

Extensive limb swelling (ELS) after administration of Pneumovax 23®

Introduction

Pneumovax 23®, a pneumococcal vaccine containing 23 polysaccharide-serotypes, is indicated for *active immunization against disease caused by pneumococci, for children from 2 years old, adolescents and adults* (1). Bacterial capsular polysaccharides induce the production of antibodies, independent of T-cells, creating immunity. Pneumovax 23® has been approved by the FDA in 1983 (2) and has received marketing authorization for the Netherlands in 2001 (1).

In 2018 the Health Council of the Netherlands advised to offer older people a vaccine that protects against pneumococci (3). The fourth quarter of 2020 was the first time that Pneumovax 23® was offered in the context of a national vaccination campaign, often administered simultaneously with the influenza vaccine 2020/2021 (4). The target audience was 73- to 79-year-olds for 2020 (5, 6).

Extensive Limb Swelling

Extensive swelling and/or erythema of the vaccinated limb (ELS) is sometimes seen after vaccination. It is a known adverse reaction to seasonal influenza vaccines, DKTP and COVID-19 vaccine Comirnaty® (7, 8). The definitions of ELS may differ on size of the swelling and erythema such as: involvement of one or two joints closest to the injection site and the circumference of the swollen limb (7, 9, 10). For a reaction to be classified as ELS, the swelling and/or erythema must extend over at least one joint from the injection site (shoulder, elbow, hip or knee) and/or cover more than half of the circumference of the limb. The reaction 'Extensive swelling of vaccinated limb' (MedDRA Preferred Term) is then added to the report.

The onset is generally within 48 hours after vaccination and an ELS disappears within a few days without sequelae (11). Concomitant inflammatory reactions may include pain, pruritus and warmth at the injection site, a decreased mobility of the vaccinated limb and fever (7, 11, 12). ELS does not require antibiotic treatment since there is no infection. Usual approaches to reduce swelling -like cooling- can be applied.

Reports

Until April 5th, 2021, The Netherlands Pharmacovigilance Center Lareb has received 52 reports of ELS after administration of Pneumovax 23®. In only three of them, ELS is reported literally by the reporter (all consumers). In the other cases, the reported reactions were considered by Lareb to be compatible with the diagnosis ELS. Most reports concern older patients, which is also the target audience for Pneumovax 23® in the Netherlands. Of the 52 reports, 42 patients were between 70-80 years, 8 patients were younger than 70 years, and the age was unknown in 2 reports. Gender was evenly distributed: 27 reports concerned females and 25 concerned males.

The majority of ELS cases (39x) were vaccinated in 2020, the year that Pneumovax 23® was added to the national vaccination campaign. Four ELS cases were vaccinated in 2021 up until April 5th, 2021. Lareb also received 9 reports from before the campaign: 4 reports from vaccination in 2018, and 5 in 2019. Of these 9 cases, 4 had been given Pneumovax 23® in the context of a splenectomy (in history or future). One case had a weakened immune system because of tocilizumab. The indication is not clear for the other 4 cases.

Most cases were reported by consumers (39x), 8 by physicians, 3 by physician assistants, and 2 by other health professionals. ELS usually appeared on the day of vaccination, often within 1-4 hours. However, a lot of the reports only mentioned 'same day' instead of how many hours until onset, so the timeframe of 1-4 hours is not very accurate. On day 2, there were 13 cases and on day 3 there was only 1 case. Almost all reporters mentioned recovery or being in the process of recovery at the time of reporting. In 12 reports the ELS lasted 3-6 days, in 11 reports 7-10 days, and in 1 report 14 days. It remains unclear if this is representative for all of the ELS cases, since the duration of the ELS in the other 28 reports was unknown.

Some reports include concurrent systemic reactions such as pyrexia, headache and nausea, which are known adverse events following immunization and are mentioned in the Summary of Product

Characteristics of Pneumovax 23® (1). All reports (with concurrent reactions) can be found in table 2 in the addendum. There were 4 serious reports (by CIOMS criteria), of which 3 were classified as serious in view of hospitalization and 1 because of temporary inability to walk, which restricted daily life (other medically important condition). These reports are indicated in the table as 'serious' in the comments column in table 2 in the addendum.

