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Late onset of injection site reactions after vaccination with the 13-valent pneumococcal conjugate vaccine in adult study populations

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ABSTRACT

Injection site reactions (ISRs; redness, swelling and pain) commonly occur within 1–2 days after vaccination. After administration of toxoid vaccines including diphtheria toxoid, a later onset of ISRs has also been observed. As the serotype capsular polysaccharides in the 13-valent pneumococcal conjugate vaccine (PCV13) are conjugated to cross-reactive material 197 (CRM_{197}), a nontoxic variant of diphtheria toxin, the onset of ISRs over 14 days was explored in 8 adult studies with 19 cohorts. Subjects received PCV13 with aluminum phosphate ($AlPO_4$, n = 5667) or without $AlPO_4$ (n = 304); 1097 subjects received 23-valent pneumococcal polysaccharide vaccine (PPSV23). Late ISRs with onset between days 6–14 were observed in 8/8 cohorts aged ≥65 years after PCV13 with $AlPO_4$ (incidence across cohorts for redness, 2.3%-19.6%; swelling, 0.9%-10.8%; pain, 1.6%-10.0%) and in 1/1 cohort after PCV13 without $AlPO_4$ (redness 10.5%; swelling 7.5%; pain 12.3%); and in 2/4 cohorts aged 50 to 64 years after PCV13 (redness 3.1%-4.8%; swelling 1.0%-3.2%; pain 3.7%-5%). Late ISRs were not generally observed in 1/1 cohort aged 18 to 49 years after PCV13; in 2/2 cohorts aged ≥53 years after PCV13 revaccination; and in 3/3 cohorts aged ≥60 years who received PPSV23, which does not contain CRM_{197}. Post hoc analysis demonstrated numerically higher pneumococcal immune responses in subgroups with late ISRs versus those without. In conclusion, causality of late ISRs is likely multifactorial, with age and the PCV13 carrier protein CRM_{197} potentially associated. $AlPO_4$, a vaccine adjuvant, did not appear causally related. Observations do not affect the favorable risk-benefit profile of PCV13.

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Introduction

In clinical studies with the 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar 13®; Pfizer Inc, New York, NY), injection site reactions (ISRs), characterized by redness, swelling, and pain, were common, mainly mild to moderate in severity, and self-limiting.[1] The distribution of ISRs on each day over a 14-day observation period have been collected from PCV13 clinical studies but not previously published. The distribution is of interest because although ISRs commonly occur within 1 to 2 days of vaccination, a later onset of ISRs has been observed after toxoid vaccines, including tetanus toxoid, diphtheria toxoid, and acellular pertussis (containing inactivated pertussis toxin), as early as the 1970s.[2,3] Because capsular polysaccharides from serotypes in PCV13 are conjugated to a protein carrier, cross-reactive material 197 (CRM_{197}), a nontoxic variant of diphtheria toxin, the distribution of ISRs over a 14-day observation period and any association with immunogenicity were explored. In the studies reviewed,[4-13] participants received either the final formulation of PCV13, which contains aluminum phosphate ($AlPO_4$); PCV13 without $AlPO_4$; or the 23-valent pneumococcal polysaccharide vaccine (PPSV23), which does not contain the carrier protein CRM_{197}.

Results

Injection site reactions

In studies A through H,[4-13] ISRs after PCV13 and PPSV23 vaccination were mostly mild to moderate in severity, and all were self-limiting. Over the 14-day observation period, the incidence of subjects with injection site pain was highest (range across studies, 29.2%–96.7%), followed by redness (7.1%–30.5%) and swelling (6.7%–39.4%; Supplementary Table 1). On each day during the 14-day observation period, the prevalence of subjects with redness and swelling after PCV13 and PPSV23 vaccination from studies A through H is presented in Fig. 1; the daily prevalence of subjects with

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injection site pain, which in contrast to redness and swelling occurred most commonly on days 1 to 5, is presented in Supplementary Figure 1.[4-13] The incidence of ISRs within days 1 to 5 exclusively, within days 6 to 14 exclusively, and within both days 1 to 5 and days 6 to 14 is presented in Table 1 and Supplementary Table 2.

