HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

HPRA Safety Update

COVID-19 Vaccines, Overview of National Reporting Experience

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Highlights from this update:

- Up to 25 February, a total of 3,484 reports of suspected side effects were notified to the HPRA.
- The cumulative figure of total doses of COVID 19 vaccines administered as of that date was reported as 271,594 (dose 1) and 137,935 (dose 2)[1].
- The most commonly reported suspected side effects notified to the HPRA are in line with those typically associated with vaccination, including the types of side effects described in COVID-19 vaccine product information.
- National reporting experience to date continues to support the favourable assessment that the benefits of COVID-19 vaccines outweigh the risks.
- The European Medicines Agency (EMA) Safety Committee reviewed worldwide data for mRNA vaccines on 25 February, and have assessed the latest safety data as in line with the known benefit-risk profile. EMA have published safety update reports describing the assessment for both Comirnaty® and COVID-19 Vaccine Moderna®.[2]
- The next HPRA safety update is due for publication on 25 March.

Understanding the data presented within this safety update

This update includes an overview of reports of ***suspected side effects*** notified to the HPRA safety monitoring system and is provided as an enhanced transparency measure for members of the public and healthcare professionals.

Reports included in the overview are those notified to the HPRA on a voluntary basis by healthcare professionals and members of the public, with reporting of suspected side effects to COVID-19

[1] *https://covid19ireland-geohive.hub.arcgis.com/*
[2] *https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty#safety-updates-section*
https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-moderna#safety-updates-section

vaccines (www.hpra.ie/report) encouraged. Any reports received by the HPRA from the company (i.e. the licence holder, to date, BioNtech, Moderna, Astra Zeneca) responsible for the vaccine are also included within this update. This overview provides an up-to-date summary of national reporting experience.

However, it is important to understand that conclusions on the safety of a vaccine cannot be drawn based on the information provided, given well-established and known limitations in interpreting such data in isolation, examples of which are described below.

Causation

- The HPRA receives reports based on ***suspicion*** that an adverse experience may be associated with vaccination. This does not mean the vaccine ***caused*** the adverse experience**.** As such, these are referred to as ***"suspected"*** side effects.
- Reports may describe coincidental events, which have occurred post-vaccination, but would have occurred even if vaccination had not taken place (e.g. they may be due to an underlying medical condition, or be signs and symptoms of another illness).
- Each individual report is carefully reviewed, however, the totality of data from all sources (e.g. clinical and epidemiological studies and literature) must be considered as part of ongoing safety monitoring to ensure ***evidenced based conclusions*** are drawn.

Number/volume

- As the HPRA system is based on voluntary reporting, ***not all*** suspected side effects will be reported. As such, the number and types of reports notified can vary for a variety of reasons.
- An increased number of reports is expected for COVID-19 vaccines, given public interest as well as HPRA calls encouraging reporting. This is known as ***stimulated reporting***.
- A single report may describe more than one suspected side effect in an individual (e.g. headache and nausea reported together), therefore, the number of side effects may exceed the total number of reports received.

Comparisons

- The type and number of reports received for different COVID-19 vaccines are ***not directly comparable*** as, for example, the vaccines have not been used in the vaccination programme for the same length of time, and will have been administered to different numbers of people, with different underlying medical conditions and across different settings.
- Each vaccine is authorised on the basis that its benefits-risk profile has and continues to be favourable.

Changes to data over time

- The description of suspected side effects in this update reflects available information known at the time by the HPRA. These data may undergo changes as more information about individual reports becomes available through follow-up, and as more data are reported and evaluated.

For these reasons, the information in this report is not sufficient in isolation to draw conclusions on the safety profile of a vaccine. Like all vaccines, some side effects are to be expected, with the vast majority mild or moderate in intensity and resolving within a few days. Vaccines are approved for use on the basis of robust scientific evidence that demonstrates their benefits outweigh any risks.

Always refer to the product information for information on the established safety profile, including known side effects of a COVID-19 vaccine.

This includes the Package Leaflet (for members of the public) and Summary of Product Characteristics (for healthcare professionals)

Product information is accessible from
www.hpra.ie/homepage/medicines/covid-19-updates

Authorised COVID-19 vaccines

COVID-19 vaccines currently authorised for use in the European Union by the European Medicines Agency include:

- Comirnaty® (licence holder: BioNTech), granted conditional marketing authorisation on 21 December 2020. For further information on this vaccine click here.
- COVID-19 Vaccine Moderna® (licence holder: Moderna), granted conditional marketing authorisation on 6 January 2021. For further information on this vaccine click here.
- COVID-19 Vaccine AstraZeneca® (licence holder: Astra Zeneca), granted conditional marketing authorisation on 29 January 2021. For further information on this vaccine click here.

