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 13 May, 7,862 reports of suspected side effects were notified to the HPRA. As of 11 May, the cumulative figure of total doses of COVID-19 vaccines administered was reported as 1,408,105 (dose 1) and 514,808 (dose 2).[1]

- All vaccines have some side effects, the vast majority of which are mild to moderate in nature. These side effects need to be continuously balanced against the benefits in preventing COVID-19 illness. Overall, the national reporting experience continues to support the favourable assessment that the benefits of COVID-19 vaccines outweigh the risks. An overview of national reports is provided on page 4.

- On 7 May, the European Medicines Agency (EMA) published highlights from its monthly safety committee meeting, including information on COVID-19 vaccines. On 11 May, the EMA published safety update reports for Comirnaty®, Moderna®, Vaxzevria® and COVID-19 Vaccine Janssen®. These publications describe safety issues under evaluation, as well as any new recommendations.

- The EMA's safety committee has issued additional advice arising from an ongoing review of very rare cases of unusual blood clots occurring in combination with low platelets, which are associated with Vaxzevria® and COVID-19 Vaccine Janssen®. A description of this advice, as well as a summary of national reporting experience, is provided on page 8.

- The next HPRA safety update is due for publication on 17 June.

[1] *https://covid19ireland-geohive.hub.arcgis.com/*

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 (HCPs). All vaccines have some side effects, the vast majority of which are mild to moderate in nature. These side effects need to be continuously balanced against the expected benefits in preventing COVID-19 illness.

Reports included in the overview are those notified to the HPRA on a voluntary basis by HCPs and members of the public, with reporting of suspected side effects to COVID-19 vaccines (www.hpra.ie/report) encouraged. Any reports of Irish cases received by the HPRA from the company (i.e. the licence holder, to date, BioNtech, Moderna, AstraZeneca, Janssen) 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:

mRNA vaccines:

- Comirnaty® (licence holder: BioNTech Manufacturing GmbH), granted conditional marketing authorisation on 21 December 2020. For further information on this vaccine click here.

- COVID-19 Vaccine Moderna® (licence holder: Moderna Biotech Spain, S.L.), granted conditional marketing authorisation on 6 January 2021. For further information on this vaccine click here.

Adenoviral Vector Vaccines:

- Vaxzevria® (licence holder: AstraZeneca AB), granted conditional marketing authorisation on 29 January 2021. For further information on this vaccine click here.

- COVID-19 Vaccine Janssen® (License holder: Janssen-Cilag International NV), granted conditional marketing authorisation on 11 March 2021. For further information on the vaccine click here.

Overview of suspected side effect reports

Up to 13 May, the HPRA received 7,862 reports of suspected side effects [2,3] in association with COVID-19 vaccines, as follows:

mRNA vaccines (Comirnaty® and COVID-19 Vaccine Moderna®)	3734
Adenoviral Vector Vaccine (Vaxzevria®)	4085
Brand unknown/not specified	43

*no reports have been received for COVID-19 Vaccine Janssen®

The most regularly reported suspected side effects notified to the HPRA include the following: [4]

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

10% or more of reports describe side effects such as:

- Chills, fever, tiredness
- Dizziness, headache
- Muscle pain, other pain (non-specific)
- Nausea

1% to less than 10% of reports describe side effects such as:

- Abdominal pain, diarrhoea, tingling sensation in mouth, vomiting
- Altered taste, fainting/feeling faint, migraine, numbness/reduced sensations, tingling/pins and needles, tremor
- Back pain, joint/limb pain, muscle weakness/stiffness, neck pain
- Chest discomfort/pain, feeling unwell, feeling hot/cold, flu-like symptoms, lack of energy/feeling weak/tiredness, swelling including of legs/hands, underarm pain
- Cough, shortness of breath, sore throat
- Difficulty carrying out daily tasks (such as temporarily unable to attend work)
- Enlarged lymph nodes
- Insomnia/trouble sleeping
- Increased heart rate/racing heart, increased blood pressure
- Injection site redness, pain, itchiness, swelling
- Lack of appetite
- Pale appearance
- Skin red/red rash, sweating, general rash, itchy rash, hives