PCV13 with or without $AlPO_4$

In study A,[7] which included PPSV23-naive subjects aged ≥65 years, 1 cohort received PCV13 with $AlPO_4$ (the formulation of choice for further development), and 1 cohort received PCV13 without $AlPO_4$. ISRs on each day were generally more common in the PCV13 with $AlPO_4$ cohort. Late onset of ISRs was observed in both cohorts with and without $AlPO_4$ (Fig. 1 and Supplementary Fig. 1, study A). Some subjects recorded exclusively early ISRs on days 1 to 5, some recorded exclusively late ISRs on days 6 to 14, and some had both early and late ISRs (Table 1). Among subjects reporting ISRs after PCV13 with and without $AlPO_4$, fewer subjects reported redness within days 1 to 5 exclusively (3.8% and 0.8%, respectively) than within days 6 to 14 exclusively (19.6% and 10.5%); some subjects reported both early and late redness (2.9% and 2.1%). A similar distribution was observed for swelling, although overall swelling was less frequent than redness (Table 1). Among subjects receiving PCV13 with $AlPO_4$, more subjects had injection site pain on days 1 to 5 exclusively (21.9%) than on days 6 to 14 exclusively (8.7%); some subjects recorded pain on days 1 to 5 and 6 to 14 (13.2%). Among subjects receiving PCV13 without $AlPO_4$, fewer subjects had injection site pain on days 1 to 5 exclusively (8.2%) than on days 6 to 14 exclusively (12.3%); some subjects recorded pain on days 1 to 5 and 6 to 14 (6.6%; Supplementary Table 1).[7-11,13]

PCV13 in PPSV23-naive cohorts aged ≥65 years

In studies A through E,[7-11] which included PPSV23-naive subjects aged ≥65 years, 7 cohorts received a single dose of PCV13. In all 7 cohorts, late onset of redness, swelling, and injection site pain was observed (Fig. 1 and Supplementary Fig. 1, studies A–E). ISRs on days 6 to 14 exclusively were more common in PCV13 cohorts from studies A (South Africa; PCV13 with and without $AlPO_4$), B (Japan), and C (Japan) than in the cohorts aged ≥65 years in studies D (Mexico) and E (Europe; PCV13 administered concomitantly with and without trivalent inactive influenza vaccine). Among subjects reporting ISRs in the 7 PCV13 cohorts, the majority had either exclusively early ISRs or exclusively late ISRs; a minority had both early and late ISRs (Table 1; Supplementary Table 2). No study was performed in the United States in PPSV23-naive adults aged ≥65 years.

PCV13 in PPSV23-prevaccinated cohorts aged ≥68 years

In studies F and G,[12,13] which included sites in the United States and Europe, subjects aged ≥70 and ≥68 years, respectively, were prevaccinated with PPSV23 ≥5 or ≥3 years before receiving a single dose of PCV13. In both cohorts, late onset of injection site redness, swelling, and pain was recorded (Fig. 1 and Supplementary Fig. 1, studies F–G). The incidence of late ISRs within days 6 to 14 was lower than in PPSV23-naive cohorts in studies A through E after PCV13 vaccination (Table 1 and Supplementary Table 2).

PCV13 in PPSV23-naive cohorts aged ≤64 years

In studies B, D, and H,[4,5,8,10] which included PPSV23-naive subjects, 4 cohorts aged 50 to 64 years and 1 cohort aged 18 to 49 years received a single dose of PCV13. In 2 of the 5 cohorts aged 50 to 64 years in Japan and Mexico (studies B and D), the presence of redness, swelling (studies B and D), and pain (study

Table 1. Incidence of early and late injection site redness and swelling after PCV13 vaccination.

			Injection Site Reaction					
			Redness			Swelling		
Study[a]	Age, y	Vaccine	Days 1–5 only % (n^b/N^c)	Days 6–14 only % (n^b/N^c)	Days 1–5 and 6–14 % (n^b/N^c)	Days 1–5 only % (n^b/N^c)	Days 6–14 only % (n^b/N^c)	Days 1–5 and 6–14 % (n^b/N^c)
A	≥65	PCV13+$AlPO_4$	3.8 (9/240)	19.6 (47/240)	2.9 (7/240)	6.8 (16/237)	9.7 (23/237)	4.2 (10/237)
	≥65	PCV13−$AlPO_4$	0.8 (2/238)	10.5 (25/238)	2.1 (5/238)	1.7 (4/239)	7.5 (18/239)	0.8 (2/239)
B	50–64	PCV13	2.1 (2/97)	3.1 (3/97)	1.0 (1/97)	3.1 (3/97)	1.0 (1/97)	2.1 (2/97)
	≥65	PCV13	0.9 (1/108)	17.6 (19/108)	0.9 (1/108)	1.9 (2/108)	10.2 (11/108)	1.9 (2/108)
C	≥65	PCV13	7.1 (25/353)	16.1 (57/353)	5.1 (18/353)	7.1 (25/351)	10.8 (38/351)	3.1 (11/351)
D	50–64	PCV13	3.2 (4/124)	4.8 (6/124)	5.6 (7/124)	8.1 (10/124)	3.2 (4/124)	6.5 (8/124)
	≥65	PCV13	3.4 (4/116)	6.0 (7/116)	3.4 (4/116)	3.4 (4/116)	0.9 (1/116)	6.0 (7/116)
E	≥65	PCV13+TIV[d]	6.9 (30/437)	5.7 (25/437)	3.4 (15/437)	6.7 (29/434)	3.7 (16/434)	2.1 (9/434)
	≥65	PCV13[e]	3.3 (14/428)	4.9 (21/428)	3.3 (14/428)	3.3 (14/427)	3.5 (15/427)	2.6 (11/427)
F	≥70	PCV13[f]	2.6 (8/302)	2.3 (7/302)	4.3 (13/302)	5.0 (15/302)	1.7 (5/302)	2.3 (7/302)
G	≥68	PCV13[f]	5.8 (38/651)	2.3 (15/651)	4.1 (27/651)	6.6 (43/648)	1.5 (10/648)	2.5 (16/648)

