Overview of lymphadenopathy after Covid-19 Booster vaccination

Introduction

To date, the European Medicines Agency (EMA) authorised four COVID-19 vaccines *for active immunisation against SARS-CoV-2*: BioNTech/Pfizer (Comirnaty®), Moderna (SpikeVax®), AstraZeneca (Vaxzevria®) and Janssen that have been used in the Netherlands. BioNTech/Pfizer and Moderna are both mRNA vaccines, encoding the viral spike (S) protein while AstraZeneca and Janssen are using an Adenovirus vector [1-4]. All COVID-19 vaccines are subject to additional monitoring. The most widely given vaccine in the Netherlands is the Pfizer/BioNTech vaccine (Comirnaty®).

For the booster vaccination campaign in the Netherlands, the mRNA vaccines from Pfizer and Moderna are currently used. A booster dose (third dose) of Comirnaty may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older [1]. For the Moderna vaccine a booster dose (0.25 mL, containing 50 micrograms mRNA, which is half of the primary dose) may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older [2].

Lymphadenopathy refers to lymph nodes that are abnormal in size (e.g., greater than 1 cm) or consistency. Palpable supraclavicular, popliteal, submental and iliac nodes, and epitrochlear nodes greater than 5 mm, are considered abnormal, since in these regions, lymphnodes are more easy papable. In most patients, lymphadenopathy is benign and self-limiting.
Lymphadenopathy can have many potential causes, like infection, auto-immune disorder, malignancy, medication and an iatrogenic cause. The location is often helpful in identifying specific etiologies. The etiology is typically associated with the lymphatic drainage pattern. Lymphadenopathy is classified as localized when it involves one region (e.g. the neck or axilla). Generalized lymphadenopathy is defined as two or more involved regions and is more often associated with systemic diseases [5].

Lymphadenopathy is a well-known AEFI for the Covid-19 vaccines, which is mentioned in the SmPC of the Pfizer and the Moderna vaccine that are used in the booster vaccination campaign [1, 2].

In the Lareb report on adverse reactions after the Covid-19 Booster-vaccination, it could be seen that certain adverse events following immunization (AEFI) were reported at a higher percentage of the total reported AEFI after the booster vaccination than after vaccination moment 1 and 2. In this overview we will focus specifically on the reports of lymphadenopathy after the booster vaccination.

