Delayed Local Adverse Reactions and the Moderna COVID-19 vaccine

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Summary

A cluster analysis, a grouping of cases based on reported adverse event terms, of COVID-19 vaccine individual case safety reports (ICSRs) was performed on 1st March 2021, using data from VigiBase, the WHO global database of ICSRs. Two clusters of reports describing local adverse reactions to the Moderna COVID-19 vaccine were identified as having a delayed median time to onset (TTO) compared to other local reactions. Firstly, a cluster of 64 reports that commonly reported a lymphadenopathy that was typically localised to the ipsilateral axilla of the injection site, with a median TTO of 5 days. When compared to other COVID-19 vaccines, there was a second peak of onset for the term lymphadenopathy five days after vaccination with the Moderna COVID-19 vaccine. A possible mechanism is a robust immune response. The second cluster, of 605 reports, commonly reported the terms relating to a localised, erythematous and pruritic injection site skin reaction with a median onset of 7 days. For the Moderna vaccine, there was a second peak in TTO of these terms that describe a local skin reaction around seven days after vaccination. The skin reaction may represent a delayed hypersensitivity reaction. Both lymphadenopathy and local skin reactions are labelled adverse reactions for all COVID-19 vaccines investigated, but there is limited information on delayed events. For both reactions, the majority of cases were non-serious. These cases appear to cause no contraindication to further vaccine doses and most cases seem to resolve over time.

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Introduction

The vaccines being used against COVID-19 include the first mRNA-based vaccines authorised for use in humans. As the vaccines employ new technology, vigilance is required to further understand the profile of the adverse events related to them. We aimed to investigate the delayed adverse reactions of lymphadenopathy and a local skin reaction to the Moderna COVID-19 vaccine in comparison to other COVID-19 vaccines.

Reports from VigiBase

VigiBase, the WHO global database of individual case safety reports (ICSRs), was updated on 28th February 2021. A cluster analysis, a data-driven grouping of ICSRs according to their adverse event profiles based on reported terms, was performed on 1st March 2021. The clustering algorithm has been developed over several years and previously used for retrospective analysis[1, 2]. Reports with only one term reported were excluded. The clustering was divided according to vaccine manufacturer for all vaccines that had over 1,000 suitable ICSRs (Pfizer-BioNTech, Moderna, and AstraZeneca). After initial assessment, a lymphadenopathy cluster which was seen to have a delayed time to onset (TTO) compared to other clusters reporting similar reactions for both Moderna and other COVID-19 vaccines, went through in-depth clinical analysis. Similarly, a localised skin reaction was also identified, with a more delayed TTO compared to other clusters reporting similar reactions for both Moderna and other vaccines, but the cluster was too large for a complete manual assessment.

"Delayed lymphadenopathy" cluster

For the Moderna COVID-19 vaccine the cluster analysis identified a group of unique ICSRs (n=64), after one duplicate was removed following in-depth analysis, with the following adverse events: Lymphadenopathy (n=57, 89%), Lymph node pain (n=23, 36%), Axillary pain (n=22, 34%) and Pain in extremity (n=9, 14%). The median TTO for these adverse events was five days. Most commonly, the narrative outlined the onset of painful lymphadenopathy on the ipsilateral side to the injection several days after the vaccination. The most frequently reported area of lymphadenopathy was the axillary region (n=47, 73%), then the supraclavicular (n=12, 19%) and cervical (n=7, 11%). Most cases occurred after the first dose (n=45, 70%) and the only case after the second dose was atypical for the general presentation with an onset of lymphadenopathy two days after vaccination, while 28% (n=18) of cases did not report the dose number. The lymphadenopathy seemed to persist, with several cases reporting symptoms that lasted a week or more. Slightly more cases (n=17, 27%) were reported as recovered or recovering than as not recovered (n=13, 20%), however most cases were reported early in the timeline of the reaction, while symptoms were ongoing. One case noted an ultrasound scan, which showed a reactive lymphadenopathy 10 days after onset of symptoms. No cases required further management other than simple analgesia in the cases that were in keeping with the pattern of symptoms commonly described. There were no other medications that were suspected to have caused the reaction and no concomitant medication was reported more than once.