PCV13 = 13-valent pneumococcal conjugate vaccine; $AlPO_4$ = containing aluminum phosphate; TIV = trivalent inactivated influenza vaccine.
[a]Study location A = South Africa; B = Japan; C = Japan; D = Mexico; E = European Union; F = United States, Sweden; G = United States, Sweden and Germany; study H was not included due to the absence of late injection site reactions.
[b]Number (n) of subjects reporting the specified reaction in the specified interval in the 14-day diary.
[c]Number (N) of subjects reporting the specified reaction as "yes" in the specified period, or "no" for all 14 days. Subjects were excluded from N if the subject reported the reaction as a combination of "no" and missing in a specified period.
[d]TIV given concomitantly with PCV13 but in opposite limb.
[e]TIV given 1 month before PCV13.
[f]PPSV23 preimmunized subjects.

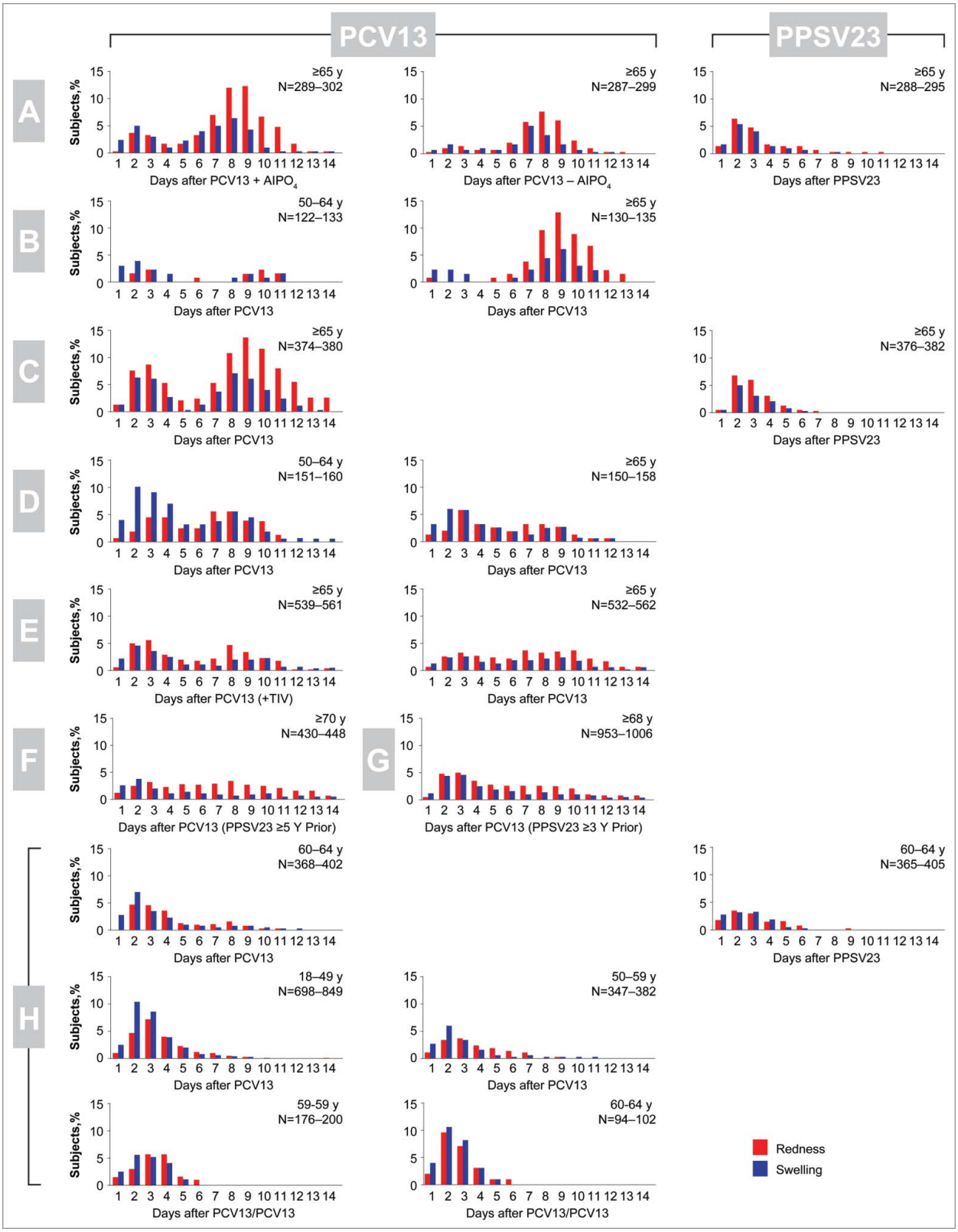

Figure 1. Subjects reporting redness and swelling on days 1–14 after vaccination in studies A–H.[4-13] N = Number of subjects reporting the specified injection site reaction as "yes" on any day, or "no" on all 14 days in the 14-day diary; subjects reporting "no" on some days and with missing data on other days in the 14-day diary were not included. $AlPO_4$ = aluminum phosphate; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; TIV = trivalent inactivated influenza vaccine. A = South Africa[7]; B = Japan[8]; C = Japan[9]; D = Mexico[10]; E = Europe[11]; F = United States and Sweden[13]; G = United States and Europe[12]; H = United States.[4-6]

Table 2. PCV13 Adult Studies Reviewed

Study	Location	Study Description	Age,y	Vaccine Administered	Subjects Vaccinated, N[a]
A	South Africa[7]	A randomized, open-label study to assess safety and immunogenicity of PCV13 formulated with vs without $AlPO_4$ and to assess safety and immunogenicity of PCV13 chosen formulation (PCV13+$AlPO_4$) vs PPSV23 in subjects naive to PPSV23	≥65	PCV13+$AlPO_4$ PCV13–$AlPO_4$ PPSV23	309 304 301
B	Japan[8]	An open-label, multicenter study to assess safety and immunogenicity of PCV13 in 2 age groups naive to PPSV23	50–64 ≥65	PCV13 PCV13	134 136