Treatment of ELS

The case descriptions reported different treatments of ELS, as seen in table 1. Treatments for other reactions were not included in the table. ELS was treated most often with analgesics, of which paracetamol was most frequently used. Antibiotics were used as well, even though antibiotics were not indicated since there is no bacterial component involved in ELS, and there was no documentation of a proven iatrogenic bacterial infection. Streptococcal and staphylococcal skin infections, however, remain important differential diagnoses to consider and might not always be easily distinguished from ELS. Prednisone and allergy medication NOS were rarely used but may have been beneficial in case of ELS symptoms. Non-drug treatment was also used 5 times, for example by cooling the limb.

Table 1: Summary of applied ELS treatments. In 52 cases, 24 treatments were given. One case can contain multiple treatments.

Treatment of ELS as reported	
Analgesics:	
Paracetamol	6
Analgesic NOS	2
Antibiotics:	
Amoxicillin/clavulanic acid	2 (of which 1x suspicion of erysipelas)
Azithromycin	1
Clindamycin	1
Flucloxacillin	3 (of which 1x suspicion of erysipelas and 1x suspicion of cellulitis)
Antibiotic NOS	1
Other drugs:	
Prednisone	1
Allergy medication NOS	2
Non-drug treatment:	
Cooling (e.g. with cold pack)	3
Elastic bandage	1
Wet cloths	1

Other sources of information

SPC

The SPC of Pneumovax 23® (1) does not include ELS as possible adverse reaction, but it does include injection site reactions such as erythema, induration, pain, sensitivity, swelling, warmth, cellulitis, decreased mobility and peripheral edema of vaccinated limb. Even though ELS can consist of some of these events, it differs from all of them: it is more extensive in size, inflammatory in nature, generally harmless and characterized by time of onset and duration. ELS describes a specific clinical presentation of multiple of these events at once, on the limb and through time.

Literature

Woo et al. reported a case series of ELS from the Vaccine Adverse Event Reporting System (VAERS) by the FDA and Centers for Disease Control and Prevention (7) They defined approximately 97 cases of ELS after polyvalent pneumococcal vaccination (PPV) from July 1st, 1990 through January 16th, 2003. Most reports of ELS came from PPV, more than for DT(a)P, tetanus and diphtheria toxoids, influenza and hepatitis B. This might mean that PPV is more reactogenic than most other vaccines, but the VAERS data has been obtained through a passive surveillance system, so incidence rates and relative risks cannot be calculated (7).

There is one case report available through PubMed by Recher et al. which describes a 67-year-old woman with ELS after administration of 13-valent pneumococcal conjugate vaccine (13). Within 4 days after the first vaccination, she developed ELS (which mimicked erysipelas). She received treatment with 20 mg cortisone, and symptoms disappeared within 2 days. In a skin biopsy a lot of CD4+ T cells and macrophages were seen.

ELS is not very well-known, and it might be confused with the more severe cellulitis or erysipelas. Injection site inflammation is common with vaccines in general and are also reported for Pneumovax 23® by Miller et al., who have categorized 25,168 adverse event reports from 1990-2013 for Pneumovax 23® in the VAERS database. In adults, the most common non-serious reactions were injection site erythema (32%), injection site pain (27%) and injection site swelling (23%). Thirteen percent of the non-serious cases reported peripheral edema (14). It is possible that some of the subjects with these reactions unknowingly had ELS.

Other databases

According to the VigiBase database, the WHO has received 502 reports of 'Extensive swelling of vaccinated limb' with Pneumovax 23® in total, worldwide (15).

Prescription data

During the influenza season 2020-2021, more than 850,000 Pneumovax 23® vaccines have been distributed in the Netherlands (16).

Mechanism

It is plausible that ELS is an exaggerated inflammatory injection site reaction, possibly influenced by humoral immunity responses. But it is not known which factors play a role in susceptibility to ELS, such as prior sensitization to antigens or recipients (ELS was reported more after revaccination with DT(a)P, but not for other vaccines) or injection technique (7).

