Prolonged duration of COVID-19 vaccine-induced lymphadenopathy

Introduction

To date, five COVID-19 vaccines have been authorized for *active immunization against SARS-CoV-2* in The Netherlands: BioNTech/Pfizer (Comirnaty®), Moderna (Spikevax®) , AstraZeneca (Vaxzevria®), Janssen (Jcovden®), and Novavax (Nuvaxovid®) [1-6]. BioNTech/Pfizer and Moderna are both mRNA vaccines, AstraZeneca and Janssen are both vector-based vaccines, and Novavax is a protein subunit vaccine containing a saponin based matrix-M immune-stimulating adjuvant. All five COVID-19 vaccines encode the SARS-CoV-2 spike glycoprotein and induce a cellular and humoral immune response, including SARS-CoV-2 neutralising antibodies. The Pfizer/BioNTech vaccine was administered most frequently in the Netherlands [7].

Lymphadenopathy refers to lymph nodes that are abnormal in size (e.g., greater than 1 cm) or consistency [8]. In most patients, lymphadenopathy is benign and self-limiting. Potential causes of lymphadenopathy are infections, auto-immune diseases, malignancy, or lymphoproliferative disorders. 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. If lymph nodes remain swollen for a longer period of time, diagnostic tests are warranted. These can include blood tests, ultrasound, CT or PET scan, and ultimately biopsy or excision for histological examination. Lymphadenopathy is a well-known Adverse Event Following Immunization (AEFI) for COVID-19 vaccines [1-6]. In February 2022, the Netherlands Pharmacovigilance Center Lareb published an overview of lymphadenopathy cases induced by a BioNTech/Pfizer or Moderna booster vaccination [9]. Compared to the first or second vaccination dose, time to onset was shorter (1 vs 2-4 days) and severity was higher for booster vaccinations. Mean duration was 6 to 7 days. However, safety reports describing prolonged duration of lymphadenopathy were also received. Reports with a minimum duration of 6 months and time to onset of 28 days or less after COVID-19 vaccination were selected for further investigation. Duration was calculated for not recovered or recovering cases by extracting the time between receive date of safety report and start date of lymphadenopathy.

Reports

Untill August 16th 2023, the Netherlands Pharmacovigilance Centre Lareb received a total of 18,986 safety reports on lymphadenopathy after COVID-19 vaccination. Median time between startdate of lymphadenopathy and date of reporting was 2 days (Figure 1). Since reports were received early after onset, most cases were not recovered at time of reporting. Calculation of median duration based on startdate of lymphadenopathy and receive date of safety report was therefore not meaningfull. For recovered cases at time of reporting (3,855 cases) median duration was 4 days (Figure 2).

Figure 1. Time between receive date safety report and startdate COVID-19 vaccine-induced lymphadenopathy.