C	Japan[9]	A randomized, modified double-blind study to assess safety and immunogenicity of PCV13 in subjects naive to PPSV23	≥65	PCV13 PPSV23	382 382
D	Mexico[10]	An open-label, multicenter study to assess safety and immunogenicity of PCV13 in 2 age groups naive to PPSV23	50–64 ≥65	PCV13 PCV13	162 161
E	Europe (Germany, Belgium, Hungary, Netherlands)[11,33]	A randomized, double-blind study to assess safety and immunogenicity of PCV13 given concomitantly with TIV vs PCV13 and TIV given alone in subjects naive to PPSV23	≥65	PCV13+TIV[b] PCV13[c]	576 575
F	United States, Sweden[13]	A multicenter, randomized, modified double-blind study to assess safety and immunogenicity of PCV13 vs PPSV23 in subjects who received PPSV23 ≥5 years before	≥70	PCV13	463
G	United States, Germany, Sweden[12]	An open-label, multicenter study to assess safety of PCV13 in elderly adults who received PPSV23 ≥3 years before	≥68	PCV13	1049
H	United States[4-6]	A multicenter study to assess safety and immunogenicity of PCV13 vs PPSV23 in adults aged 60−64 years (randomized, modified double-blind)	60–64	PCV13 PPSV23	417 414
		and to assess PCV13 in 2 other age groups (open-label) in subjects naive to PPSV23	50–59 18–49	PCV13 PCV13	404 899
		An open-label extension to assess revaccination after a 3.5- to 4-year interval in 2 age groups	53–63 63–68	PCV13/PCV13 PCV13/PCV13	214 108

$AlPO_4$=aluminum phosphate; PCV13=13-valent pneumococcal conjugate vaccine; PCV13/PCV13=revaccinated with PCV13 after an interval of 3.5–4 years; PPSV23=23-valent pneumococcal polysaccharide vaccine; TIV=trivalent inactivated influenza vaccine.
[a]Number (N) of subjects who received the study vaccine in each cohort.
[b]TIV given concomitantly with PCV13.
[c]TIV given 1 month before PCV13.

D) was observed within days 6 to 14 (Fig. 1 and Supplementary Fig. 1, studies B and D). Conversely, in study H (United States), which included 3 cohorts with subjects aged 18 to 49, 50 to 59, and 60 to 64 years, late ISRs were generally not observed. The majority of ISRs occurred within 5 days (Fig. 1 and Supplementary Fig. 1, study H).