Ultrasound assessment of ELS after vaccination with DTaP in preschools shows that ELS is different from the clinical measurements of skin swelling. The thickness of subcutaneous and muscle tissue of the vaccinated arm expanded to 281% and 111% compared to the tissue thickness of the control arm (17), which illustrates its extensiveness.

Discussion and conclusion

Lareb has received 52 reports of ELS following immunization with Pneumovax 23® up until April 5th, 2021, of which 39 were vaccinated in 2020. Some reports had multiple suspect vaccines, therefore only the reports where ELS occurred on the Pneumovax 23® side were included. To put the 39 ELS reports in 2020 in perspective: in the influenza-season 2020-2021 Lareb received a total of 250 reports (including reports with ELS), with Pneumovax 23® as only suspect. Lareb also received 353 reports in total after simultaneous administration of Pneumovax 23® and influenza vaccine.

Globally, 502 reports of ELS in relation to Pneumovax 23® have been reported (at time of writing: July 16th, 2021). The number of reports from the Netherlands (versus globally) is relatively high, which could be the result of Lareb's practice to add ELS as a reaction if the injection site inflammation matches the criteria for ELS, and to ask for a picture and a detailed description when there is a suspicion of ELS. This might not happen as extensively elsewhere in the world.

Because Pneumovax 23® has mostly been administered to older people, most of the reports concern this age group. This signal does not automatically indicate that they are more susceptible to developing ELS. It is generally seen across people of all ages and also with different vaccines (7).

Finally, an ELS might be mistaken for a regular injection site inflammation, or look similar to cellulitis or erysipelas if there is no bacteriological information. This could result in more antibiotic treatment than needed. Recovery from ELS is usually spontaneous and without sequelae, but the clinical presentation might raise concern among patients and health care providers if they are not aware of ELS. It is therefore suggested to raise awareness for ELS after administration of Pneumovax 23®.

References

1. Dutch SPC Pneumovax 23[®] and details marketing authorization. Last update SPC: 09-07-2019. Available from: https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,25853.
2. Centers For Disease Control And Prevention. Pneumococcal Vaccines. Last update: 09-09-2020. Available from: <https://www.cdc.gov/vaccinesafety/vaccines/pneumococcal-vaccine.html>.
3. Health Council of the Netherlands. Vaccinatie van ouderen tegen pneumokokken. The Hague: Health Council; 2018 28-02-2018. Contract No.: publication nr. 2018/05.
4. Blokhuis P. Letter government: Vaccinatiegraadrapport 2018 en voortgang 'Verder met vaccineren'. The Hague, 2019.
5. Health Council of the Netherlands. COVID-19 en vaccinatie tegen pneumokokken. The Hague: Health Council; 2020. Contract No.: publication nr. 2020/04.
6. Blokhuis P. Kamerbrief aanpassingen neonatale gehoorscreening en vaccinaties. From: Staatssecretaris van Volksgezondheid WeS, editor. The Hague 2020.
7. Woo EJ, Burwen DR, Gatumu SN, Ball R. Extensive limb swelling after immunization: reports to the Vaccine Adverse Event Reporting System. Clin Infect Dis. 2003;37(3):351-8.
8. Netherlands Pharmacovigilance Center Lareb. Comirnaty and Extensive swelling of the vaccinated limb (internal document). 2021.
9. Australian Government Department of Health. Australian Immunisation Handbook, Glossary of technical terms. Last update: 12-06-2017. Available from: <https://immunisationhandbook.health.gov.au/technical-terms>.
10. Babl FE, Lewena S. Chapter 102 - Vaccination-Related Complaints and Side Effects. Baren JM, Rothrock SG, Brennan JA, Brown L, editors Pediatric Emergency Medicine 2008.
11. David S, Bondt PV-d, Maas Nvd. Toename van lokale verschijnselen bij 4-jarigen na revaccinatie met DKTP. Ned Tijdschr Geneeskd. 2010;154:A980.
12. Rennels MB, Black S, Woo EJ, Campbell S, Edwards KM. Safety of a fifth dose of diphtheria and tetanus toxoid and acellular pertussis vaccine in children experiencing extensive, local reactions to the fourth dose. Pediatr Infect Dis J. 2008;27(5):464-5.
13. Recher M, Hirsiger JR, Bigler MB, Iff M, Lemaitre B, Scherer K, et al. Immune system correlates of extensive limb swelling in response to conjugated pneumococcal vaccination. NPJ Vaccines. 2018;3:17.
14. Miller ER, Moro PL, Cano M, Lewis P, Bryant-Genevier M, Shimabukuro TT. Post-licensure safety surveillance of 23-valent pneumococcal polysaccharide vaccine in the Vaccine Adverse Event Reporting System (VAERS), 1990-2013. Vaccine. 2016;34(25):2841-6.
15. Uppsala Monitoring Centre. VigiBase. Cited: 16-07-2021. Available from: <https://vigilyze.who-umc.org/>.
16. Dienst Vaccinvoorzieningen Preventieprogramma's (RIVM-DVP) Rijksinstituut voor Volksgezondheid en Milieu - DVP Centraal Logistiek 2021. Afleveraantallen Pneumovax 23[®] seizoen 2020/2021.
17. Marshall HS, Gold MS, Gent R, Quinn PJ, Ptotto L, Clarke MF, et al. Ultrasound examination of extensive limb swelling reactions after diphtheria-tetanus-acellular pertussis or reduced-antigen content diphtheria-tetanus-acellular pertussis immunization in preschool-aged children. Pediatrics. 2006;118(4):1501-9.