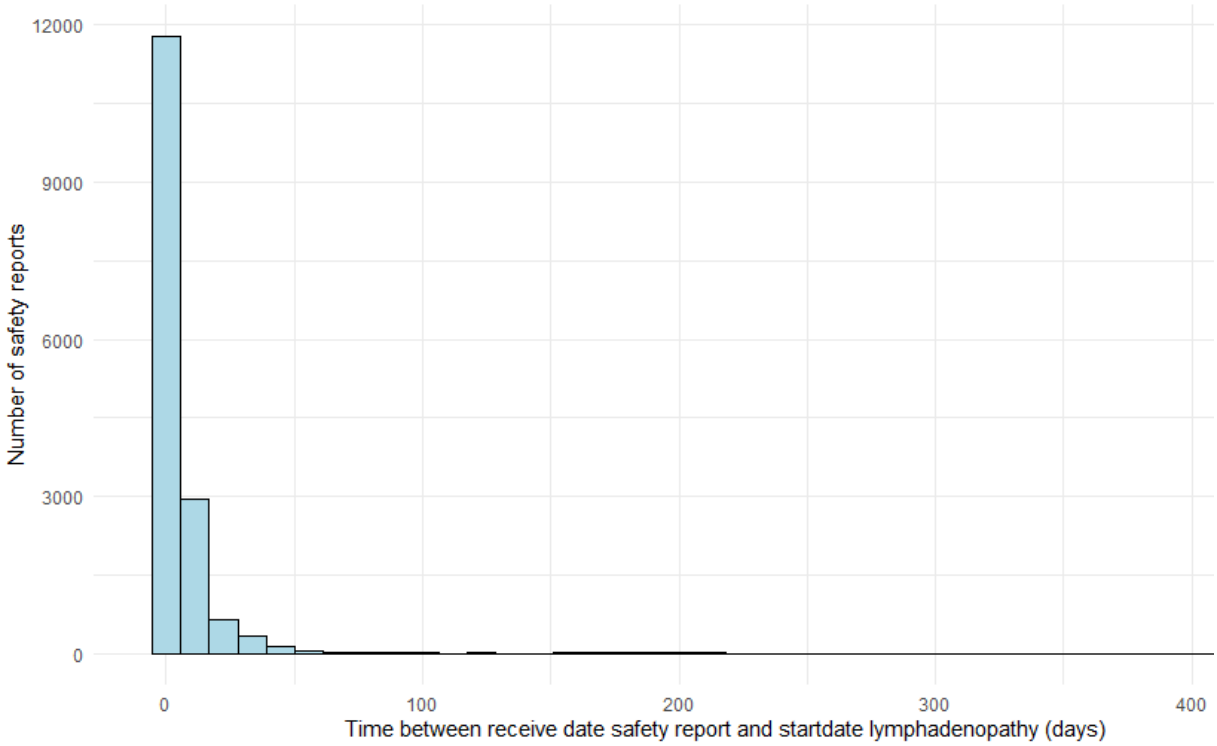
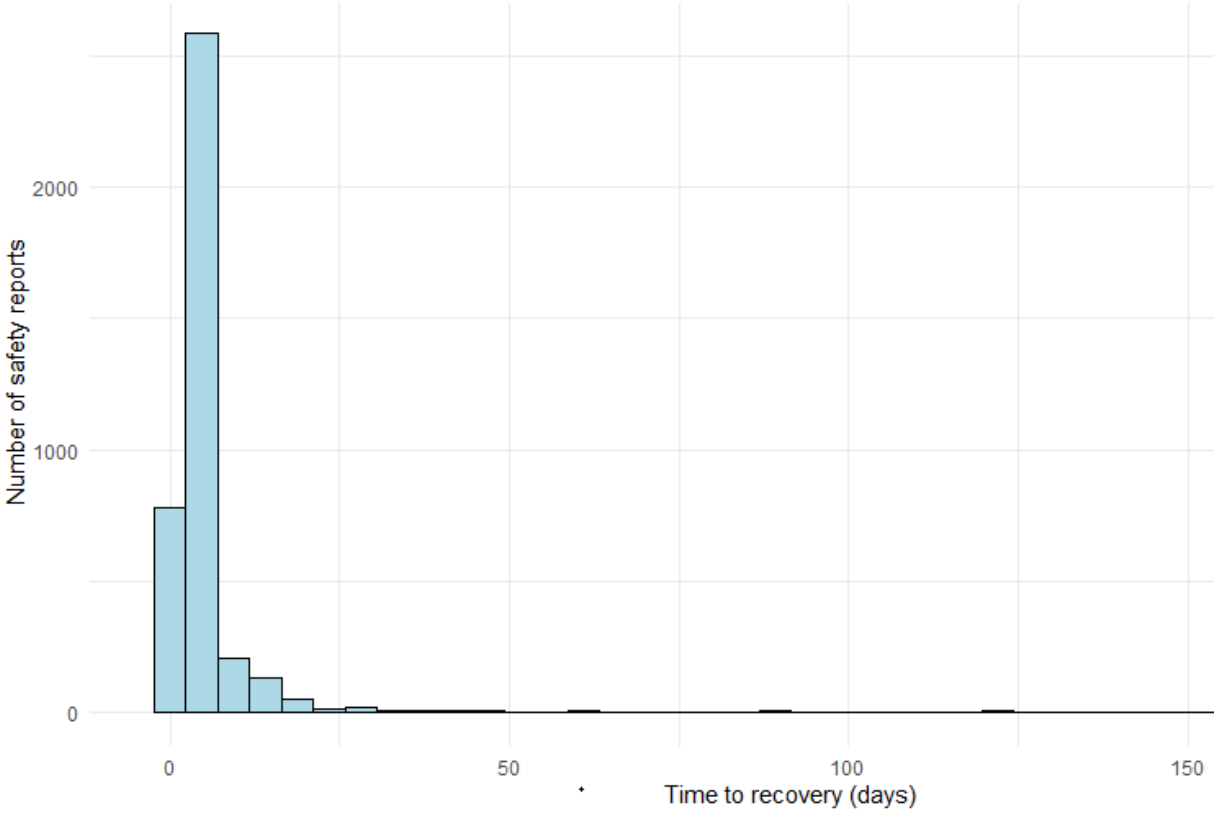


Figure 2. Duration of recovered COVID-19 vaccine-induced lymphadenopathy.