PCV13 cohorts revaccinated with PCV13

In study H (United States),[6] cohorts aged 53 to 63 and 63 to 68 years received a second dose of PCV13 3.5 to 4 years after initial PCV13 vaccination. No late onset of ISRs was observed after PCV13 revaccination (Fig. 1 and Supplementary Fig. 1, study H). The majority of ISRs occurred within 5 days of revaccination. Similarly, no late onset of ISRs was observed in study A (South Africa) in subjects aged ≥66 years revaccinated 1 year after initial PCV13 vaccination (Pfizer data not shown).

PPSV23 in PPSV23-naive cohorts aged ≥60 years

In studies A, C, and H,[4,7,9] which included PPSV23-naive subjects, 2 cohorts aged ≥65 years and 1 cohort aged 60 to 64 years received a single dose of PPSV23. Late onset of ISRs was not observed after PPSV23. ISRs occurred within 5 days of PPSV23 vaccination (Fig. 1 and Supplementary Fig. 1, studies A, C, and H).

Post hoc immunogenicity analyses associated with late injection site reactions

Immunogenicity was examined in subgroups of subjects with a higher incidence of late ISRs on days 6 to 14; these included

studies A (South Africa)[7] and C (Japan),[9] which included PCV13 cohorts aged ≥65 years, and study D (Mexico),[10] which included PCV13 cohorts aged ≥50 years. At 1 month postvaccination, serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) were numerically higher for all PCV13 serotypes in the subgroups with ISRs compared with those subgroups without ISRs on days 6 to 14; the only exception was serotype 14 in study D (Mexico; Fig. 2). In contrast, baseline OPA GMTs showed no trends toward predominantly higher or lower GMTs (Fig. 2).

Discussion

The distribution of ISRs (redness, swelling and pain) over a 14-day observation period was reviewed in 8 adult clinical studies (A–H)[4-13] including 19 cohorts, of which 15 received PCV13 with $AlPO_4$ (2 of which were revaccinated with PCV13 after an interval of 3.5–4 years), 1 cohort received PCV13 without $AlPO_4$, and 3 received PPSV23. Across the 8 adult studies, ISRs were well tolerated, self-limiting, and resolved in all vaccinated subjects. The onset of late ISRs was observed in 9/9 study cohorts that included subjects aged ≥65 years who received PCV13 with (8 cohorts) or without $AlPO_4$ (1 cohort); however, the presence of late ISRs was generally less pronounced in 2 of the 9 cohorts prevaccinated with PPSV23 in the previous ≥3 years. Of the 4 cohorts aged 50 to 64 years and 1 cohort aged 18 to 49 years that received 1 dose of PCV13, late onset of ISRs was observed in only 2/4 cohorts aged 50 to 64 years. Of the cohorts showing late onset of ISRs, subjects had exclusively early (days 1–5) or exclusively late (days 6–14) ISRs; a minority had both. The presence of late ISRs after PCV13 vaccination on days 6 to 14 was more pronounced in PPSV23-naive cohorts in South Africa and Japan than in other countries.

In addition to the 8 studies presented here, late onset of ISRs was observed in another PCV13 study, the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), which included subjects aged ≥65 years in the Netherlands.[14] Because ISRs were reported for 7 days only, it was excluded from the current review. The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) demonstrated efficacy of PCV13 against vaccine-type pneumonia and invasive pneumococcal disease; therefore, placebo recipients were offered PCV13 after completion of the study. All PCV13 recipients were encouraged to report ISRs to the Netherlands Pharmacovigilance Centre (LAREB).[15] A total of 21,000 adults aged 70 years and older received PCV13 between September 2014 and February 2015. LAREB received 390 spontaneous reports (1.3% of the vaccinees), which included 216 reports of injection site inflammation and 20 reports of extensive swelling of the vaccinated limb. Eighty individuals (34%) reported a