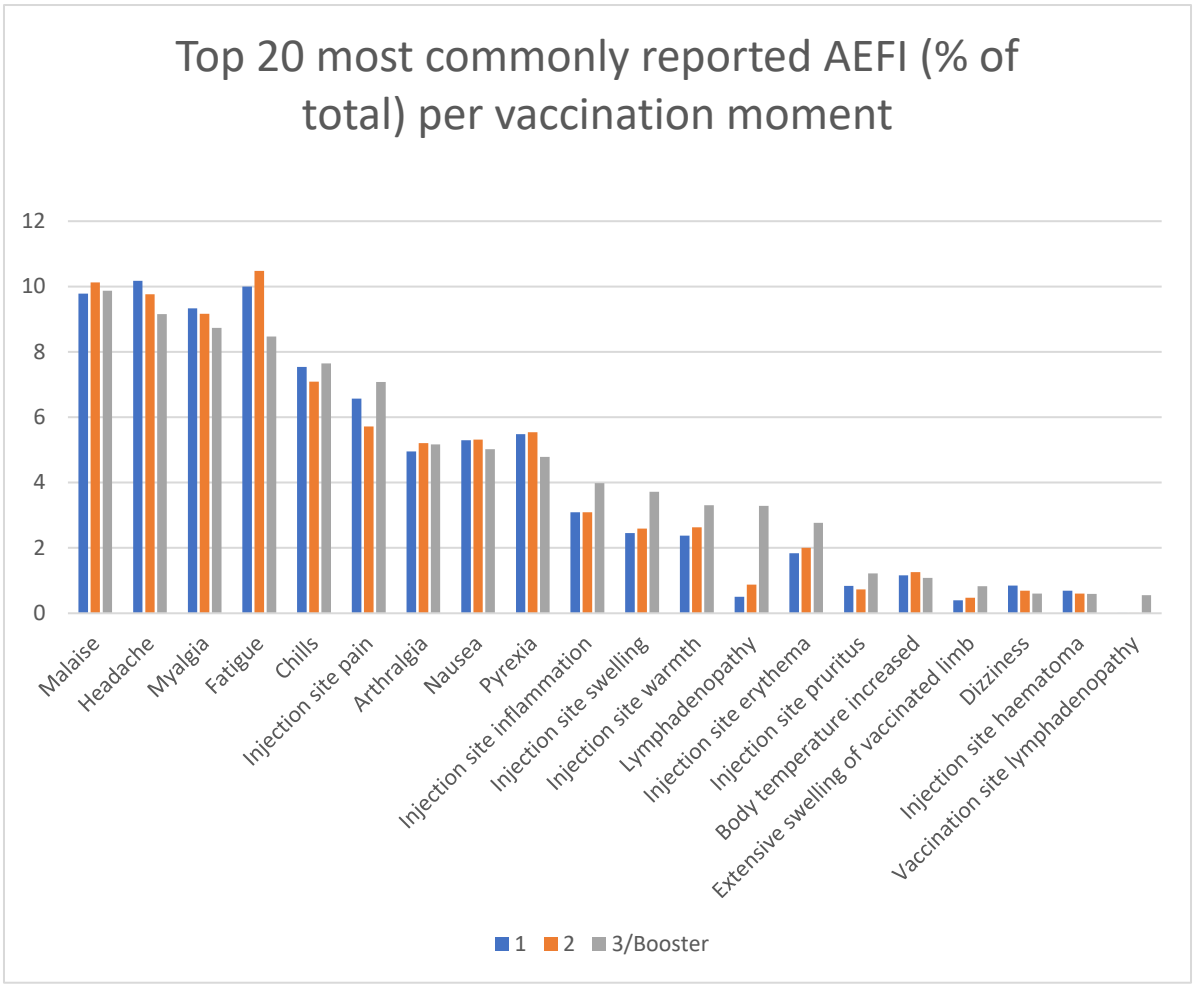

Figure 1. Top 20 of most commonly reported AEFI (percentage of total number of AEFI) per vaccination moment

Reports

During the daily triage of reports it was noted that a large part of reports concerned lymphadenopathy. Until 25-01-2022 a total of 714 reports relating to lymphadenopathy for the booster vaccination were processed by Lareb. It should be noted that not all received reports for the booster vaccination campaign have been processed and coded yet, hence they are not part of the current overview.

Table 1. Reports on lymphadenopathy per vaccination moment on MedDRA PT level

	Reports per vaccination moment			
MedDRA PT	**1**	**2**	**3**	**Total**
Injection site lymphadenopathy	1	4	18	23
Lymphadenitis	27	24	12	63
Lymphadenopathy	2792	2539	582	5913
Lymphadenopathy mediastinal	1	3		4
Paratracheal lymphadenopathy	1	1		2
Vaccination site lymphadenopathy	2	20	102	124
Total	**2824**	**2591**	**714**	**6129**

Table 1 a. Reports on lymphadenopathy per vaccination moment on LLT level

	Reports per vaccination moment			
MedDRA LLT	**1**	**2**	**3**	**Total**
Axillary adenopathy	4	4		8
Axillary lymph nodes enlarged	5	2		7
Axillary lymphadenitis	2			2

Enlarged lymph nodes (excl infective)	2			2
Generalised lymphadenopathy	2			2
Gland in neck	1			1
Glands swollen	3	2		5
Groin nodes		1		1
Inguinal lymph nodes enlarged	1	3		4
Injection site lymphadenopathy	1	4	18	23
Lymph node disorder			1	1
Lymph node inflammation			1	1
Lymph nodes cervical swollen	1			1
Lymph nodes enlarged	4	3		7
Lymph nodes, enlarged (excl lymphadenitis)	1			1
Lymphadenitis	21	22	10	53
Lymphadenitis cervical	2	2		4
Lymphadenitis NOS	1			1
Lymphadenopathy	812	607	73	1492
Lymphadenopathy axillary	1158	1378	434	2970
Lymphadenopathy cervical	476	288	39	803
Lymphadenopathy inguinal	45	18	5	68
Lymphadenopathy mediastinal		1		1
Lymphadenopathy paratracheal	1			1
Lymphadenopathy thoracic		1		1
Mediastinal lymphadenopathy	1	2		3
Mesenteric adenitis	1		1	2
Occipital lymphadenopathy	1			1
Painful lymphadenopathy	1			1
Paratracheal lymphadenopathy		1		1
Postauricular lymphadenopathy	4	1		5
Preauricular lymphadenopathy		1		1
Subclavicular lymphadenopathy	127	95	13	235
Submandibular lymphadenopathy	6	2		8
Supraclavicular lymph nodes enlarged	120	126	16	262
Swollen glands	6	3		9
Swollen lymph nodes	12	4	1	17
Vaccination site lymphadenopathy	2	20	102	124
total number of reported EAFIs	**2824**	**2591**	**714**	**6129**

Table 2. Reports on lymphadenopathy per vaccination brand

	Reports per vaccination moment			
Vaccine brand	**1**	**2**	**3**	**Total**
Astrazeneca	244	25		269
Janssen	163			163
Moderna	776	363	60	1174
Pfizer	1636	2203	653	4492
Non specified	4		1	5
Total	**2824**	**2591**	**714**	**6129**

The mean latency period for the occurrence of lymphadenopathy after each vaccination moment is given in table 3. It can be seen that the latency period is shorter for each subsequent vaccination moment. The duration of the reaction is also slightly longer for vaccination moment 3.

