, nausea 16x) and Nervous disorders (headache 28x).

The most reported local injection site reaction is injection site inflammation. Injection site inflammation is a well-known AEFI and is defined by Lareb as at least two symptoms of inflammation out of swelling, redness, warmth, pain or disturbance of function (functio laesa) of the arm. If the inflammation extended over the adjacent joint or if the swelling is around the vaccinated limb it is coded as extensive swelling of the vaccinated limb (ELS).

Table 2 Overview reported AEFI's after Prevenar13®-vaccination per system organ class (SOC). The SOC General disorder has been divided based on the lower level term (LLT) in General disorder (administration site conditions) and general disorder (systemic).

SOC	Number	Perc.
Blood and lymphatic system disorders	2	0,3%
Cardiac disorder	5	0,8%
Ear and labyrinth disorders	3	0,5%
Eye disorders	3	0,5%
Gastrointestinal disorders	44	7,1%
General disorders (administration site conditions)	294	47,7%
General disorders (systemic)	84	13,6%
Infections and infestations	25	4,1%
Investigations	11	1,8%
Metabolism and nutrition disorders	1	0,2%
Musculoskeletal and connective tissue disorders	39	6,3%
Nervous system disorders	44	7,1%
Reproductive system and breast disorders	1	0,2%
Respiratory, thoracic and mediastinal disorders	21	3,4%
Skin and subcutaneous tissue disorders	37	6,0%

Vascular disorders	2	0,3%
Total	616	100,0%

Of the 294 reports in the SOC General disorder (administration site conditions), 216 reports were coded as injection site inflammation according to criteria described above and 20 reports as ELS. In addition there were 58 reports of other injection site reaction related AEFIs reported as single symptoms. For an overview of the number and type of these AEFIs, see table 3.

Table 3: Overview of injection site reaction related AEFIs

Reported reactions (MedDRA® Lower Level Term)	Number
Extensive swelling of vaccinated limb	20
Injected limb mobility decreased	1
Injection site cellulitis	3
Injection site erythema	8
Injection site haematoma	3
Injection site inflammation	216
Injection site movement impairment	1
Injection site oedema	1
Injection site pain	33
Injection site pruritus	2
Injection site rash	2
Injection site reaction	1
Injection site swelling	1
Injection site vesicles	1
Vaccination site pruritus	1
total	294

Figure 2 shows the time to onset (latency) in days for injection site inflammation and ELS. Eighty persons (34%) reported a time to onset of 2 day or shorter and 156 persons (66%) reported a time to onset of 4-7 days.

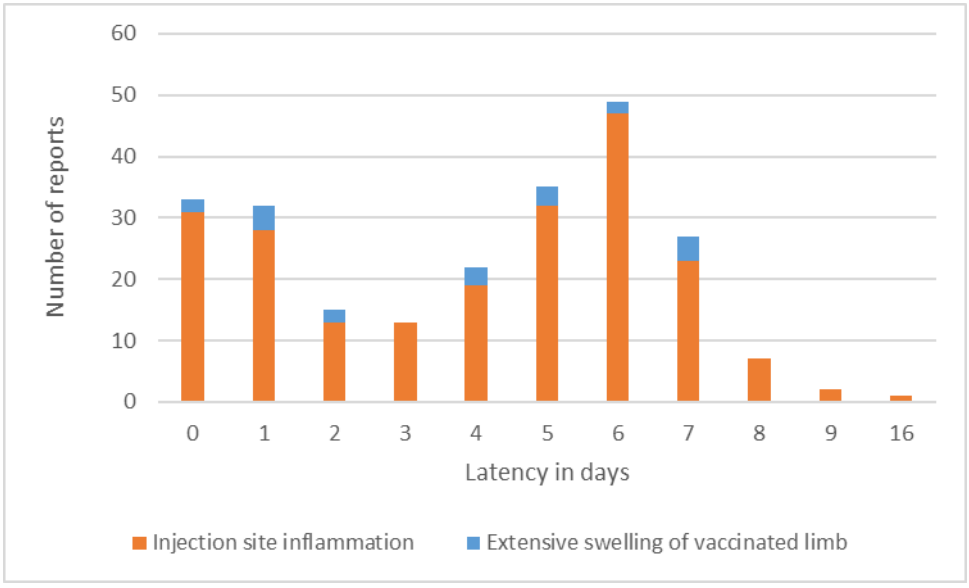

Figure 2 Time to onset in days

The duration of the injection site inflammation is unknown as most of the reports were made at the moment that the injection site inflammation was still present. A few persons reported a biphasic duration of the local reactions. First injection site pain or injection site redness with a short time to onset, then (partial) recovery followed by an injection site inflammation after 4-7 days.