Within the 18,986 reports on lymphadenopathy following COVID-19 vaccination, we identified 67 cases with prolonged duration *of 6 months or more*. These reports contained a total of 73

lymphadenopathy-related MedDRA preferred terms (PT) since some patients developed lymphadenopathy at multiple sites. All cases were reported by consumers or other non-health care professionals. The most frequently reported COVID-19 vaccine brand was BioNTech/Pfizer (66%), followed by Moderna (22%), AstraZeneca (8%), Janssen (3%), and unspecified brand (2%). Most cases were reported for the primary series (85%; 55% for the first vaccination and 30% for the second). Only 15% of cases was reported for the booster vaccination. Of these cases, 48 concerned females and 19 males with a median age of 48 years. Median time to onset of lymphadenopathy was 2 days, with a minimum of 0 (within the same day of vaccination) and a set maximum of 28 days. Figure 3 shows the distribution of time to onset. Median duration of lymphadenopathy was 230 days, with a set minimum of 183 and a maximum of 678 days. Figure 4 shows the distribution of duration. Outcome of lymphadenopathy was “not recovered” in 59% of cases and “recovering” in 41% at the time of reporting. Of these 67 lymphadenopathy cases with prolonged duration, 1 was considered serious according to CIOMS criterium “Other medically important condition”. In 19 cases (28.4%) a previous COVID-19 infection was reported.

Figure 3. Time to onset of COVID-19 vaccine-induced lymphadenopathy cases with prolonged duration.

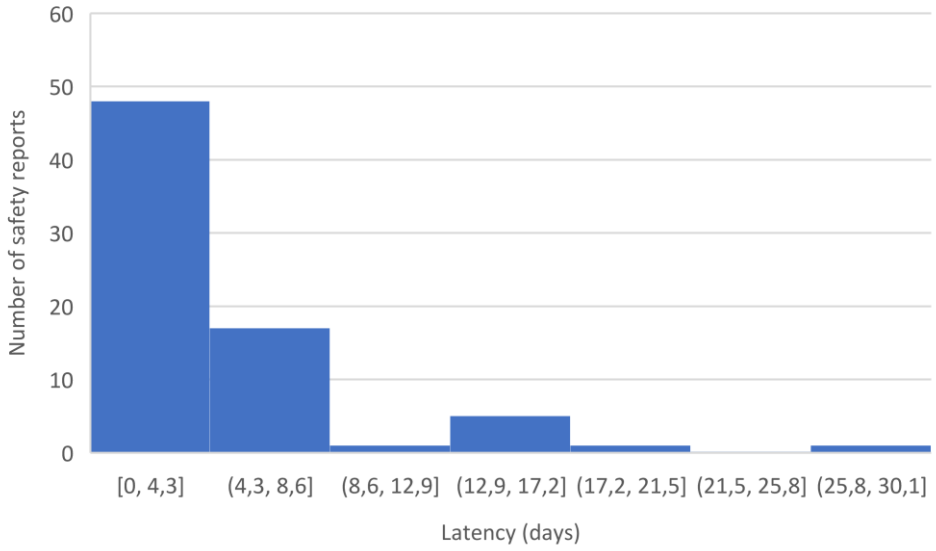
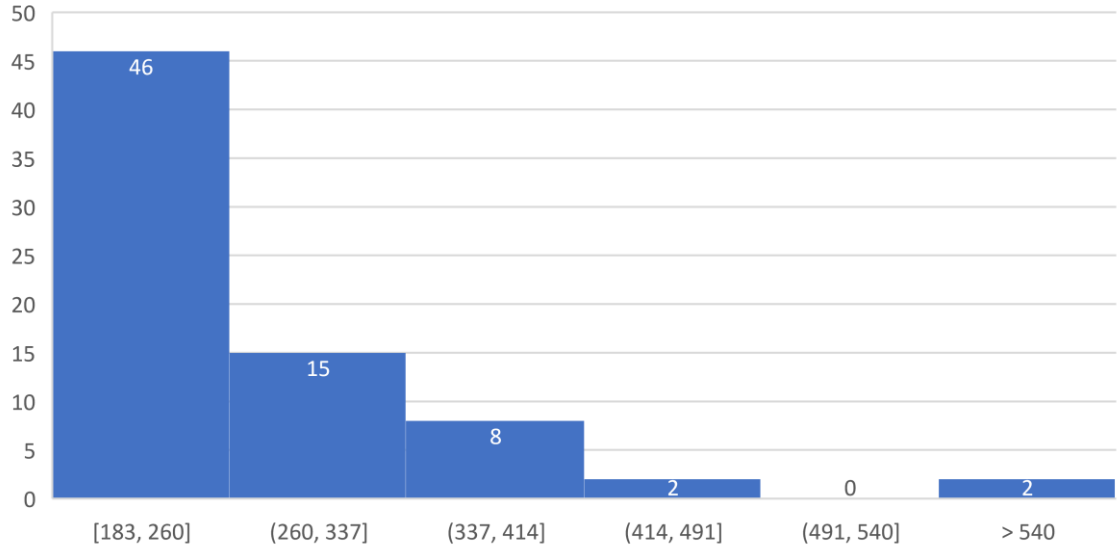