Table 3. Mean latency period and duration for lymphadenopathy per vaccination moment

	Vaccination moment		
	1	**2**	**3**
Number of reports	2824	2591	714
Mean latency period in days	3,45	1,92	1,13
Mean duration in days	6,72	6,14	6,96

To quantify the severity/impact of the reported complaints, we used a custom-made field on the Lareb reporting form, which asks how people were affected by the reaction. The average score per vaccination moment and per vaccine brand is shown in table 4.

Table 4. Mean of impact score on reporting form per vaccination moment and brand

Mean of Impact Score on Reporting form (from 1-5)	**Vaccination moment**		
Vaccine brand	**1**	**2**	**3**
Astrazeneca	2,97	3,00	
Janssen	2,74		
Moderna	2,63	2,92	2,88
Pfizer	2,75	2,82	3,00
Not specified	3,00		2,00
TOTAL	**2,74**	**2,84**	**2,99**

In some reports the swelling was referred to as a tennis-ball, golf ball or avocado. To highlight, some cases with a clear description of the reaction were selected:

NL-LRB-00729552
This spontaneous report from a consumer or other non-health professional concerns a female aged 20-30 years, with vaccination site lymphadenopathy, chills, headache, malaise, fatigue, injection site swelling, injection site induration, extensive swelling of vaccinated limb, pyrexia following administration of covid-19 vaccine for Covid 19 immunisation with a latency of 1 day. The patient is recovering from vaccination site lymphadenopathy. Lymphadenopathy is described as a thick bump which is painful/bruised of 20-10 cm, under the armpit. Because of this, her arm couldn't hang down or move and was numb and she due to this couldn't sleep. The patient visited a general practitioner who said that due to the enlarged lymph node at the vaccinated arm a nerve was pinched.

NL-LRB-00774950
This spontaneous report from a consumer or other non-health professional concerns a female aged 50-60 years, with lymphadenitis following administration of covid-19 vaccin Pfizer for covid 19 immunisation with a latency of 16 days.
She was vaccinated on December 21 2021 and on January 6 2021 was still suffering from painful lymph nodes in her neck. Het General Practitioner diagnosed this as lymphadenitis. The patient has not recovered from lymphadenitis at the time of reporting. She is using analgesics for the pain.

NL-LRB-00726694
This spontaneous report from a consumer or other non-health professional concerns a female aged 30-40 years, with vaccination site lymphadenopathy, chills, headache, malaise, fatigue, injection site pain, injection site warmth, injection site inflammation following administration of covid-19 vaccin pfizer for covid 19 immunisation with a latency of two days. The patient has not recovered from chills, has not recovered from fatigue, has not recovered from headache, The reaction is described as an enormous swelling underneath the armpit at the vaccinated arm. At the moment of reporting she is recovering from local injection site reactions but the lymphadenopathy has not recovered.

NL-LRB-00719617
This spontaneous report from a consumer or other non-health professional concerns a female aged 30-40 years, with lymphadenopathy, chills, headache, malaise, injection site erythema, injection site warmth, injection site pruritus, injection site swelling, injection site inflammation following administration of covid-19 Pfizer vaccin for covid 19 immunisation with a latency of 1 day. The reaction is described as swelling in the left armpit (tennis ball size) and breast tissue (left breast) is also swollen. At the moment of reporting she has not recovered from lymphadenopathy. She is treated with paracetamol.

NL-LRB-00721846
This spontaneous report from a consumer or other non-health professional concerns a female age unknown, with lymphadenopathy cervical, myalgia following administration of covid-19 vaccin Pfizer for covid 19 immunisation with a latency of two days. The reaction is described as swelling the size of a tennis ball in my armpit of the arm where it was pricked. Extending to the chest and thick glands in the neck. The patient has not recovered from lymphadenopathy cervical and has not recovered from myalgia.

SmPC
In the SmPC for the Pfizer vaccine lymphadenopathy is listed as an Uncommon (incidence ≥ 1/1,000 to < 1/100) ADR after vaccination. A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a booster dose (third dose) compared to participants receiving 2 doses [1]. In the Moderna SmPC lymphadenopathy is listed as very common. Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site. Other lymph nodes (e.g., cervical, supraclavicular) were affected in some cases [2].