This signal has been raised on September 8, 2021. 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.cbq-meb.nl

Addendum

Table 2: Summary of reports until April 5th 2021*.

No	ID, sex, age, primary source	Drug	Concomitant medication	Reported ADRs	Latency after start	Outcome	Comments
1	NL-LRB-00298188, male, 10-20 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Folic acid Tablet 0,5Mg	Extensive swelling of vaccinated limb, Injection site swelling, Fever, Nausea, Injection site warmth, Injection site pain	Fever 6 hours, nausea unknown, the rest 2 hours	Recovered, nausea unknown	ELS is not seen in the provided picture. Reaction was reported as ELS. Indication: preparation for splenectomy. Medical history: spherocytosis. Past drug therapy: 60 days earlier the boy had Prevenar 13 [®] .
2	NL-LRB-00300138, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Clopidogrel Tablet 75Mg, Atorvastatin Tablet 10Mg, Ezetimib Tablet 10Mg	Extensive swelling of vaccinated limb, Injection site swelling, Injection site warmth, Injection site pain	2 Hours	Recovering	none
3	NL-LRB-00343357, male, 4-7 Years, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Act Hib Injectiepoeder Flac 10Mcg +Solv 0,5MI Syr ----- Nimenrix [®] Injldr Flacon + Solvens In Syr		Extensive swelling of vaccinated limb, Injection site erythema, Injection site warmth, Injection site pain, Injection site swelling, Pyrexia	3-4 hours	Recovering, pyrexia unknown	Pneumovax 23 [®] and ActHIB vaccine were injected in the same arm. Treatment with Augmentin. Serious report (hospitalization). Sister has had similar reaction. Indication: preparation for splenectomy
4	NL-LRB-00306807, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Tiotropium Inhalatiecapsule 18Ug, Oxazepam Tablet 10Mg, Fluticasone Inhalation powder 250Ug/Do, Lercanidipine Tablet Coated 10Mg, Edoxaban Tablet 60Mg, Ramipril Tablet 5Mg, Bupropion Tablet CR 150Mg, Metoclopramide Hydrochloride, Cholecalciferol Tablet 400Ie, Pantoprazole Tablet GR 20Mg,	Extensive swelling of vaccinated limb, Injection site redness, Injection site swelling, Injection site pain, Feeling sick, Fainting	2 Hours	Unknown	Serious report. Treatment with prednison. Later in the evening she passed out on the hard bathroom floor, the ambulance came and she was hospitalized with a concussion.

