HPRA Safety Update

COVID-19 Vaccines, Overview of National Reporting Experience
Publication date: 12 August 2021 (Update #10)

Highlights from this update:

- Up to 03 August, a total of 13,529 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 3,135,842 (dose 1), 218,127 (single dose) and 2,594,735 (dose 2).[1]

- Whilst not experienced by everyone, 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 received is provided in this safety update on page 5.

- On 06 August, the European Medicines Agency (EMA) published highlights from its monthly safety committee meeting, including information on COVID-19 vaccines. On 11 August , the EMA published safety update reports for mRNA vaccines (Comirnaty®, Spikevax® [*previously COVID-19 Vaccine Moderna]*) and adenoviral vector vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®). These publications describe safety issues under evaluation, as well as any new recommendations.

- The EMA's safety committee recently issued new safety advice on immune thrombocytopenia (ITP), a disorder where the number of blood cells that are needed for normal blood clotting is reduced, and which has been reported very rarely following vaccination with COVID-19 Vaccine Janssen®. A description of the review, as well as a summary of national reports, is provided on page 9.

- The HPRA issued a Drug Safety Newsletter (Edition 104) for healthcare professionals summarising current safety advice for COVID-19 vaccines.

- The next HPRA safety update is due for publication on 09 September.

[1] *https://www.hse.ie/eng/services/news/newsfeatures/covid19-updates/vaccination-programme-dashboard-as-of-3-august-2021.pdf*

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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. 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 healthcare professionals 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 https://www.hpra.ie/homepage/medicines/covid-19-updates/covid-19-vaccines-product-information

AUTHORISED COVID-19 VACCINES

COVID-19 vaccines currently authorised for use in the European Union by the EMA 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. On 28 May, the EMA extended the marketing authorisation for Comirnaty® beyond the initial authorised use in adults and adolescents aged 16 years and above, to include use in adolescents aged 12 to 15 years.
- Spikevax® (previously 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. On 23 July, the EMA extended the marketing authorisation for Spikevax® beyond the initial authorised use in adults to include use in adolescents aged 12 to 17 years.

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 03 August, the HPRA received 13,529 reports describing suspected side effects[2, 3] in association with COVID-19 vaccines, as follows:

mRNA vaccines (Comirnaty® and Spikevax® *[previously Moderna]*)	7589
Adenoviral vector vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®)	5850
Brand unknown/not specified	100

Doses administered by vaccine type, as of 03 August, were reported as follows:[1]

- mRNA vaccines: 4,029,719 Comirnaty®, 515,350 Spikevax® *(previously Moderna)*.
- Adenoviral vector vaccines: 1,185,508 Vaxzevria®, 218,127 COVID-19 Vaccine Janssen®.

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

mRNA vaccines (Comirnaty® and Spikevax® *[previously 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, drowsy, fainting/feeling faint, migraine, numbness/reduced sensations, tingling/pins and needles/burning sensation, tremor
- Back pain, joint/limb pain, muscle weakness/stiffness, neck pain
- Chest discomfort/pain, general discomfort, feeling unwell, feeling hot/cold, flu-like symptoms, lack of energy/feeling weak/tiredness, swelling including of legs/arms/face, 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, rash
- Lack of appetite
- Menstrual disturbances
- Skin reactions, skin red/red rash, sweating, general rash, itching, itchy rash, hives
- Tinnitus (ringing in the ears), vertigo-like symptoms

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[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 vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®)
10% or more of reports describe side effects such as: ▪ Chills, fever, 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, general discomfort, feeling unwell/ill, feeling hot/cold, flu-like symptoms, lack of energy/weakness, swelling including of legs/arms ▪ Cough, shortness of breath, sore throat, nose bleed ▪ 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), vertigo-like symptoms ▪ Enlarged lymph nodes ▪ Eye pain, vision blurred ▪ Hives, skin warm, skin red/red rash, general rash, sweating/cold sweat, itching ▪ Increased heart rate/racing heart ▪ Injection site pain, redness, swelling, bruising, difficulty moving injected arm ▪ Insomnia/trouble sleeping ▪ Lack of appetite ▪ Menstrual disturbances

The 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.