Data on usage
In total 7,985,352 booster and third vaccinations have been given in the Netherlands until 19 January 2022. Since 6 October, approximately 132,478 people with a serious immune disorder have received their third vaccination at the GGD [6]. Since not all lymphadenopathy cases Lareb received have been processed and coded, we have not yet calculated reporting rates per vaccination moment.

Literature
Axillary lymphadenopathy ipsilateral to the vaccination site has been clinically and radiologically reported after administration of COVID-19 vaccines [7-10]. Özütemiz et al [10]. describe that this can be an important diagnostic dilemma, particularly in cancer patients who are being staged or re-staged, as this benign entity may mimic metastasis, cause unnecessary biopsies and changes in therapy. They report on a breast cancer patient and a patient with squamous cell carcinoma of the head and neck, who had already received the first two doses of mRNA type COVID-19 vaccines before, now presenting with new hypermetabolic reactive lymphadenopathy on FDG PET/CT after the third booster dose.
Cohen et al. [8] performed a study to determine the overall incidence of hypermetabolic lymph nodes after vaccination with the Pfizer vaccine and also its relevance to PET-CT scan interpretation in oncologic patients. A total of 728 vaccinated patients (All-Vac group) were included: 346 received the first dose only (Vac-1 group) and 382 received the 2nd dose as well (Vac-2 group). The incidences of hypermetabolic lymph nodes were 45.6%, 36.4%, and 53.9% in All-Vac, Vac-1, and Vac-2 groups, respectively. Cohen et al. [9] furthermore explored the incidence of hypermetabolic lymph nodes over time after the third Pfizer administration, and its relevance to [18F]FDG PET-CT interpretation in oncologic patients. A total of 179 consecutive oncologic patients that underwent [18F]FDG PET-CT scan after a third Pfizer vaccine dose were included. The incidences of all-grade hypermetabolic lymph nodes and grade 3-4 hypermetabolic lymph nodes were 47.5% and 8.9%, respectively. Hypermetabolic lymph nodes were identified on 82.5% of studies performed within the first 5 days from vaccination.

Mechanism
Vaccination-associated reactive lymphadenopathy is considered a local adverse reaction to vaccination (similar to pain and swelling) and is more commonly observed after receipt of the novel COVID-19 mRNA vaccines compared with other vaccines [11-14]. Similar to many vaccines, mRNA vaccines depend on antigen-presenting cells migrating to regional lymph nodes to elicit both a cellular (T-cell) and humoral (B-cell) immune response. Compared with protein-based vaccines, mRNA vaccines elicit a more robust and rapid B-cell proliferation in the germinal center of the lymph node, likely increasing the incidence of lymphadenopathy [11].
Cohen et al. [7] reported a high correlation between the presence of hypermetabolic lymph nodes after COVID-19 vaccine and serologic antibody testing after vaccination. Cohen et al. [7] describe that based on literature the characteristics of COVID-19 vaccine-associated hypermetabolic lymphadenopathy following the first and second vaccine doses were reported to be different. This probably reflects the difference between the immune response elicited by a first vaccine dose and the amnestic response induced by a booster given 3 weeks later. Unlike the naive cells involved in the primary immune response following a first vaccination, the memory B cell and T cell responses are different following booster vaccinations. The memory cells have already undergone clonal expansion, differentiation, and affinity maturation, so the amnestic immune response has a minimal lag period.

Discussion and conclusion
Local reactogenicity, such as injection site swelling, warmth, inflammation and erythema have been reported to Lareb relatively with a higher percentage after the booster vaccination compared to other AEFIs. Lymphadenopathy (MedDRA PT) is reported with a percentage of 3.29 % of the total reported AEFIs, while this is 0.87% for the second and 0.51% for the 1st vaccination moment. The SmPCs of

the Pfizer and Moderna vaccine and the literature also reflect that lymphadenopathy occurs with a higher incidence after the booster vaccination. In Australia, the most common adverse event reported to the Therapeutic Goods Agency (TGA) following a booster dose is lymphadenopathy [15].
Based on an additional question on the Lareb reporting form, we see that the impact/severity of the reaction is on average higher for the booster vaccination than for any of the previous vaccination moments. Also, the reaction occurs with a on average shorter latency period and the duration is slightly longer.
Although lymphadenopathy is labelled adverse reaction for the Pfizer and Moderna vaccine, not all vaccinated persons will have been prepared for the occurrence and potential severity of this reaction after the booster vaccination. The relative obscurity of raises unnecessary concerns.

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This signal has been raised on February 3, 2022. 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.cbg-meb.nl