As of 1st March 2021, there were 7,790 reports in VigiBase for lymphadenopathy and all COVID-19 vaccines, and of these, 261 concerned the Moderna COVID-19 vaccine. The other COVID-19 vaccines with the most cases reporting lymphadenopathy were the Pfizer-BioNTech vaccine (n=6,589) and the AstraZeneca COVID-19 vaccine (n=858). The distribution of the TTO of lymphadenopathy for each vaccine is seen in Figure 1. For the Moderna vaccine, the most commonly co-reported terms with lymphadenopathy were: Headache (n=61, 23%), Pyrexia (n=53, 20%), Fatigue (n=46, 18%), and Chills (n=45, 17%). There were no other medications that were suspected to have caused the reaction and no concomitant medication was reported more than once. The demographics of all lymphadenopathy cases for the Moderna, Pfizer-BioNTech and AstraZeneca COVID-19 vaccines, as well as the "Delayed lymphadenopathy" cluster, are in Table 1.

"Delayed local skin reaction" cluster

Another cluster (n=605) identified for the Moderna vaccine had the following adverse events: Injection site erythema (n=489, 81%), Injection site swelling (n=325, 54%), Injection site pruritus (n=280, 46%), and Injection site warmth (n=253, 42%). The median TTO of these adverse events was seven days. Although not all case narratives were reviewed, due to the size of the cluster, they typically described a

skin reaction that was a red, raised, pruritic rash of several centimetres in diameter, and often circular in shape and hard to the touch. The rash either developed after resolution of immediate injection site discomfort, or there was no immediate reaction. Resolution of the rash was typically reported between two and five days after onset, mostly without the use of medications other than anti-pruritics. There were no other medications that were suspected to have caused the reaction and the most commonly reported concomitant medications were: Levothyroxine (n=7, 1%), Acetylsalicylic acid (n=4, 0.7%) and Sertraline (n=2, 0.3%). A non-exhaustive free-text search of the narratives revealed 25 patients who had been prescribed an antibiotic for the reaction. One individual was prescribed antibiotics but chose not to take them as they were already improving, and the symptoms resolved without antibiotic use.

As of 1st March 2021, there were over 4,000 cases reporting one of the four most commonly reported terms for this cluster (Injection site erythema, Injection site swelling, Injection site pruritus, and Injection site warmth) across all COVID-19 vaccines. The distribution of the TTO for these terms for each vaccine is seen in Figure 2. There were 986 cases after vaccination with the Moderna vaccine. There was a notable difference between the median TTO for the Moderna vaccine (six days), and the Pfizer-BioNTech and AstraZeneca vaccines (both one day). The demographics of these cases are further described in Table 2.

Labelling and literature

Lymphadenopathy is a labelled adverse reaction for the Moderna COVID-19 vaccine, Pfizer-BioNTech COVID-19 vaccine and the AstraZeneca COVID-19 vaccine[3–10]. For the Moderna COVID-19 vaccine the MHRA and FDA describe axillary swelling and tenderness on the ipsilateral side to the vaccination[3, 5]. Moderna clinical trial data suggest that lymphadenopathy and axillary swelling were more common after the second dose[11] and within the first few days of vaccination[12].

Localised injection site reactions are labelled as an adverse reaction in the authorisation documents of the Moderna, Pfizer-BioNTech and AstraZeneca vaccines[3–10]. The FDA outline a delayed local skin reaction occurring seven days or more after the Moderna vaccine[3], but this is not mentioned by the MHRA or EMA[4, 5]. Delayed injection site reactions, with a TTO of seven days or more, was reported in the large clinical trials (n=30,351) for the Moderna vaccine[11]. These reactions were characterised by localised erythema, in duration and tenderness that resolved within four to five days. These were more common after the first dose (n=244, 0.8%) rather than the second dose (n=68, 0.2%). It is not explicitly stated if those who had a delayed reaction after the first dose received the second, however overall withdrawal rates from the clinical trial were low. Similar delayed local reactions have also been described with the use of the Moderna COVID-19 vaccination[13].

There was some overlap between the two groups of reactions; 14 cases had a TTO of greater than five days for a localised skin reaction and described lymphadenopathy. In these ICSRs, the lymphadenopathy was recorded to have occurred prior to the localised skin reaction for half of the cases. One case described lymphadenopathy starting on the fifth day after vaccination and persisting for more than five days, whilst the rash in the same person developed on the seventh day and was fully resolved within two days. Although most cases of the reactions occurred separately, they do not appear to be mutually exclusive.

Discussion and Conclusion

The pathophysiology of these reactions is unknown, but there are several mechanisms that may contribute to or cause them. The lymphadenopathy described in clinical trials of an mRNA vaccine candidate were likely to occur due to a robust immune response to the vaccine[14]. Ipsilateral axillary lymphadenopathy has been reported with previous vaccines, which is often early in onset and prolonged[15]. Lymphadenopathy can also present as part of a delayed hypersensitivity reaction[16, 17]. However, some delayed hypersensitivity reactions are not immunologically mediated and can be caused by non-specific irritation or reactions to vaccine adjuvants[18].