[2] *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.*

[3] *In accordance with EU guidance, reports are valid if the minimum reporting criteria are met. These include an identifiable reporter, an identifiable patient, one or more suspected medicine known to have been administered and one or more suspected adverse reaction.*

[4] *Terms listed as frequently reported are presented according to standard coding classification system (MedDRA) adopted for use in the EU, and grouped by system organ class (SOC) and listed alphabetically. It should be noted that regular reporting of a side effect is not the same as the incidence of occurrence.*

Adenoviral Vector Vaccine (Vaxzevria®)
10% or more of reports received describe side effects such as: ▪ Fever, feeling cold, tiredness ▪ Dizziness, headache ▪ Joint pain, muscle pain, other pain (non-specific) ▪ Nausea **1% to less than 10% of reports received describe side effects such as:** ▪ Abdominal discomfort/pain, diarrhoea, vomiting ▪ Back pain, bone pain, limb pain, muscle spasms/weakness/stiffness, neck pain ▪ Chest discomfort/pain, feeling unwell/ill, feeling hot/cold, flu-like symptoms, lack of energy/weakness, swelling including of legs/hands ▪ Cough, shortness of breath, sore throat ▪ Difficulty carrying out daily tasks (such as temporarily unable to attend work, need to stay in bed) ▪ Drowsy, fainting, headache, migraine, numbness/reduced sensations, tingling/pins and needles, tremor ▪ Ear pain, tinnitus (ringing in the ears) ▪ Enlarged lymph nodes ▪ Eye pain, vision blurred ▪ Hives, skin warm, skin red/rash, sweating/cold sweat, itchiness ▪ Increased heart rate/racing heart ▪ Injection site pain, redness, swelling, bruising ▪ Insomnia/trouble sleeping ▪ Lack of appetite

The vast majority of regularly reported suspected side effects are consistent with the types of events typically observed following vaccination, including those described in the product information for the individual vaccines, and are mild to moderate in nature.

Where information on outcome was provided, the majority of side effects had resolved/were resolving at the time of reporting.

Further information on processing of reports received by the HPRA, including the evaluation of safety signals is provided on page 9.

Links to the most recent updates from EMA's safety committee, including safety issues under evaluation, are provided in the highlights section on page 1.

Topics of interest are further described in the section below.

Topics of interest, including EMA recommendations

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

Reports of allergic type reactions (also known as hypersensitivity)

- Allergic type reactions are known side effects of mRNA vaccines.
- The HPRA has received a number of reports of allergic type reactions associated with mRNA vaccines, which mainly describe symptoms such as itchiness, hives and rash. In a minority of cases, medical treatment and/or clinical observation of the individual was needed.
- The HPRA continues to monitor reports of anaphylaxis, which is a serious allergic reaction. All reports suggestive of anaphylaxis (e.g. sudden onset of symptoms such as low blood pressure, collapse, rapid heart rate, shortness of breath, swelling of lips/throat and itchy skin) are carefully reviewed. Cases are classified by the HPRA as anaphylaxis using a well-established set of clinical and laboratory criteria.[5] Of the reports reviewed, eight are currently classified as anaphylaxis. In these eight cases, the individuals concerned were reported to have recovered. An additional small number of suspected cases are being followed-up for further information.
- Anaphylaxis is a known side effect, and 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. Those vaccinated should discuss any signs/symptoms of allergic reaction that they are concerned about with a healthcare professional.

Reports of systemic events

- More than 1% of reports received include a comment from the reporter, describing an impact of expected systemic events on their normal daily activities. Reporters have commented on the need to take time off work or to rest in bed, typically for a short period.
- Systemic events can be similar to flu-like symptoms, and can include fatigue, headache, muscle/joint pain, chills and fever, in the day(s) following vaccination.
- These types of systemic events post vaccination are common, 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 observed in clinical trials was increased after the second dose of the mRNA vaccines.[6]
- Product information (package leaflet) indicates that some of the possible side effects may temporarily affect ability to operate machinery or drive. Vaccine recipients should be alert to this warning.