For reports evaluated which include information on outcome, just under half of the suspected side effects had resolved or were resolving at the time of reporting. For others, the suspected side effects had not yet resolved, or the outcome was reported as unknown, at the time of initial reporting. Information on reports with a fatal outcome is provided on page 12.

A full breakdown of all suspected side effects described in reports is provided on page 13. Further information on how reports received by the HPRA are processed, including how safety signals are evaluated, is given on page 16.

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

Topics of interest are further described in the sections below.

TOPICS OF INTEREST, INCLUDING EMA RECOMMENDATIONS

Topics of interest included in this update are listed below, with new topics since the last update highlighted.

For mRNA vaccines (Comirnaty® and Spikevax® *[previously Moderna]*)

- Vaccination of adolescents
- Allergic type reactions (also known as hypersensitivity)
- Systemic events
- Myocarditis and pericarditis

For adenoviral vector vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®)

- Immune thrombocytopenia (ITP)
- Dizziness and tinnitus
- Allergic type reactions (also known as hypersensitivity)
- Systemic events
- Thrombosis with thrombocytopenia syndrome (TTS)
- Guillain-Barré syndrome (GBS)

Common topics

- Menstrual disturbances following COVID-19 vaccination
- Anxiety and stress-related reactions
- Deaths following vaccination

mRNA vaccines (Comirnaty® and Spikevax® *[previously Moderna]*)

Vaccination of adolescents

- As the national vaccination programme continues, the HPRA are closely monitoring any reports of suspected side effects received in adolescents aged 17 and under.
- Up to 03 August, 24 reports of suspected side effects have been notified following vaccination with an mRNA vaccine. The types of suspected side effects most frequently reported include dizziness, abdominal pain or nausea, headache, blurred vision, fainting, fever, itchy/red rash and feeling tired or weak. A small number of reports describe a cardiac related symptom, which oftentimes can be linked with anxiety and stress-related reactions associated with vaccination (see page 12). These reports are being followed up to better understand the type of event which occurred, with only preliminary information currently available. Overall, the reports received are consistent with the types received in adults, with most being mild to moderate in nature.

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 such reports, mainly describing symptoms such as itchiness, hives and rash. In some 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, 11 are currently classified as anaphylaxis. In these 11 cases, the individuals concerned were reported to have recovered/are recovering. 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 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.
- 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]
- The product information (package leaflet) for Comirnaty® and Spikevax® *(previously Moderna)* 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 myocarditis and pericarditis

- Myocarditis and pericarditis, which are inflammatory conditions of the heart, are possible side effects of Comirnaty® and Spikevax® *(previously Moderna).* Cases reported internationally primarily occurred within 14 days, more often in younger men and after the second dose. The clinical course of myocarditis and pericarditis following vaccination has been observed as similar to that which can occur in unvaccinated people, for example, when myocarditis or pericarditis develop after a viral infection or due to an immune disorder.
- Those vaccinated are reminded to seek immediate medical attention if symptoms indicative of myocarditis or pericarditis occur. These symptoms can vary but often include breathlessness, a forceful heartbeat that may be irregular (palpitations), and chest pain.
- For Comirnaty® or Spikevax®, as of 03 August, the HPRA has received a total of 24 reports, that describe suspected side effects of myocarditis (six reports), pericarditis (nine reports) or a combination of both (nine reports). In these 24 cases, 15 occurred after the first dose and nine after the second dose, with most occurring within 14 days of vaccination. Suspected cases were reported in both males and females, with a median age of 48 years (range 17 to 81). The reports describe symptoms such as chest pain/discomfort, palpitations, dizziness, irregular heartbeat and shortness of breath. In a number of cases, possible alternative explanations (other than vaccination) for the individual developing the condition were described, or the diagnosis was provisional and not yet finalised at the time of reporting. In the majority of cases, the individuals were reported to have recovered or were recovering with symptoms ongoing in some.

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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

- An additional ten reports of myocarditis and/or pericarditis have been received following vaccination with Vaxzevria® and COVID-19 Vaccine Janssen®. A review of reports of this nature following administration of these vaccines by EMA's safety committee is ongoing, however, at this point in time, no causal relationship with myocarditis or pericarditis is established.
- All reports of myocarditis and pericarditis notified to the HPRA are carefully reviewed however, it can be expected that medical events due to various causes will continue to occur, including following vaccination, but which are not all necessarily caused by the vaccine.
- Previous advice issued to healthcare professionals on this topic is available from the HPRA website here.