			Magnesium, Calcium, Vitamin B Complex Tablet (different manufacturers), Macrogol 300				
5	NL-LRB-00360069, female, 30-40 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site erythema, Injection site swelling, Injection site pain	3 Hours	Not Recovered,	Treatment with paracetamol
6	NL-LRB-00360465, female, 70 Years and older, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Simvastatin Tablet Fo 10Mg, Irbesartan/Hydrochlorothiazide Tablet 150/12,5Mg, Metoprolol Tartrate	Extensive swelling of vaccinated limb, Injection site erythema, Injection site swelling, Injection site warmth, Injection site pain	2 Hours	Recovered	x
7	NL-LRB-00365743, female, 50-60 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site erythema, Injection site swelling, Injection site warmth, Injection site pain, Injection site pruritus	30 Minutes	Recovering	Indication/medical history: asplenia
8	NL-LRB-00370053, female, 40-50 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Tocilizumab Intr sol Conc 20Mg/MI	Extensive swelling of vaccinated limb, Injection site pain, Injection site pruritus, Malaise, Fever, Injection site swelling, Injection site redness	Pain direct; ELS not reported	Injection site pruritus and fever unknown, the rest recovered	Treatment with pain killers. Indication: weakened immune system because of tocilizumab
9	NL-LRB-00415907, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Tiotropium inhalation liquid 2,5Ug/Do, Formoterol inhalation powder 12Ug/Do	Injection site erythema, Injection site swelling, Injection site pain, Injection site warmth, Extensive swelling of vaccinated limb, Body temperature increased	-	Not Recovered	x
10	NL-LRB-00416243, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Etanercept Inj fld 50Mg/MI	Injection site pain, Injection site erythema, Injection site warmth, Extensive swelling of vaccinated limb, Myalgia, Headache, Influenza like symptoms, Pain in arm	6 Hours	Not Recovered	No swelling (only erythema, which is still considered ELS according to Lareb definition)
11	NL-LRB-00416261, male, 70 Years and	Pneumovax 23 [®] Inj fl disp syr 0,5MI -----	Clopidogrel Tablet 75Mg, Acetyl salicylic acid Tablet 80Mg,	Injection site pain, Injection site swelling, Injection site erythema,	1 Hour	Not Recovered	Treatment with cold pack

	older, Consumer or other non health professional	Vaxigrip Tetra® Inj susp 2020/2021 Syr 0,5MI ----- Influvac Tetra® Inj susp 2020/2021 Syr 0,5MI	Pantoprazole Tablet GR 40Mg, Rosuvastatin Tablet 10Mg, Tamsulosin Tablet CR 0,4Mg	Extensive swelling of vaccinated limb, Fever			
12	NL-LRB-00416289, female, 70 years and older, Physician	Pneumovax 23® Inj fl disp syr 0,5MI	Rivaroxaban Tablet 20Mg, Candesartan Tablet 8Mg	Injection site swelling, Injection site erythema, Extensive swelling of vaccinated limb	1 Day	Not Recovered	Also very sensitive to mosquito bites
13	NL-LRB-00416203, male, 70 Years and older, Consumer or other non health professional	Vaxigrip Tetra® Inj susp 2020/2021 Syr 0,5MI ----- Pneumovax 23® Inj fl disp syr 0,5MI		Injection site pain, Injection site swelling, Injection site erythema, Extensive swelling of vaccinated limb, Vesicular rash, Itchy rash	1 Day	Recovered	x
14	NL-LRB-00416436, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23® Inj fl disp syr 0,5MI ----- Vaxigrip Tetra® Inj susp 2020/2021 Syr 0,5MI		Injection site swelling, Injection site pain, Extensive swelling of vaccinated limb, Injected limb mobility decreased, Peripheral swelling	Local reactions (including ELS) 6 hours. Peripheral swelling: 31 hours	Recovered	x
15	NL-LRB-00416455, male, , Consumer or other non health professional	Pneumovax 23® Inj fl disp syr 0,5MI		Pain in arm, Injection site swelling, Injection site erythema, Extensive swelling of vaccinated limb	-	Recovering	Elbow was not swollen, but swelling continued after elbow
16	NL-LRB-00417114, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23® Inj fl disp syr 0,5MI ----- Vaxigrip Tetra® Inj susp 2020/2021 Syr 0,5MI		Injection site pain, Injection site erythema, Extensive swelling of vaccinated limb	1 Day	Recovering	Pneumovax 23® was administered on the left side (as opposed to what guidelines suggest), where the reaction occurred. Therefore it is not 100% sure that the reaction occurred on the pneumococcal side. Reaction was reported as ELS.
17	NL-LRB-00417680, male, 70 Years and older, Physician	Pneumovax 23® Inj fl disp syr 0,5MI	Meloxicam Tablet 15Mg, Dabigatran Etexilate Capsule 150Mg, Bisoprolol Tablet 10Mg, Rosuvastatin Tablet Fo 20Mg (As Ca-salt) - Non-Current Drug	Injection site erythema, Injection site swelling, Injection site warmth, Extensive swelling of vaccinated limb, Injection site pain	4 Hours	Recovered	x