A potential mechanism for the local skin reactions is a delayed hypersensitivity reaction, which are most commonly rashes[18]. Delayed hypersensitivity reactions can occur within hours or several weeks after vaccination[18, 19] and are largely dependent on Th1 induction[20]. COVID-19 mRNA vaccines have been shown to produce a robust Th1 immune response[14, 21, 22]. A delayed hypersensitivity reaction

as a cause of the localised injection site reaction is supported by findings from a case where a biopsy of a similar local injection site reaction after vaccination with the Moderna COVID-19 vaccine, was suggestive of a delayed hypersensitivity reaction[13]. It is worth noting that large, local, delayed hypersensitivity reactions with T-cell infiltration are associated with prolonged and effective immunity[18].

It is unclear why these delayed reactions have been identified with the Moderna vaccine but not the other COVID-19 vaccines. The Moderna and Pfizer-BioNTech COVID-19 vaccines are the first mRNA vaccines authorised for use in humans and they both use novel ingredients such as polyethylene glycols as carrier molecules, which can infrequently cause hypersensitivity reactions. There are further differences of additional components between the mRNA vaccines, but the role of the specific active or inactive ingredients in acute and delayed hypersensitivity reactions to the vaccines is unclear[19, 23]. Research is therefore required to understand the adverse effects of this vaccine platform and specific carrier molecules[24].

There are some limitations with the current review: 1) Reporting patterns are likely to be affected by other factors such as geographical distribution of use and different qualifications of reporters, with differences between the vaccines highlighted in Tables 1 and 2. 2) The delayed, local injection site reaction already has attracted significant media attention[25, 26] and this may have skewed reporting of such reactions. 3) The discrepancies of adverse event reporting platforms may also affect reporting, for example it can be difficult to list concomitant medications and in some platforms it is not possible to give times of onset for different adverse events. However, in general the clinical patterns from the case narratives tend to match the reported TTO. 4) There is no follow up information regarding the second dose.

For both the localised lymphadenopathy and skin reactions, the cases reported here are generally non-serious, with a small minority of cases being labelled as serious. Most cases in the delayed lymphadenopathy occurred after the first dose and, although limited, when the dose number was recorded for the local skin reaction, cases occurred after the first dose, in keeping with Moderna clinical trial data[11]. Delayed hypersensitivity reactions and injection site reactions to vaccines do not typically contraindicate further doses[18, 19, 27], nor are most systemic reactions. In the 12 cases that presented with large, local, delayed injection site reactions, all of them went on to receive the second vaccination. Of these 12 cases, 50% did not have a reoccurrence with the second dose, 25% had similar recurrent reactions and 25% had a less severe reaction[13]. However, further longitudinal studies to examine the safety profile of repeated vaccinations in these patients are recommended. Another concern is the use of antibiotics in the cases of a delayed local skin reaction, and here we have identified a small number of cases where antibiotics were prescribed, but one of these cases resolved without antibiotics, this is supported by a previous report, where only one patient received antibiotics out of 12 cases and all recovered[13]. Unilateral lymphadenopathy following vaccination has also caused concern for healthcare providers and patients, and there have been suggestions to change management to reduce patient anxiety and healthcare provider burden[15].

In summary, this signal further outlines new characteristics of known adverse reactions, a delayed ipsilateral lymphadenopathy and a delayed local skin reaction to the Moderna COVID-19 vaccine. Improving the knowledge of the clinical patterns of these new aspects of known reactions will hopefully be of benefit to healthcare professionals and patients as the use of the Moderna vaccine is expanded. The reactions could be driven by either an immunological response to the vaccine or a delayed hypersensitivity reaction. Most cases were reported as non-serious and have not required further treatment. Lymphadenopathy and delayed hypersensitivity reactions do not typically contraindicate further vaccine doses.

Table 1. Case demographics of the delayed lymphadenopathy cluster of reports for the Moderna COVID-19 vaccine and for all lymphadenopathy reports for COVID-19 vaccines, stratified by manufacturer of vaccine.