Figure 4. Duration of COVID-19 vaccine-induced lymphadenopathy cases with prolonged duration.



Most cases of lymphadenopathy were localised at the axilla (19%), supraclavicular space (9%), or cervical region (8%). In only one case generalized lymphadenopathy was reported. In almost half

of the 67 lymphadenopathy cases with prolonged duration medical diagnostics were performed, which led to a diagnosis in only 5 cases, see Table 1 for an overview of all characteristics. Each diagnosis provides a plausible alternative explanation for the reported lymphadenopathy. Ultrasounds were performed in 14 patients, 7 of these patients reported follow-up ultrasounds, additional imaging studies like X-rays, CT, MRI and PET scan were reported in 11 cases, and biopsies in 5 cases. Few reports described ultrasound or biopsy results, which was described as reactive in all cases.

Table 1. Characteristics of COVID-19 vaccine-induced lymphadenopathy cases with prolonged duration.

Characteristic	Times reported
Localisation	
Axilla	13
Supraclavicular space	6
Cervical region	5
Inguinal region	2
Retro-auricular	1
Unknown	40
Classification	
Localized	28
Generalized	1
Unknown	38
Alternative causes present	
Yes	1
Sarcoidose	1
No	0
Unknown	66
Medical diagnostics performed	
Yes	32
Blood laboratory investigations	8
Ultrasound	14
1 or more follow-up ultrasounds	7
Biopsy	5
CT	3
MRI	2
Mammography	2
X-ray thorax	2
X-ray clavicula	1
PET scan	1
ACE measurement	1
No	4
Unknown	31
Referred to a medical specialist	
Yes	0
No	0
Unknown	67
Diagnosis was made	
Yes	5
Sinusitis	1
Myositis	1
Sarcoidosis exacerbation	1
Indolent non-Hodgkin lymphoma	1
Lymphoma stage IV	1
No	0
Unknown	62
Received treatment	
Yes	6
Antibiotics	3
Prednisone	1
Surgery	1
Chemotherapy	1
No	0
Unknown	61

Other Sources of information

SmPC

Lymphadenopathy is listed as Adverse Drug Reaction (ADR) in the SmPC of all COVID-19 vaccines [2-6]. The listed frequency is Often (≥1/100, < 1/10) for BioNTech/Pfizer with a higher frequency for the booster vaccination compared to the primary series (2.8% vs 0.9%); Very often (≥1/10) for Moderna; Sometimes (≥ 1/1.000, < 1/100) for AstraZeneca and Novavax; and Rare (≥ 1/10.000, < 1/1.000) for Janssen. None of the SmPC mention prolonged duration of lymphadenopathy.