18	NL-LRB-00418005, female, , Other health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Injection site swelling, Injection site erythema, Burning sensation, Fever, Extensive swelling of vaccinated limb	2 Days	Recovered	This report includes multiple people. Treatment with wet cloths and pain killers
19	NL-LRB-00418753, female, 70 Years and older, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI ----- Influvac Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Injection site swelling, Injection site erythema, Extensive swelling of vaccinated limb	-	Not Recovered	x
20	NL-LRB-00418784, male, 70 Years and older, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Fever	1 Day	Unknown	Treatment with flucloxacillin because of suspicion cellulitis
21	NL-LRB-00416698, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Pain in arm, Injection site swelling, Injection site erythema, Injection site warmth, Pyrexia, Vaccine administered at inappropriate site, Extensive swelling of vaccinated limb	1 Day	Recovering	Pneumovax 23 [®] and influenza were administered in same arm because of breast cancer in history
22	NL-LRB-00419127, male, 70 Years and older, Other health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influenza vaccine (not specified)		Injection site warmth, Injection site erythema, Extensive swelling of vaccinated limb	1 Day	Not Recovered	Treatment with flucloxacillin 500mg, 4 times a day 1 tablet for 10 days
23	NL-LRB-00419660, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site swelling, Injection site erythema, Injection site pain	1 Hour	Not Recovered	x
24	NL-LRB-00419753, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Pain in leg, Shivering, Nausea, Injection site swelling, Injection site warmth, Extensive swelling of vaccinated limb	-	Recovered, Recovered, Recovered, Recovering, Recovering, Recovering	x
25	NL-LRB-00420246, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influenza vaccine (not specified)	Metoprolol/Hydrochlorot hiazide Tab CR 100/12,5Mg, Phenprocoumon Tablet 3Mg, Pantoprazole Tablet GR 40Mg	Extensive swelling of vaccinated limb, Injection site pain, Injection site erythema, Injection site swelling, Injection site warmth,	3 Hours	Recovering	x

				Injected limb mobility decreased			
26	NL-LRB-00420644, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site pain, Injection site erythema, Injection site swelling	8 Hours	Recovering	x
27	NL-LRB-00421080, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Etoricoxib Tablet Fo 30Mg, Omeprazole Capsule GR 20Mg	Extensive swelling of vaccinated limb, Injection site erythema, Injection site pain, Injection site pruritus, Headache, Feverish, Nausea, Decreased appetite	3 Hours	Recovering	Treatment with allergy medication and paracetamol
28	NL-LRB-00419964, female, 70 Years and older, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influenza vaccine (not specified)	Levothyroxine Tablet 25Ug (Natrium), Desloratadine Tablet 5Mg, Cholecalciferol Capsule 25.000Ie, Esomeprazole Tablet GR 20Mg, Mometasone Nasal spray 50Ug/Do, Fluorouracil Cream 50Mg/G	Injection site pain, Injection site swelling, Extensive swelling of vaccinated limb, Injected limb mobility decreased, Injection site erythema	1 Day	Recovered	Serious report. Patient was not able to walk for 2 days (administered in leg).
29	NL-LRB-00422438, female, 70 Years and older, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influenza vaccine (not specified)	Amlodipine Tablet 5Mg, Lisinopril Tablet 10Mg, Salbutamol Inhalation powder 100Ug/Do, Bisoprolol Tablet 2,5Mg, Tiotropium/Olodaterol Inhalation fluid 2,5/2,5Ug/Do	Injection site erythema, Injection site swelling, Injection site warmth, Extensive swelling of vaccinated limb, Injection site burning	-	Recovered	x
30	NL-LRB-00422450, male, 70 Years and older, Other health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Injection site swelling, Injection site pain, Injection site erythema, Extensive swelling of vaccinated limb	1 Day	Recovering	Treatment with clindamycin 300 mg, 3 times a day 1 tablet, 20 pc total.
31	NL-LRB-00419715, female, 70 Years and older, Other health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI ----- Influvac Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Extensive swelling of vaccinated limb, Injection site swelling, Injection site warmth, Injection site discomfort, Injection site pruritus	-	Recovered	x