Adenoviral vector vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®)

Reports of immune thrombocytopenia (ITP)

- Immune thrombocytopenia (ITP) is a condition in which the immune system mistakenly reacts to blood cells called platelets that are needed for normal blood clotting.
- EMA's safety committee recently assessed very rare reports of ITP which occurred after vaccination with COVID-19 Vaccine Janssen®, together with available scientific evidence, including that from the literature. Following this assessment, the safety committee recommended that product information for COVID-19 Vaccine Janssen® be updated to alert both healthcare professionals and those being vaccinated of ITP as a potential risk. Further details will be included in the anticipated product information update.
- As of 03 August, the HPRA has received ten reports of ITP following COVID-19 vaccination, however, none occurred following administration of COVID-19 Vaccine Janssen®.

Reports of dizziness and tinnitus

- Product information for COVID-19 Vaccine Janssen® will be updated to include dizziness and tinnitus (ringing or other noises in one or both ears) as potential side effects.
- Dizziness and tinnitus are two of the more regularly reported suspected side effects with COVID-19 vaccines to the HPRA (see pages 5 & 6). Up to 03 August, the HPRA received 49 reports of dizziness and nine reports of tinnitus following administration of 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 such reports, mainly describing symptoms such as itchiness, hives and rash. In some 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)[7] are currently classified as anaphylaxis. In these cases, some of the individuals concerned are reported to have recovered and the remaining 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

[7] *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*

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.
- 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.[8]
- The product information (package leaflet) for Vaxzevria® and COVID-19 Vaccine Janssen® 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)

- Thrombosis with thrombocytopenia syndrome (TTS) is a very rare side effect associated with Vaxzevria® and COVID-19 Vaccine Janssen®. The syndrome involves an unusual combination of thrombosis (blood clots) with thrombocytopenia (abnormally low level of the components that help blood to clot, known as platelets). Vaccine recipients are reminded to seek immediate medical attention if they experience any of the following signs and symptoms: shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain post vaccination, severe or persistent headaches, blurred vision, confusion, seizures (fits) or bruising beyond the site of vaccination after a few days.
- Healthcare professionals are advised that individuals diagnosed with thrombocytopenia within three weeks after vaccination should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia. Healthcare professionals should be alert to the signs and symptoms of TTS and consult applicable guidance and/or appropriate specialists to diagnose and treat this condition. A second dose of Vaxzevria® is contraindicated in any person who experienced TTS following their first dose.
- As of 03 August, the HPRA has received eight reports that are suspected cases of TTS, and which describe the unusual combination of blood clotting in combination with low platelets. In relation to these suspected TTS cases, symptoms occurred between 1-5 weeks of vaccination with a first dose of Vaxzevria®. The types of symptoms reported include shortness of breath, severe and/or persistent headache, unusual skin bruising, abdominal pain, leg pain and leg swelling. Cases occurred in both males and females, with a median age of 49 (age range, 29 to 63 years). In a small number, blood clots occurred in unusual locations, including in the brain (cerebral venous sinus thrombosis, CVST) and liver (hepatic and portal veins). Based on information currently available, the individuals are either discharged or recovering in hospital after receiving specialist medical care.
- Previous advise issued to healthcare professionals on this topic is available from the HPRA website here.

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[8] *European Public Assessment Report (EPAR) for Vaxzevria® available from the EMA website https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca*

Reports of Guillain-Barré syndrome (GBS)