Recent product information updates recommended by the EMA

- Localised facial swelling in people who, previously, have had cosmetic injections with dermal fillers, has been identified as a new side effect for Comirnaty®. The product information will be updated to alert vaccine recipients, who have had a cosmetic injection of dermal fillers previously, of this side effect[7]. To date, the HPRA has not received any reports of this nature. This side effect

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

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

[7] *EMA COVID-19 vaccine safety update for Comirnaty® available from the EMA website* https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

is already known to occur with COVID-19 Vaccine Moderna®, and is considered rare (between 1 in 1000 and 1 in 10,000 people may experience this side effect). In clinical trials for COVID-19 Vaccine Moderna®, the onset of swelling was reported to occur within 1-2 days post vaccination.

- COVID-19 Vaccine Moderna®: Diarrhoea will be added to the list of side effects in the product information.[8] Reports of gastrointestinal symptoms, including diarrhoea, are regularly reported to the HPRA for mRNA vaccines. The product information for Comirnaty® already describes diarrhoea as a 'very common' side effect, meaning it can affect 1 in 10 people. An estimate of how often this reaction might occur after vaccination with COVID-19 Vaccine Moderna® remains under review at this time.

- COVID-19 Vaccine Moderna®: Delayed injection site reactions have been identified as a new side effect and will be added to the product information. [8] A delayed injection site reaction is where symptoms (e.g. pain, redness, itchiness, rash, localised swelling at the injection site) starts approximately 5-7 days after the person receives the vaccine. These reactions typically resolve within a few days and do not require treatment. How often this side effect might occur remains under review. To date, the HPRA has received reports of this nature, with symptoms resolved/ resolving in most cases at the time of reporting.

Adenoviral Vector Vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®*)
no reports received for COVID-19 Vaccine Janssen®

Reports of allergic type reactions (also known as hypersensitivity)

- Allergic type reactions are known side effects of Adenoviral Vector Vaccines.
- The HPRA has received a number of reports of allergic type reactions associated with Vaxzevria®, which mainly describe symptoms such as itchiness, hives and rash. In a minority of cases, medical treatment and/or clinical observation of the individual was needed.
- The HPRA continues to monitor reports of anaphylaxis, which is a serious allergic reaction. All reports suggestive of anaphylaxis (e.g. sudden onset of symptoms such as low blood pressure, collapse, rapid heart rate, shortness of breath, swelling of lips/throat and itchy skin) are carefully reviewed. Cases are classified by the HPRA as anaphylaxis using a well-established set of clinical and laboratory criteria[5]. Of the reports received, a small number (less than five)[9] are currently classified as anaphylaxis. In all case(s) the individual concerned was reported to have recovered.
- Anaphylaxis is a known side effect, and 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. Those vaccinated should discuss any signs/symptoms of allergic reaction that they are concerned about with a healthcare professional.

Reports of systemic events

- More than 1% of reports received by the HPRA include a comment from the reporter describing an impact of expected systemic events on their normal daily activities. Reporters have commented on the need to take time off work, or to rest in bed typically for a short period.

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[8]EMA COVID-19 vaccine safety update for COVID-19 Vaccine Moderna® available from the EMA website https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-moderna
[9]When the relevant number is less than five, it is described as a small number to avoid any potential, inadvertent identification of the individuals concerned.

- Systemic events can be similar to flu-like symptoms, and can include fatigue, headache, muscle/joint pain, chills and fever, in the day(s) following vaccination.
- These types of systemic events post vaccination are common, with the vast majority mild to moderate in nature and usually resolve within a few days of vaccination.
- For Vaxzevria®, 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.
- Product information (package leaflet) indicates that some of the possible side effects may temporarily affect ability to operate machinery or drive. Vaccine recipients should be alert to this warning.