32	NL-LRB-00419372, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influvac Tetra [®] Inj susp 2020/2021 Syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Extensive swelling of vaccinated limb, Injection site swelling, Injection site pain, Injection site erythema, Injection site discomfort	-	Recovered	Duration of reaction was 10 days.
33	NL-LRB-00419790, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site swelling, Injection site erythema, Injection site pain	2 Hours	Recovered	Treatment with paracetamol
34	NL-LRB-00419191, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Injection site pain, Injection site erythema, Injection site swelling, Extensive swelling of vaccinated limb	6 Days	Recovered	Reactions started on vaccination date. The latency of 6 days is not accurate.
35	NL-LRB-00419736, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influvac Tetra [®] Inj susp 2020/2021 Syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Injection site erythema, Injection site pain, Injection site swelling, Injection site warmth, Extensive swelling of vaccinated limb	2 Hours	Recovering	x
36	NL-LRB-00419656, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influvac Tetra [®] Inj susp 2020/2021 Syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI	Bisoprolol Tablet 1,25Mg, Valsartan Tablet Coated 160Mg, Rosuvastatin Tablet 5Mg, Acetyl salicylic acid, Pantoprazole Tablet GR 20Mg	Extensive swelling of vaccinated limb	7 Hours	Recovering	x
37	NL-LRB-00420376, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influvac Tetra [®] Inj susp 2020/2021 Syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI	Metoprolol Tablet CR 100Mg (Succinaat), Amlodipine Tablet 5Mg, Atorvastatin Tablet 10Mg	Extensive swelling of vaccinated limb, Injection site pain	4 Hours	Recovered, Not Recovered	Treatment with paracetamol, temazepam, elastic bandage, cooling
38	NL-LRB-00425431, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Influenza vaccine (not specified)		Injection site erythema, Injection site pain, Injection site swelling, Extensive swelling of vaccinated limb,	1 Day	Recovering	x

				Injection site burning, Injection site pruritus			
39	NL-LRB-00425515, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Rivaroxaban Tablet 20Mg, Influenza vaccine (Not specified)	Extensive swelling of vaccinated limb, Injection site pain, Injection site swelling, Injection site erythema, Injected limb mobility decreased	ELS and injected limb mobility decreased unknown. The rest 5 days	Recovered	x
40	NL-LRB-00427649, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site pain	1 Hours	Recovered	x
41	NL-LRB-00428668, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Injection site swelling, Injection site erythema, Injection site pain, Extensive swelling of vaccinated limb	2 Hours	Recovered	Treatment with azithromycin
42	NL-LRB-00430374, male, 50-60 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Alendronin/Calciumcar/C holecal Ora (Alenca D3 1000)	Injection site pain, Injection site swelling, General malaise, Flu like symptoms, Injected limb mobility decreased, Chills, Injection site warmth, Extensive swelling of vaccinated limb	Injection site swelling: 2 hours. ELS not reported	Recovering	Treatment with ice pack and paracetamol. Reaction was reported as ELS.
43	NL-LRB-00428298, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Acetylsalicylic acid Tablet 80Mg, Rosuvastatin Tablet 20Mg, Cholecalciferol	Pyrexia, Extensive swelling of vaccinated limb, Injection site erythema, Injection site swelling, Night sweats, Localised rash	Localised rash: 1 day. ELS not reported	Night sweats recovering, rest recovered	Treatment with amoxicillin/clavulanic acid because of suspicion erysipelas
44	NL-LRB-00425317, female, 70 Years and older, Other health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Atorvastatin Tablet 20Mg, Metformin Tablet 500Mg, Metoprolol Tartrate, Apixaban Tablet 2,5Mg	Extensive swelling of vaccinated limb, Injection site pain, Injection site erythema	-	Recovered	x
45	NL-LRB-00428544, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injection site pain, Injection site swelling, Injection site erythema, Injection site warmth	1 Hour	Recovered	x
46	NL-LRB-00450684, male, 70 Years and	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Glucosamine, Multi Vitamins, Magnesium	Injection site pain, Injection site swelling,	Myalgia unknown. The rest 5 minutes	Recovered, myalgia not Recovered	x