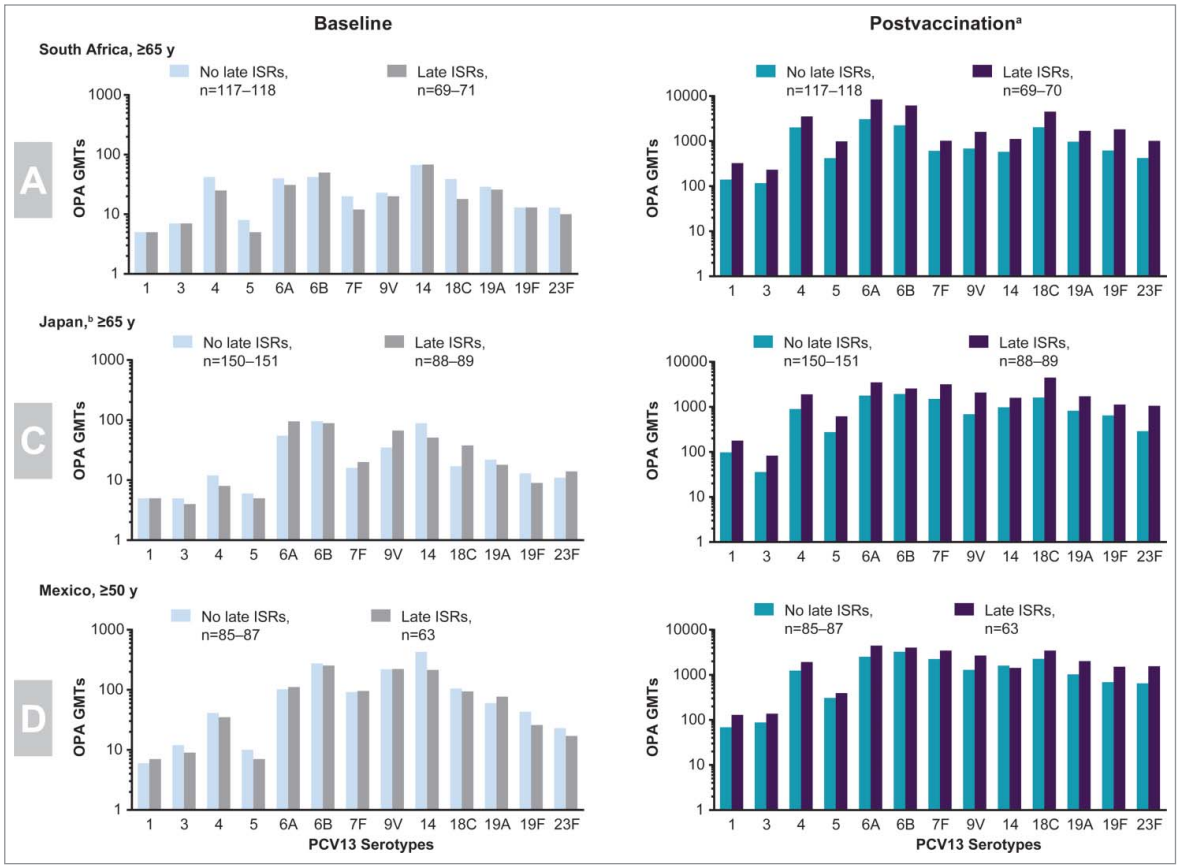

Figure 2. Baseline (day 1) and postvaccination (days 29–43) OPA GMTs among subjects with and without any late injection site reactions on days 6–14 in studies A,[7] C,[9] and D.[10] n = Number of subjects reporting/not reporting any injection site reaction on days 6–14 in the 14-day diary and with a valid and determinate OPA assay antibody titer for the specified serotype. $AlPO_4$ = aluminum phosphate; GMT = geometric mean titer; ISR = injection site reaction; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine. [a]1 month after single dose of PCV13 for Mexico and Japan studies and PCV13+$AlPO_4$ for South Africa study.[b]Randomized, modified double-blind study.

time to onset of ISRs of ≤2 days after PCV13 administration; 156 individuals (66%) reported a time to onset of ISRs of 4 to 7 days after PCV13 administration; few reported both early and late onset of ISRs.[15]

Other studies in which vaccine antigens included diphtheria, tetanus, or pertussis-inactivated toxins or in which the vaccine antigens were conjugated to a protein carrier CRM_{197}, a nontoxic variant of diphtheria toxin, have also reported late onset of ISRs.[2,3,16,17] For example, in a phase 1 study in Australia that included subjects aged 50 to 85 years, late onset of ISRs was observed after administration of a nonadjuvanted 3-antigen *Staphylococcus aureus* vaccine, for which 2 of 3 vaccine antigens were conjugated to the same carrier protein as PCV13 (ie, CRM_{197}).[16] Notably, late ISRs were not observed in the younger cohort (18–24 years),[16] consistent with findings in the cohort aged 18 to 49 years (study H) in the current review.[5] White and colleagues[17] reported early (within 48 hours) and late (within 7–14 days) ISRs after administration of a tetanus toxoid vaccine in a study of factory workers aged 15 to 65 years. Granström and colleagues[2] reported late onset of ISRs in a study population aged 23 to 58 years after 1 dose of $AlPO_4$-adsorbed acellular pertussis vaccine containing inactivated pertussis toxin and filamentous hemagglutinin. The same study reported an absence of late ISRs after revaccination with acellular pertussis vaccine,[2] which is consistent with observations after revaccination with PCV13 in study H. Granström and colleagues further demonstrated that no late ISRs occurred in subjects receiving a placebo containing $AlPO_4$ as an adjuvant,[2] suggesting that $AlPO_4$ is not causally related to the late onset of ISRs. Similarly, in the current review, it is unlikely that $AlPO_4$ was a contributing factor for the development of late onset of ISRs in study A (South Africa) because late ISRs were observed after PCV13 was administered with and without $AlPO_4$.[7] Keitel and colleagues[18] also reported late onset of ISRs associated with administration of 5 acellular pertussis vaccines (toxoid vaccines containing inactivated pertussis toxin) in a population aged 18 to 45 years. Pappenheimer and colleagues[3] described early and delayed onset of ISRs (days 5–7) after booster doses of diphtheria toxoid in older children and adults.