Other sources of information

SmPC
Prevenar13® is an aluminum-phosphate adjuvanted CRM_{197} protein conjugated 13-valent pneumococcal vaccine. The SmPC of Prevenar13® describes injection site erythema; induration/swelling 2.5 cm -7 cm or vaccination pain/tenderness, including impaired movement as a very common AEFI in adults 18 to 39 years. According to the SmPC report adults of 65 years of age or older have fewer AEFIs compared with adults 18 to 29 years [5].

Literature
In a study after immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine (PCV13) in people aged over 70 years of age compared with 23-valent pneumococcal polysaccharide vaccine (PPSV23), less local reactions were reported after PCV13 than after PPSV23. In total 56.5% of PCV13 group had some form of local reaction. In this study redness and swelling were code as absent (< 2,5 cm), mild (≥ 2,5 cm and ≤ 5 cm), moderate (> 5 cm and ≤ 10 cm) and severe (> 10 cm). Mild redness was reported by 9.5%, moderate redness by 4.7%, and severe redness by 1.7% of the vaccinees. Mild swelling was reported by 8.9%, moderate swelling by 4% and severe swelling by 0% of the vaccinees. Injection site pain and limitation of the arm movement was reported by 51.7% respectively 10.5% of the vaccinees. Furthermore, there were more reports of fatigue, rash, new or worsening myalgia, and other systemic reactions following PPSV23 than after PCV13 [6].

In the CapiTa study the frequencies of prespecified local reactions and systemic events reported by the 13-valent pneumococcal conjugate vaccine (PCV13) group were higher than in the placebo group [3]. Of the PCV13 group 4.9% versus 1.2% of the placebo group reported any redness (redness ≥ 2.5 cm), 6.8% versus 1.2% reported any swelling (swelling ≥ 2.5 cm), 36.1% versus 6.1% any pain and 14.1% versus 3.2% any limitation of the arm [7].

In an open-label study (Phase 3 October 2007 – December 2007) after the immunogenicity and safety of PVC13 administered to Japanese adults aged ≥ 50 years any redness, moderate redness and moderate swelling were significant reported lower in the age group 50-64 years compared to the age ≥ 65 years. In the age group ≥ 65 years a statistically higher ($P<0.05$) percentage of subjects in the Japanese study reported any local reaction, redness and limitation of arm movements compared with the European study [8]. The immune response in the age group 50-64 years were lower than in the group ≥ 65 years in the Japanese study. This was in contrast to observations in US and EU, which showed generally higher immune responses in younger subjects than in older subjects. In the Japanese study, baseline levels of diphtheria antitoxin antibodies were significantly lower in the age group 50-64 years, as were the majority of pneumococcal responses compared with the ≥ 65 years.

Discussion
Between September 2014 and February 2015 received Lareb in a relative short period 390 reports with in total of 616 adverse events following vaccination Prevenar13®. The reports come from a selected group of 21,000 people of 70 years or above, who received during the CAPiTA study a placebo and after the study a Prevenar13®-vaccination. The total number of reports of this selected group is relatively high. In the vast majority the vaccinees reported themselves and only few reports came from health care professionals. Since most vaccinees were still under the assumption that this vaccination campaign was part of the study, they were highly motivated to report all AEFI to the Netherlands Pharmacovigilance Centre Lareb. This combined with the ability and the encouragement (giving a leaflet with telephone number after the vaccination) to report reports by telephone to Lareb, could be an explanation for the large number of relatively mild AEFI's.

Injection site reactions are the most common AEFI reported to the Netherlands Pharmacovigilance Centre Lareb. Injection site reactions usually manifests as redness, warmth and swelling often in

combination with pain and an itching at the injection site. The time to onset is usual 2 hours to 2 days and the duration of the injection site reaction is a few days [9].The large number of local reactions that we found is consistent with previous efficacy trials of Prevenar13® [3,6,7]. Also the long time to onset (4-7 days) of injection site inflammation after Prevenar13® in this selected population is striking and confirms earlier signals in smaller population studied before [4]. Some persons reported during the telephone conversation a biphasic duration of the injections site reactions.

The late time to onset of the reported reaction suggests that a secondary cause of inflammation may be induced by the vaccine. It is conceivable that prior immunity to a vaccine constituent may be boostered from immunological memory. Both the polysaccharide antigens and the CRM_{197}-diphtheria toxin (carrier protein) may in theory induce such response. As all vaccinees reported here had received an aluminum-adjuvant as a placebo some years before, we cannot exclude that this may have contributed to the remarkable pattern of injection site reactions.

It is likely that the vaccines, which are used in 2014 belong to another batch than the vaccines used during the study. A batch problem related to the single batch used in the campaign should also be taken in consideration.

Conclusion

In addition to the previously reported signal of many reports of injection site inflammation and the late time to onset of the injection site inflammation, in this overview no other signals were found.

It is advised to further investigate why this atypical time to onset is seen in this population of elderly people.

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This overview was published in September 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbgmeb.nl