		Delayed lymphadenopathy cluster (n=64)	All lymphadenopathy Moderna (n=261)	All lymphadenopathy Pfizer-BioNTech (n=6589)	All lymphadenopathy AstraZeneca (n=858)
Age (years)	Median	36	38	43	49
	Q1-Q3	31 – 43	31 – 48	32 – 51	36 – 64
Gender	Male (%)	8 (13)	32 (12)	944 (14)	96 (11)
	Female (%)	56 (88)	228 (87)	5516 (84)	734 (86)
TTO (days)	Median	5	3	1	1
	Q1-Q3	2 – 6	1 – 6	1 – 3	1 – 2
Serious	Serious cases (%)	3 (4.7)	29 (11)	1041 (16)	563 (66)
Vaccine Dose	1st dose (%)	45 (70)	22 (8.4)	642 (10)	423 (49)
	2nd dose (%)	1 (1.6)	3 (1.1)	409 (6.2)	0 (0)
	Unknown (%)	18 (28)	236 (90)	5535 (84)	435 (51)
Region	Americas	44 (69)	178 (68)	359 (5.4)	2 (0.2)
	Europe	20 (31)	83 (32)	6229 (94)	851 (99)
	South-East Asia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Eastern Mediterranean	0 (0.0)	0 (0.0)	1 (0.0)	4 (0.5)
Reporter Qualification	Physician	10 (16)	39 (15)	1889 (29)	23 (2.7)
	Pharmacist	1 (1.6)	4 (1.5)	588 (8.9)	13 (1.5)
	Other Health Professional	4 (6.3)	19 (7.3)	2038 (31)	129 (15)
	Consumer or non-health professional	5 (7.8)	21 (8.0)	1781 (27)	697 (81)

Abbreviations: TTO, Time to onset

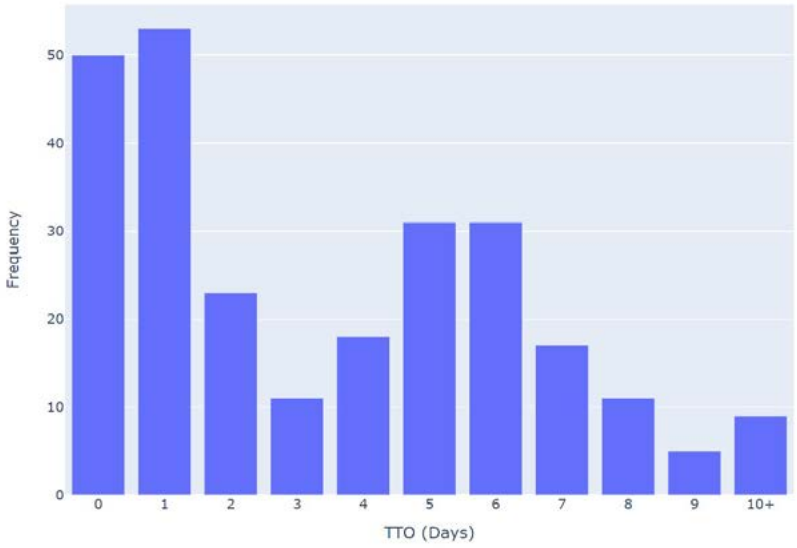
Table 2. Case demographics of the delayed, local skin reaction cluster for the Moderna COVID-19 vaccine and for all local skin reaction* reports for COVID-19 vaccines, stratified by manufacturer of vaccine.

		Delayed local skin reaction cluster (n=605)	Local skin reaction Moderna (n=986)	Local skin reaction Pfizer-BioNTech (n=2877	Local skin reaction AstraZeneca (n=331)
Age (years)	Median	43	43	44	44
	Q1–Q3	35–57	33–56	32–54	32–58
Gender	Male (%)	42 (6.9)	83 (8.4)	273 (9.5)	23 (6.9)
	Female (%)	563 (93)	902 (91)	2583 (90)	301 (91)
TTO (days)	Median	7	6	1	1
	Q1–Q3	1–8	1–7	0–1	1–2
Serious	Serious cases (%)	15 (2.5)	44 (4.5)	174 (6.0)	160 (48)
Vaccine Dose	1st dose (%)	15 (2.5)	27 (2.7)	190 (6.6)	166 (50)
	2nd dose (%)	0 (0.0)	0 (0.0)	34 (1.2)	0 (0.0)
	Unknown (%)	590 (98)	959 (97)	6653 (92)	165 (50)
Region	Americas	512 (85)	833 (84)	460 (16)	1 (0.3)
	Europe	93 (15)	153 (16)	2408 (84)	310 (94)
	Eastern Mediterranean	0 (0.0)	0 (0.0)	9 (0)	9 (2.7)
	South-East Asia	0 (0.0)	0 (0.0)	0 (0.0)	11 (3.3)
Reporter Qualification	Physician	59 (10)	89 (9)	387 (13)	32 (9.6)
	Pharmacist	5 (0.8)	9 (0.9)	1 (0.0)	9 (2.7)
	Other Health Professional	20 (3.3)	20 (2)	372 (13)	49 (15)
	Consumer or non-health professional	9 (1.5)	24 (2.4)	1483 (52)	244 (74)