Literature
A 60-70-years-old woman who received regular follow up ultrasounds of breast and axilla because of a breast calcification was diagnosed with axillary lymph node swelling 7 days after her first COVID-19 vaccination which was still present 6 months later [10]. This lymph node was not palpable and lymph node structure was normal as seen in inflammatory reactions. A larger study described the follow-up of 94 patients with suspected COVID-19 vaccine-related axillary lymphadenopathy, as seen on breast imaging [11]. In 32 patients a biopsy was performed which revealed a benign outcome in 29 patients and a malignant outcome in 3 patients. All patients with benign biopsy findings had non-suspicious sonographic features in contrast to the highly suspicious sonographic features in the 3 other cases. The authors of this study advocated a lengthening of the follow up recommendations to 12-16 weeks after the second vaccine dose, in cases of non-suspicious sonographic features, in order to minimize unnecessary follow-up examinations and biopsies. A recent study described time to resolution of axillary lymphadenopathy in 54 patients with unilateral axillary lymphadenopathy ipsilateral to the vaccination-site of a mRNA COVID-19 booster dose [12]. Axillary lymphadenopathy had resolved after a mean time of 102 days (with a standard deviation of 56 days) and a mean time of 84 days after the initial ultrasound (standard deviation of 49 days). In a previous study by the same authors they examined time to resolution of axillary lymphadenopathy after the first COVID-19 vaccination, which was a mean of 127 days (standard deviation of 43 days) [13]. Another study evaluating axillary lymphadenopathy following COVID-19 vaccination with long-term follow-up, found persistent axillary lymphadenopathy up to 43 weeks after vaccination [14].

Mechanism
Vaccination-induced 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 [15-18]. 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 [15]. A high correlation between the presence of hypermetabolic lymph nodes after COVID-19 vaccination and serologic antibody testing after vaccination was found [19]. Characteristics of COVID-19 vaccine-induced hypermetabolic lymphadenopathy were different following the first and second vaccine doses. Unlike the naive cells involved in the primary immune response following a first vaccination, the memory B and T cell responses following booster vaccinations react different. The exact mechanism for prolonged duration remains unclear.

Discussion and conclusion
COVID-19 vaccine-induced lymphadenopathy is a well-known and labelled AEFI with an expected short duration. However, pharmacovigilance centre Lareb has received 67 safety reports which describe a different course with a prolonged duration of COVID-19 vaccine-induced lymphadenopathy. Suggestive factors for a causal relationship with COVID-19 vaccination are the short median time to onset of 2 days in combination with the absence of an alternative explainatory diagnosis in 62 cases, despite medical diagnostics which were performed in almost half of the cases (48%). Only a smal proportion of safety reports on COVID-19 vaccine-induced lymphadenopathy describe a prolonged duration. However, since safety reports on lymphadenopathy are filed soon after start, with a median of 2 days, most cases are not recovered at time of reporting (80%) therefore duration is unknown in these cases. In addition, there are several large case series describing, imaging confirmed, prolonged duration of COVID-19 vaccine-induced lymphadenopathy.
Of note, a total of 327 cases of supraclavicular lymphadenopathy following COVID-19 vaccination were reported of which 6 had a prolonged duration. This is interesting since supraclavicular

lymphadenopathy is closely associated with malignancy and should therefore always be investigated regardless of duration [20]. In cases series presenting results of supraclavicular lymph node biopsies, malignancy rates of 54 to 85 percent have been seen. Several case reports describing transient supraclavicular lymphadenopathy after COVID-19 vaccination have been published [18, 19, 21-23].
Since lymphadenopathy can be a sign of malignancy for which imaging and ultimately invasive procedures are routine clinical practice, this safety signal provides clinical relevant information for general physicians, oncologists, and radiologists, amongst others. Based on a study by breast imaging radiologists from Johns Hopkins Medicine, The Society of Breast Imaging (SBI) revised their follow-up recommendations for patients who present with unilateral axillary lymphadenopathy in the setting of recent COVID-19 vaccination in cases of non-suspicious sonographic features, in order to minimize unnecessary follow-up examinations and biopsies [24, 25]. Instead of a 4–12 weeks follow-up interval, as recommended in March 2021, an interval of 12 weeks or more was recommended in February 2022. The European Society of Breast Imaging (EUSOBI) also made guidelines on the management of axillary lymphadenopathy after COVID-19 vaccination in August 2021 [26]. In their latest revision from July 2023, they recommend that symptomatic and asymptomatic imaging-detected unilateral lymphadenopathy on the same side of recent COVID-19 vaccination (within 12 weeks) should be classified as a benign finding and that no further work-up should be pursued in patients without breast cancer history and no imaging findings suspicious for cancer [27].