Importantly, no trend for late onset of ISRs was observed after PPSV23 vaccination in 3 cohorts aged ≥60 years in studies A (South Africa),[7] C (Japan),[9] and H (United States;)[4] ISRs after PPSV23 were observed within the first 5 days. This is of interest because PPSV23 contains free capsular polysaccharides which generally elicit a T-cell-independent immune response, whereas the capsular polysaccharides in PCV13 are each conjugated to a protein carrier CRM_{197} to elicit a T-cell–dependent memory immune response.[19,20] This suggests that a T-cell–dependent immune response, which is observed after toxoid vaccines,[19] may be associated with late onset of ISRs. However, as memory and plasma cells were not measured in these studies, it is not possible to confirm any association between late ISRs and T-cell-mediated responses.

A direct association between late ISRs and the magnitude of the functional antibody immune responses elicited by PCV13 was not confirmed. On one hand, there was a trend toward higher functional antibody immune responses in 3 subgroups in studies A, C, and D with late ISRs compared with the corresponding subgroups without late ISRs. However, late ISRs were not observed in adults 18 to 49 years of age (study H) in which OPA immune responses after PCV13 are known to be higher compared with populations aged ≥65 years, where late ISRs were observed (studies A–G).

The cause of the late onset of ISRs after PCV13 vaccination observed in studies A through G remains unexplained and is likely multifactorial. One possible explanation may involve the development of an immunocompromised cutaneous district (ICD), a concept proposed to describe an area that is subject to cutaneous disorders as the result of a skin injury, such as vaccination.[21,22] In this scenario, a "form fruste inflammatory reaction" could form at the vaccination site, a location that may be susceptible to localized immunologic changes due to skin injury.[23]

Early onset of acute local inflammatory responses is thought to follow the formation of immune complexes between the preexisting circulating antibodies and the injected vaccine antigens with increased vascular permeability in the surrounding tissue.[24] Several reports suggest a correlation between elevated prevaccination IgG concentrations and onset of acute ISRs. However, the later onset of ISRs after PCV13 vaccination suggests a secondary local inflammatory response, which may be cell mediated.[24] Cell-mediated inflammatory responses do not involve antibodies but rather involve the activation of phagocytes, natural killer cells, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.[25] As described above, T-cell–mediated immune responses are elicited by CRM_{197}-conjugated vaccines on exposure to preexisting pneumococcal and/or diphtheria antigens and have a temporal association with the onset of late ISRs.[26] In addition, cell-mediated inflammatory responses have been reported after toxoid vaccines.[27,28]

As late ISRs were observed in all study cohorts aged ≥65 years in studies A through G and were not observed in younger subjects aged 18 to 49 years in study H, immunosenescence may also play a role in cell-mediated inflammatory responses. Age is associated with a progressive decline in immune system function and with dysregulated T-cell function, including increased frequency of effector memory and effector CD8+ T cell subsets (both of which secrete effector cytokines) compared with younger individuals.[29,30]

Conclusion

Late onset of ISRs was observed in elderly study cohorts after a single dose of CRM_{197}-conjugated PCV13 but not after PPSV23 (where capsular polysaccharides from the serotypes are not conjugated to a toxoid carrier protein). $AlPO_4$, a vaccine adjuvant, did not appear causally related. Late onset of ISRs was more common in studies in Japan and South Africa than in studies in other countries. The cause of the late ISRs after PCV13 vaccination is likely multifactorial; age, environmental factors, and T-cell–dependent memory responses of CRM_{197}-conjugated PCV13 on re-exposure to vaccine antigens may contribute. Understanding the pathophysiology of these early and late inflammatory reactions requires further investigation. Across studies, late ISRs were mainly mild to moderate and did not affect the favorable risk-benefit assessment of PCV13 in

adults. Nevertheless, physicians should be aware of the possible occurrence of late onset of ISRs after PCV13 and other toxoid or CRM_{197}-conjugated vaccines, particularly in the elderly.