Reports of Thrombosis with Thrombocytopenia syndrome (TTS)

- The EMA has issued additional advice regarding the very rare side effect known as thrombosis with thrombocytopenia syndrome (or TTS). TTS is a condition that involves blood clotting in combination with low levels of blood platelets (cells that help the blood to clot). Current advice is, as follows:

    - The signs and symptoms for which vaccine recipients are advised to seek medical attention have been updated to include mental status change (e.g. confusion), seizures (fits) or leg swelling.
    - This is in addition to the existing list, which include severe or persistent headaches, blurred vision, shortness of breath, chest pain, leg pain or persistent abdominal pain, unusual skin bruising or pinpoint round spots beyond the site of vaccination.
    - Vaccine recipients are advised to seek medical attention if any of these signs/symptoms are experienced within 3 weeks of vaccination.
    - Healthcare professionals are advised that individuals diagnosed with low platelets (thrombocytopenia) within three weeks of being vaccinated should be assessed for signs of blood clotting (thrombosis). Similarly, individuals who experience blood clots within three weeks following vaccination should be assessed for low platelets.
    - The product information for COVID-19 Vaccine Janssen® has been updated with the above advice, and a similar update to the product information for Vaxzevria® is expected.

- The HPRA continues to monitor national reports that describe blood clotting events or low platelets. A summary of national reporting experience with Vaxzevria®, as of 13 May, is provided below:

    - The HPRA has received 41 reports that describe a blood clotting type event. However, only a small number (less than five)[9] describe the unusual combination of blood clotting in combination with low platelets, and as such, are suspected to be TTS. In relation to these suspected TTS cases, symptoms occurred within 1-2 weeks of vaccination with the first dose. The types of symptoms reported include shortness of breath, severe and/or persistent headache, unusual skin bruising, abdominal pain and leg pain. All cases occurred in adults under 40 years of age. The individuals concerned were discharged from hospital after receiving specialist medical care. In relation to the other cases (i.e. blood clotting but without low platelets), the vast majority describe clots typically seen in the general population, such as those that occur in the legs (e.g. deep vein thrombosis), and lung (e.g. pulmonary embolism). In many reports, the individuals concerned had risk factors for clotting.

- Further information on TTS is available for HCPs through the following links (Vaxzevria ®: HPRA Drug Safety Newsletter 102, Direct Healthcare Professional Communication, COVID-19 Vaccine Janssen®: HPRA Drug Safety Newsletter 103, Direct Healthcare Professional Communication).

mRNA Vaccines and Adenoviral Vector Vaccines - Reports of deaths following vaccination

- A total of 56 reports have been received describing an individual who was known to have been vaccinated and subsequently passed away. Of these, 50 were reported with an mRNA vaccine. The remaining six fatalities were related to Adenoviral Vector Vaccines or brand unknown/not specified. The types of events reported mainly include fatalities often seen in the general population, such as those due to natural causes, progression of underlying disease. In some cases, the individuals concerned tested positive for COVID-19.
- Reports describing a death are 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.
- In January, the EMA undertook a specific review of reports of fatalities following mRNA vaccination, and did not identify a safety concern. In most cases, progression of (multiple) pre-existing diseases was considered a plausible explanation. A safety concern has not been identified through subsequent EU coordinated reviews, performed as part of continuous monitoring for all vaccines, and which consider the totality of all reports and available data.

Further information on processing of 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.

The EMA publishes regular safety updates for COVID 19 vaccines, as well as highlights from meetings of the EMAs safety committee (Pharmacovigilance Risk Assessment Committee), which describe safety issues under review, as well as recommendations to revise product information. These are available via www.ema.europa.eu.

The EMA also make available anonymised information on all reports, including reports initially notified to the HPRA, publicly available through the following link www.adrreports.eu and regularly publish recommendations made by the EMA Safety Committee (www.ema.europa.eu).

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. This 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