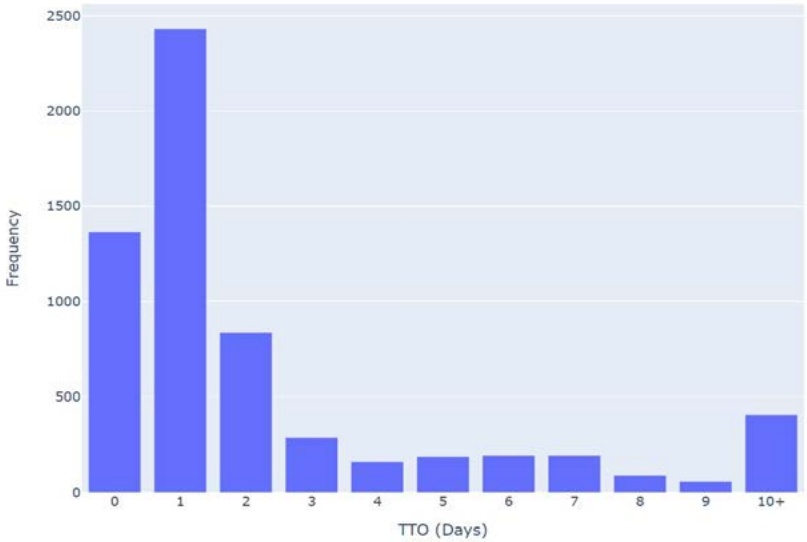
Abbreviations: TTO, Time to onset

*Local skin reaction here is defined by reporting of one of the following MedDRA preferred terms: Injection site erythema, Injection site swelling, Injection site pruritus and Injection site warmth.

a)



b)



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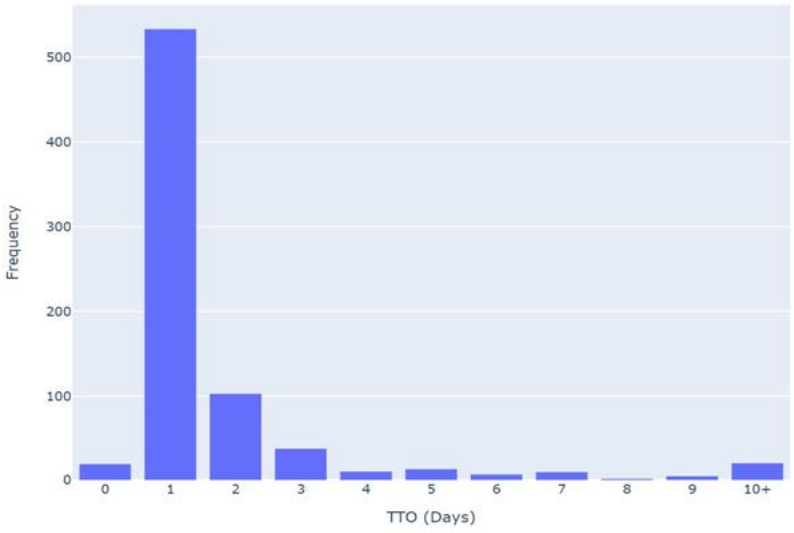
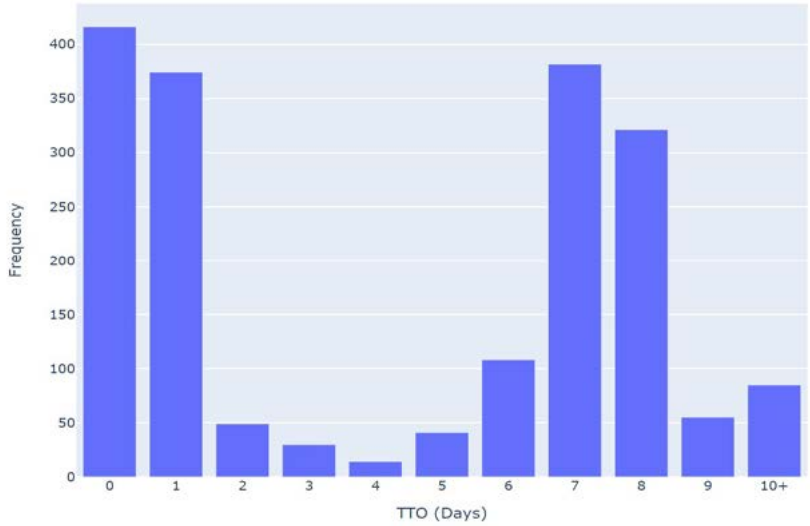