Overview of suspected side effect reports

Up to 25 February, the HPRA received 3,484 reports[3] in association with COVID-19 vaccines, as follows:

Comirnaty® and COVID-19 Vaccine Moderna® (mRNA vaccines)	2508
COVID-19 Vaccine AstraZeneca®	954
Brand unknown/not specified	22

[3] *A single report may contain more than one suspected side effect for an individual (e.g. rash and hives reported together). Therefore, the total number of suspected side effects will exceed the total number of reports.*

The most commonly reported suspected side effects are as follows:

mRNA vaccines (Comirnaty® and COVID-19 Vaccine Moderna®)

10% or more of suspected side effects reported:

- Dizziness, headache
- Muscle Pain, general pain
- Nausea
- Tiredness, chills, fever

1% to less than 10% of suspected side effects reported:

- Altered taste, cough, difficulty breathing
- Enlarged lymph nodes
- Insomnia,
- Increased heart rate/racing heart, blood pressure increase
- Injection site redness, injection site pain, injection site swelling
- Itchiness, rash, hives
- Joint pain, pain in limbs, chest pain, neck pain
- Numbness, tingling/pins and needles
- Vomiting, diarrhoea, abdominal pain
- Weakness, feeling unwell, feeling hot and/or cold, decreased appetite, fainting, sweating, flushing

COVID-19 Vaccine AstraZeneca®

10% or more of suspected side effects reported:

- Headache
- Muscle pain, pain in limbs
- Nausea
- Feeling unwell, fever

1% to less than 10% of suspected side effects reported:

- Altered taste, cough, difficulty breathing
- Dizziness, increased heart rate/racing heart, insomnia
- Enlarged lymph nodes
- Injection site pain, injection site redness
- Joint pain, muscle weakness/stiffness, back pain, migraine
- Vomiting, diarrhoea, abdominal discomfort/pain
- Numbness, tingling/pins and needles, tremor
- Weakness, tiredness, chills, feeling hot and/or cold, sweating, decreased appetite

These reports are consistent with the types of events typically observed following vaccination, including those described in the vaccine package leaflets. The majority were mild to moderate in nature and had resolved/were resolving at the time of reporting.

Further points of interest regarding the reports received are described below.

COVID-19 mRNA vaccines

Comirnaty® product information update

- The EMA's safety committee has recommended that the product information (package leaflet and SmPC) for Comirnaty be updated to include diarrhoea and vomiting as possible side effects following vaccination. [2]
- The recommendation follows an assessment of worldwide data, including reports of suspected side effects received by national authorities, such as the HPRA.
- Nausea is already described as a very common possible side effect for both mRNA vaccines (more than 1 in 10 people).

Reports of Allergic type reactions

- The HPRA continues to closely review reports of allergic type reactions, however, no new information on this known side effect has been revealed since the last safety update.
- In relation to mRNA vaccines, and based on currently available information, a small number of reports (n=8) have been classified by the HPRA as anaphylaxis, which is a serious allergic reaction.[4] In all cases, the individuals concerned were reported to have recovered. Additional reports describing allergic type reactions have also been received, which in some cases required medical treatment and/or clinical observation of the individual for a period.
- The most recent review of allergic reactions by EMA's safety committee was on 25 February and included assessment of worldwide data for both COVID-19 Vaccine Moderna and Comirnaty. [2] The review did not lead to any changes in recommended use, however, anaphylaxis will continue to be closely monitored. Anaphylaxis is a known side effect, with information on managing this risk described in the product information. As for all vaccines, COVID-19 vaccines should be administered under close supervision with appropriate medical treatment available in case of such a reaction.

Reports of deaths following vaccination

- The HPRA has received 17 reports describing elderly patients who passed away following vaccination. In all cases, the patients concerned had underlying conditions and/or concurrent illness, with a small number having tested positive for COVID-19.
- All reports are being carefully reviewed. However, it can be expected that fatalities due to progression of underlying disease or natural causes will continue to occur, including following vaccination. This does not mean that the vaccine caused the deaths.
- The most recent review of this matter by EMA's safety committee was on 25 February and included assessment of worldwide data for both COVID-19 Vaccine Moderna and Comirnaty. [2] The assessment of the available data did not identify a safety concern. In most cases, progression of (multiple) pre-existing diseases was considered a plausible explanation.