In conclusion, COVID-19 vaccine-induced lymphadenopathy can have a prolonged duration with a median of 230 days up to a maximum of 678 days. Although most cases of COVID-19 vaccine-induced lymphadenopathy may have a short duration, prolonged duration can greatly impact patients mental and physical wellbeing and can increase hospital workload by unnecessary follow-up imaging and invasive procedures. Attention for this is warranted.

References

[1] "European Medicines Agency. COVID-19 vaccines: authorised (access date 20-5-2022)." https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised (accessed.

[2] "European Public Assessment Report – Product information of COVID-19 vaccine BioNTech/Pfizer (Comirnaty®). (version date 6-5-2022)." https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf (accessed.

[3] "European Public Assessment Report – Product information of COVID-19 vaccine Moderna (Spikevax®). (Last updated: 10-5-2022)." https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf (accessed.

[4] "European Public Assessment Report – Product information of COVID-19 vaccine AstraZeneca (Vaxzevria®). (Last updated: 25-5-2022). ." https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf (accessed.

[5] "European Public Assessment Report – Product information of COVID-19 vaccine Janssen (Jcovden®) (Last updated: 29-4-2022). ." https://www.ema.europa.eu/en/documents/product-information/jcovden-previously-covid-19-vaccine-janssen-epar-product-information_en.pdf (accessed.

[6] "European Public Assessment Report – Product information of COVID-19 vaccine Novavax (Nuvaxovid®). (Last updated: 21-3-2022). ." https://www.ema.europa.eu/en/documents/product-information/nuvaxovid-epar-product-information_en.pdf (accessed.

[7] Rijksoverheid. "Coronadashboard." https://coronadashboard.rijksoverheid.nl/landelijk/de-coronaprik (accessed 19-2-2024.

[8] H. L. Gaddey and A. M. Riegel, "Unexplained Lymphadenopathy: Evaluation and Differential Diagnosis," (in eng), *Am Fam Physician,* vol. 94, no. 11, pp. 896-903, Dec 1 2016.

[9] P. c. Lareb. "Overview of lymphadenopathy after Covid-19 Booster vaccination." https://www.lareb.nl/Knowledge/FilePreview?id=38370&p=33497 (accessed 2024).

[10] N. Yoshimoto *et al.*, "Timing and Duration of Axillary Lymph Node Swelling After COVID-19 Vaccination: Japanese Case Report and Literature Review," *In Vivo,* vol. 36, no. 3, pp. 1333-1336, May-Jun 2022, doi: 10.21873/invivo.12834.

[11] D. L. Nguyen, E. B. Ambinder, K. S. Myers, L. A. Mullen, B. Panigrahi, and E. Oluyemi, "COVID-19 Vaccine-Related Axillary Adenopathy on Breast Imaging: Follow-Up Recommendations and Histopathologic Findings," *AJR Am J Roentgenol,* vol. 218, no. 6, pp. 997-998, Jun 2022, doi: 10.2214/AJR.21.27162.

[12] E. Mema *et al.*, "Axillary Lymphadenopathy After a COVID-19 Vaccine Booster Dose: Time to Resolution on Ultrasound Follow-Up and Associated Factors," *AJR Am J Roentgenol,* vol. 221, no. 2, pp. 175-183, Aug 2023, doi: 10.2214/AJR.22.28970.

[13] E. G. Lane *et al.*, "Time for Resolution of COVID-19 Vaccine-Related Axillary Lymphadenopathy and Associated Factors," *AJR Am J Roentgenol,* vol. 219, no. 4, pp. 559-568, Oct 2022, doi: 10.2214/AJR.22.27687.

[14] S. Wolfson *et al.*, "Axillary Adenopathy after COVID-19 Vaccine: No Reason to Delay Screening Mammogram," *Radiology,* vol. 304, no. 3, p. E57, Sep 2022, doi: 10.1148/radiol.229015.