Materials and methods

Clinical studies reviewed

Eight PCV13 adult studies from the Pfizer clinical database, in which ISRs were collected for 14 days postvaccination in electronic diaries, were examined. These studies were conducted by Pfizer Inc to support PCV13 licensing globally (Table 2).[4-13] Study A, which was conducted in South Africa, assessed 2 vaccine formulations (PCV13 with or without $AlPO_4$); studies E through H were conducted to support licensing in the United States and European Union; studies B and C for licensing in Japan; and study D for licensing in Mexico. The Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA),[14] a large PCV13 efficacy study conducted in adults >65 years of age in the Netherlands, is described in the Discussion. This study was not included among the PCV13 adult studies reviewed because ISRs were collected for 7 days postvaccination.

Two studies conducted for licensing in the United States were not included herein as there was generally no late onset of ISRs. These studies include (1) a study examining PCV13 given concomitantly with influenza vaccine in a population aged 50 to 59 years[31] and (2) a US study of sequential administration of PCV13 and PPSV23 in adults aged 60 to 64 years.[32] Other PCV13 licensing studies conducted in infants, children, and adolescents where ISRs were collected in e-diaries for 4 to 7 days only were not included because of the shorter time interval for reporting ISRs. In these studies, no trend for late onset of ISRs was observed (Pfizer data on file).

From the 8 adult studies presented, 6 studies (A–E and H) were conducted in PPSV23-naive adults and 2 studies (F and G) were conducted in PPSV23-prevaccinated adults. These 8 studies included 19 cohorts: 13 received 1 dose of PCV13 with $AlPO_4$, 1 received PCV13 without $AlPO_4$, 2 received 2 doses of PCV13 with a 3.5- to 4-year interval between doses, and 3 received PPSV23. Eligibility criteria were similar across studies. All studies used a central laboratory for measuring immunogenicity. All studies were conducted in accordance with the Declaration of Helsinki and were approved by the local ethics committee in each country.

Study vaccines and administration

The final marketed vaccine formulation of PCV13 contains capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria CRM_{197} carrier protein and adsorbed on $AlPO_4$ (0.125 mg aluminum). Each 0.5-mL dose contains 2.2 μg of polysaccharides of each serotype, except for serotype 6B polysaccharides, which contain 4.4 μg. Excipients include sodium chloride, succinic acid, polysorbate 80, and water for injection. PCV13 formulations used in study A (South Africa) with and without $AlPO_4$ did not contain polysorbate 80.[7]

PPSV23 (Pneumovax® 23; Merck & Co., Inc., Whitehouse Station, NJ) contains capsular polysaccharides from serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. Each 0.5-mL dose contains 25 μg of each polysaccharide type. Excipients include 0.25% phenol as a preservative, sodium chloride, and water.

Study vaccine was administered into the deltoid muscle.

Post hoc analyses of incidence of early and late injection site reactions

In the studies A through H reviewed (Table 1), ISRs were recorded daily by vaccine recipients for 14 days using an electronic diary. The incidence and the severity of ISRs within the 14-day observation period were previously published and are presented collectively in Supplementary Table 1. For the post hoc analysis, early ISRs were defined as those recorded on days 1 to 5 (day 1 was the day of vaccination); late ISRs were defined as those recorded on days 6 to 14. Eleven cohorts from studies A through G showing late onset of ISRs after PCV13 vaccination were analyzed to identify the incidence of subjects with exclusively early (days 1–5), exclusively late (days 6–14), or both early and late ISRs (Table 1; Supplementary Table 2).

Post hoc immunogenicity analyses associated with late injection site reactions

In cohorts from studies A (South Africa), C (Japan), and D (Mexico), in which late ISRs after PCV13 administration were generally more common than in other countries, serotype-specific OPA GMTs of subjects with ISRs ≥1 on days 6 to 14 versus those without were evaluated at baseline and approximately 1 month after vaccination. Two cohorts included subjects aged ≥65 years (studies A and C); the combined cohorts of study D included subjects aged ≥50 years. Informal comparisons were made in each cohort between subsets with and without late ISRs to identify trends (Fig. 2).

Disclosure of potential conflicts of interest

CJ, YS, WW, CW, WCG, DAS, and BS-T are current employees of Pfizer and may hold stock and/or stock options. SP was an employee of Pfizer Inc during the time of the study. JT is an employee of inVentiv Health Clinical, LLC, a company contracted by Pfizer Inc. All authors approved the final article.

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Author contributions

All authors were involved in the analysis and interpretation of the data, writing of the manuscript, and in the decision to submit the manuscript for publication.

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