	older, Consumer or other non health professional			Extensive swelling of vaccinated limb, Myalgia			
47	NL-LRB-00422624, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI		Fever, Palpitations, Injection site erythema, Injection site swelling, Injection site pain, Extensive swelling of vaccinated limb	1 Hour	Recovered	Treatment with antibiotics
48	NL-LRB-00464047, female, 60-70 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI		Extensive swelling of vaccinated limb, Injected limb mobility decreased, Numbness of limbs	-	Unknown	Serious report. Treatment with allergy medication in hospital. The second time the whole arm was swollen and she was hospitalized. After this event, she did not receive Pneumovax 23 [®] again. Indication: asplenia.
49	NL-LRB-00468795, male, 70 Years and older, Physician	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Acetylsalicylic acid/Clopidogrel Tablet 100/75Mg, Tamsulosin Capsule CR 0,4Mg, Simvastatin Tablet Fo 40Mg	Erysipelas, Pain in arm, Injection site erythema, Injection site swelling, Extensive swelling of vaccinated limb	5 Hours	Recovering	Treatment with flucloxacillin because of possibility erysipelas
50	NL-LRB-00471446, female, 50-60 Years, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI	Levothyroxine Tablet 100Ug (Natrium), Valaciclovir Tablet 500Mg, Rosuvastatin Tablet 10Mg, Alendronic acid Tablet 10Mg, Calcium carbonate chewing tablet 1,25G (500Mg Ca)	Injection site swelling, Injection site pain, Injection site erythema, Extensive swelling of vaccinated limb	4 Hours	Recovered	Stem cell transplant in medical history
51	NL-LRB-00416659, female, 70 Years and older, Consumer or other non health professional	Pneumovax 23 [®] Inj fl disp syr 0,5MI ----- Vaxigrip Tetra [®] Inj susp 2020/2021 Syr 0,5MI	Amlodipine Besilate, Losartan/Hydrochlorothi azide Tab coated 50/12,5Mg, Simvastatin Tablet Fo 10Mg	Illness, Pain in arm, Injection site swelling, Injection site erythema, Extensive swelling of vaccinated limb, Injected limb mobility decreased, Hyperhidrosis, Pyrexia, Nausea, Headache, Decreased appetite, Diarrhoea, Dizziness, Pain, Cough, Hepatic enzyme increased, Tendon rupture,	-	Recovering	Treatment with paracetamol. Muscle tears could have been caused by simvastatin, she also had abnormal liver parameters.

				Inflammation localised, Unspecified derangement of upper arm joint			
52	NL-LRB-00496414, male, 70 Years and older, Consumer or other non health professional	Pneumovax 23® Inj fl disp syr 0,5MI ----- Influenza vaccine (not specified)	Lisinopril Tablet 20Mg, Metformin Tablet 1000Mg, Metoprolol Tablet CR 50Mg (Succinate), Timolol/Bimatoprost eye drops 5/0,3Mg/MI	Injection site pain, Injection site erythema, Injection site swelling, Extensive swelling of vaccinated limb, Dizziness, Retching	Local reactions: 15 minutes. Dizziness, retching: 1 day	Recovered	Pneumovax 23® was administered on the left side, as opposed to what guidelines suggest

* Some reports include both Pneumovax 23® and seasonal influenza vaccine as suspects since they were administered at the same time. The report was only included in table 2 if Pneumovax 23® was the suspect of the ELS reaction. Two reports with ELS on the influenza vaccine side were excluded. Four reports with the 'Pneumo 23®' vaccine were excluded to focus completely on Pneumovax 23®. If there was a report with only erythema and no swelling, but the erythema was extensive according to Lareb's definition, it was still included (Lareb's first requirement of ELS is swelling and/or erythema).