[15] D. L. Lam and M. R. Flanagan, "Axillary Lymphadenopathy After COVID-19 Vaccination in a Woman With Breast Cancer," *JAMA,* vol. 327, no. 2, pp. 175-176, 2022, doi: 10.1001/jama.2021.20010.

[16] N. Mehta *et al.*, "Unilateral axillary Adenopathy in the setting of COVID-19 vaccine," (in eng), *Clin Imaging,* vol. 75, pp. 12-15, Jul 2021, doi: 10.1016/j.clinimag.2021.01.016.
[17] C. E. Edmonds, S. P. Zuckerman, and E. F. Conant, "Management of Unilateral Axillary Lymphadenopathy Detected on Breast MRI in the Era of COVID-19 Vaccination," (in eng), *AJR Am J Roentgenol,* vol. 217, no. 4, pp. 831-834, Oct 2021, doi: 10.2214/ajr.21.25604.
[18] T. Washington, R. Bryan, and C. Clemow, "Adenopathy Following COVID-19 Vaccination," *Radiology,* vol. 299, no. 3, pp. E280-E281, Jun 2021, doi: 10.1148/radiol.2021210236.
[19] N. Hiller, S. N. Goldberg, M. Cohen-Cymberknoh, V. Vainstein, and N. Simanovsky, "Lymphadenopathy Associated With the COVID-19 Vaccine," *Cureus,* vol. 13, no. 2, p. e13524, Feb 23 2021, doi: 10.7759/cureus.13524.
[20] A. W. Bazemore and D. R. Smucker, "Lymphadenopathy and malignancy," *Am Fam Physician,* vol. 66, no. 11, pp. 2103-10, Dec 1 2002. [Online]. Available: https://www.ncbi.nlm.nih.gov/pubmed/12484692.
[21] B. Kim, Y. Park, E. K. Kim, and S. H. Lee, "Supraclavicular lymphadenopathy after COVID-19 vaccination in Korea: serial follow-up using ultrasonography," *Clin Imaging,* vol. 79, pp. 201-203, Nov 2021, doi: 10.1016/j.clinimag.2021.05.031.
[22] O. R. Mitchell, R. Dave, J. Bekker, and P. A. Brennan, "Supraclavicular lymphadenopathy following COVID-19 vaccination: an increasing presentation to the two-week wait neck lump clinic?," *Br J Oral Maxillofac Surg,* vol. 59, no. 3, pp. 384-385, Apr 2021, doi: 10.1016/j.bjoms.2021.02.002.
[23] C. Ozutemiz *et al.*, "Lymphadenopathy in COVID-19 Vaccine Recipients: Diagnostic Dilemma in Oncologic Patients," *Radiology,* vol. 300, no. 1, pp. E296-E300, Jul 2021, doi: 10.1148/radiol.2021210275.
[24] S. Destounis, "Axillary Lymphadenopathy Can Be Long Lasting Finding on MRI After COVID-19 Booster Vaccination," *Acad Radiol,* Dec 20 2023, doi: 10.1016/j.acra.2023.11.013.
[25] A. S. Lars Grimm, Brian Dontchos, Caroline Daly, Catherine Tuite, Emily, H. M. Sonnenblick, Jose Net, Katerina Dodelzon, Roger Yang, Sally Goudreau, Sarah, and V. D. Jacobs, Vidhi Kacharia. "Revised SBI Recommendations for the Management of Axillary Adenopathy in Patients
with Recent COVID-19 Vaccination." https://assets-002.noviams.com/novi-file-uploads/sbi/pdfs-and-documents/policy-and-position-statements/2022/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination_updatedFeb2022.pdf (accessed 13-02-2024.
[26] S. Schiaffino *et al.*, "Axillary lymphadenopathy at the time of COVID-19 vaccination: ten recommendations from the European Society of Breast Imaging (EUSOBI)," *Insights Imaging,* vol. 12, no. 1, p. 119, Aug 20 2021, doi: 10.1186/s13244-021-01062-x.
[27] S. Schiaffino *et al.*, "European Society of Breast Imaging (EUSOBI) guidelines on the management of axillary lymphadenopathy after COVID-19 vaccination: 2023 revision," *Insights Imaging,* vol. 14, no. 1, p. 126, Jul 19 2023, doi: 10.1186/s13244-023-01453-2.

This signal has been raised on April 26, 2024. 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