Reports of systemic events

- In a number of cases, reporters have commented on the impact on their normal daily activities of expected systemic events, such as fatigue, headache, muscle pain, chills, joint pain and fever, in the day(s) following vaccination.

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[4] *Reports classified using Brighton Collaboration case definition for anaphylaxis https://brightoncollaboration.us/category/pubs-tools/case-definitions/*

- Systemic events post vaccination are common, in particular in younger populations, with the vast majority mild to moderate in nature and usually resolve within a few days of vaccination.
- These events may occur after either dose. However, the frequency and intensity was observed in clinical trials to be increased after the 2nd dose of mRNA vaccine.[5]

COVID-19 Vaccine AstraZeneca®

Reports of Allergic type reactions

- The HPRA has received a number of reports of allergic type reactions associated with COVID-19 Vaccine AstraZeneca, which mainly described symptoms such as itchy rash and swelling. In some cases, medical treatment and/or clinical observation of the individual for a period of time was needed.
- None of the reports received have been classified [4] by the HPRA as anaphylaxis, which is a serious allergic reaction. However, cases of anaphylaxis have been reported in post marketing experience elsewhere for this vaccine, including in the EU and UK.[6,7]
- Information on managing this risk is described in the product information. As for all vaccines, COVID-19 vaccines should be administered under close supervision with appropriate medical treatment available in case of such a reaction.

Reports of systemic events

- In a number of cases, reporters have commented on the impact on their normal daily activities of expected systemic events, such as fatigue, headache, muscle pain, chills, joint pain and fever, in the day(s) following vaccination.
- Systemic events post vaccination are common, in particular in younger populations, with the vast majority mild to moderate in nature and usually resolve within a few days of vaccination.
- These events may occur after either dose. However, adverse reactions reported after the second dose were milder and reported less frequently than after the first dose in clinical trials. Further information is available in the product information for the COVID-19 Vaccine AstraZeneca®.

Further information on reports received by the HPRA

Reports received by the HPRA, including those not specifically described in this update, are available to the public via www.adrreports.eu. Whilst the vast majority of reports describe expected events (i.e. known side effects of a vaccine or vaccination process), reports can also be received for events that are unexpected and/or are considered serious as they required medical care or intervention. Such reports may describe events not caused by the vaccine and may have occurred coincidentally. However, all reports are carefully reviewed and if there is cause to do so, a further analysis is carried out to determine if a vaccine may have had a contributory role. If it is determined that a vaccine is a contributory factor, the public and healthcare professionals will be informed and the relevant product information will be updated.

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[5] *European Public Assessment Report (EPAR) for Comirnaty® available from the EMA website https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty*

[6] *www.adrreports.eu*

[7] *https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting*

Background information on the evaluation of suspected side effect reports

As for all medicines and vaccines, suspected side effect reports in association with COVID-19 vaccines submitted to the HPRA are recorded and stored on the HPRA's national adverse reactions database. They are subsequently submitted (with any personal identifiers and contact details removed) to the EudraVigilance database operated and managed by the European Medicines Agency (EMA). EudraVigilance provides for the transfer of reports from national regulatory agencies such as the HPRA and marketing authorisation holders to the EMA, and supports early detection and monitoring of possible safety signals in relation to reported side effects.

The EMA also make available anonymised information on all reports, based on global safety experience, publically available through the following link www.adrreports.eu and regularly publish recommendations made by the EMA Safety Committee (www.ema.europa.eu).

Information from side effect reports, together with additional safety data (e.g. from the scientific literature, cumulative safety data analysis, epidemiological studies etc.) are assessed on an on-going basis, in conjunction with our EU counterparts to consider their impact on the known safety profile of the COVID-19 vaccines and any need for regulatory changes to support safe and appropriate use.

Partially anonymised details of reports are also shared with other bodies also involved in safety monitoring of medicines, in accordance with the legislative provisions, including GDPR (please see the HPRA privacy statement here). These bodies include the World Health Organisation (WHO) and as appropriate, the company(ies) that hold the licence(s) for the medicine(s) concerned (i.e. marketing authorisation holders or 'MAHs'). Sharing of this information ensures that the information is available to all parties responsible for the ongoing safety monitoring of medicines.

Further information to support interpretation of the data provided in this update is available here