Figure 1. Frequency of different times to onset of Lymphadenopathy for different COVID-19 vaccines; a – Moderna; b – Pfizer-BioNTech; c - AstraZeneca Abbreviations: TTO – Time to onset.

a)



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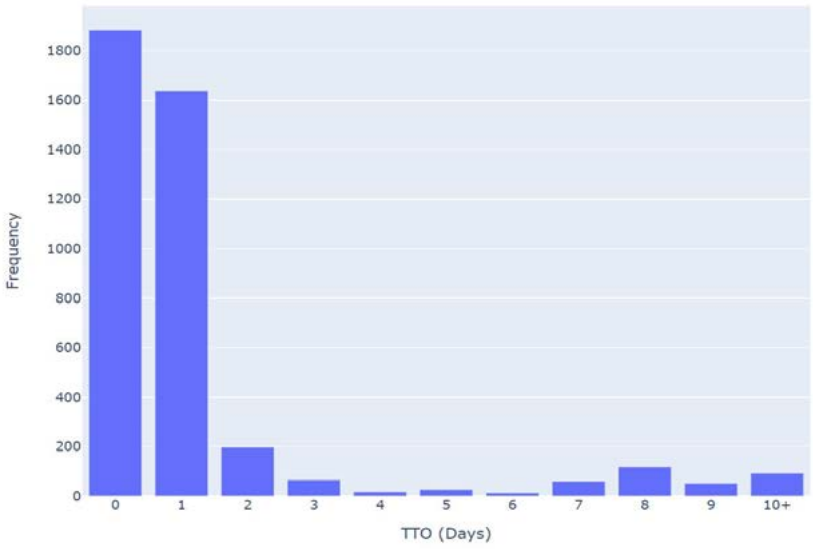

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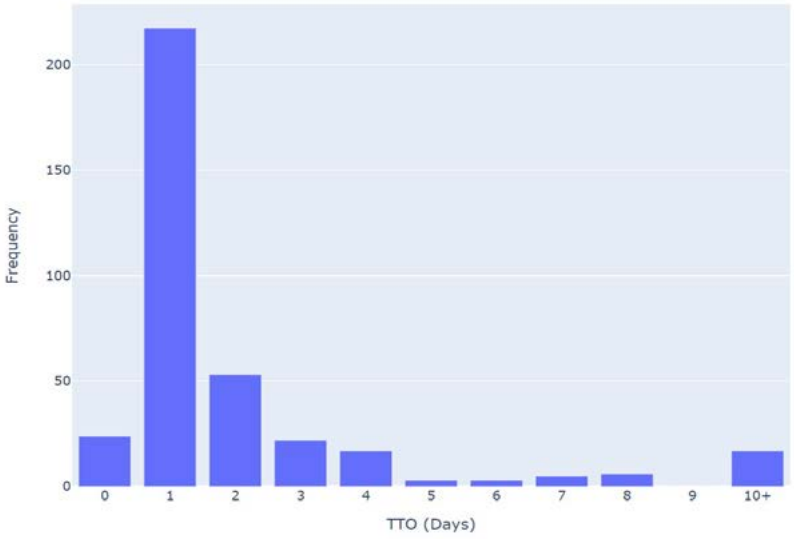

Figure 2. Frequency of different times to onset for the combination of: Injection site erythema, Injection site swelling, Injection site pruritus and Injection site warmth for different COVID-19 vaccines; a – Moderna; b – Pfizer-BioNTech; c - AstraZeneca.

Abbreviations: TTO – Time to onset.

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Note to “Delayed reactions and covid vaccines”

Moderna Tx informed on 23 June 2021 that the Company Core Data Sheet (CCDS) and the local labels were updated with the term “delayed injection site reaction”. Furthermore, it was communicated that a safety variation is currently under evaluation by the European Medicines Agency’s (EMAs) Pharmacovigilance Risk Assessment Committee (PRAC). It was anticipated that the updated Summary of Product Characteristics (SmPC) would come into force in July 2021.

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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