- Guillain-Barré syndrome (GBS) is a very rare and serious immune disorder that affects the nerves, and can result in pain, numbness, tingling sensations, muscle weakness and difficulty walking. Symptoms usually start in the legs, and can spread to the arms and face. GBS is thought to be caused by a problem with the immune system, and whilst the trigger for the condition is not known, it often happens after an infection, especially of the airways, such as flu, or an infection of the digestive system, such as food poisoning or a stomach bug (gastroenteritis).
- The EMA's safety committee recently recommended an update to the product information for COVID-19 Vaccine Janssen® to include GBS as a very rare side effect. This follows an update to the product information for Vaxzevria® last month, to include a warning to alert healthcare professionals and patients to this potential risk.
- Healthcare professionals should be alert to signs and symptom of GBS, in view of the seriousness of the condition, allowing for early diagnosis, supportive care and treatment. Those vaccinated are advised to seek immediate medical attention if they develop signs and symptoms of GBS which may include weakness in the limbs, chest or face, double vision or difficulty moving eyes, difficulty swallowing, speaking or chewing, co-ordination problems and unsteadiness, difficulty walking, tingling sensations in the hands and feet and problems with bladder control and bowel function.
- As of 03 August, the HPRA has received six reports of GBS following vaccination with an adenoviral vector vaccine. The cases occurred in both genders, with a median age of 61 years (range 51 to 62), and with symptoms occurring between 1 to 21 days post vaccination. These cases concern suspected side effects, i.e. medical events that have been observed after vaccination, but are not necessarily caused by the vaccine.
- The EMA have stated this issue will be closely monitored, and further communications will be made should new information becomes available.

COVID-19 vaccines - Common topics

Reports of menstrual disturbances following COVID-19 vaccination

- At it's most recent meeting, EMA's safety committee considered reports of menstrual disturbances following COVID-19 vaccination, and have requested further data for all COVID-19 vaccines authorised in the EU. All available evidence, including reports of suspected side effects from vaccinated woman, as well as scientific literature, will be examined. However, no causal association or link with vaccination and menstrual disturbances has been found so far.
- Recently, menstrual disturbances are one of the more regularly reported side effects to the HPRA (see pages 5 & 6). The vast majority of reports received are directly from a vaccinated woman, and describe a recent disturbance in normal menstruation, such as a period arriving earlier or later than expected, or of a heavier nature than normal. Whilst less frequent, some reports describing a bleeding event in a woman who is post menopausal have also been notified.
- The EMA's safety committee highlighted that generally, menstrual disturbances are very common and can occur with or without an underlying medical condition. Women who are concerned about prolonged or severe menstrual disturbances may wish to seek medical advice, in particular if unexpected vaginal bleeding, for example, in a postmenopausal women, is experienced.
- Whilst no link between these reports and vaccination has been found or established, the reports together with all available evidence, including the scientific literature, will continue to be monitored.

Reports of anxiety and stress-related reactions

- Anxiety and stress-related reactions are known to occur with all vaccines, and are related to the the vaccination process itself, for example, fear of a needle injection. The types of reactions that can occur include fainting, hyperventilation, dizziness and palpitations. These reactions are temporary and typically resolve on their own.
- The product information for Comirnaty® has recently been updated to include additional examples of the types of anxiety or stress-related reactions that can occur, such as an increase in heart rate, changes in blood pressure, tingling sensations and sweating as examples.
- Reports describing responses of this nature are some of the more frequently reported suspected side effects to the HPRA (see pages 5 & 6). If an individual feels nervous before vaccination, or has a history of fainting following injections, it is important to let their vaccinator know. Those vaccinated are also encouraged to bring symptoms of this nature to the attention of their vaccinator for evaluation. A warning is included in product information for all authorised COVID-19 vaccines, on the need to take precauations, so that injury incase of fainting is avoided.

Reports of deaths following COVID-19 vaccination

- A total of 82 reports have been received describing an individual who was known to have been vaccinated and subsequently passed away. Of these, 71 were reported with an mRNA vaccine, seven with adenoviral vector vaccines and the remaining four were reported with brand unknown/not specified. The majority of these events were reported in patients aged over 75 and 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. For a number of reports, the cause of death was unconfirmed at the time of reporting, with post mortem results awaited.
- 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 most cases, progression of (multiple) pre-existing diseases was considered a plausible explanation. A safety concern has not been identified through an EMA specific review in January or 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.

BREAKDOWN OF SUSPECTED SIDE EFFECTS BY CATEGORY

A full breakdown of all suspected side effects described in reports received by the HPRA is provided below by vaccine type (i.e. mRNA and adenoviral vector vaccines) and by category (i.e. the related body system).

Whilst the vast majority of reports notified to the HPRA 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.

Please read the following explanatory note in relation to understanding the data presented in the suspected side effect tables:

- A single report describes at least one suspected side effect for a vaccinated individual. Reports often describe several suspected side effects for an individual, which may include more than one category, or more than one in a specific category. For example, a single report that describes chills, fatigue and nausea in an individual, includes three suspected side effects, two in general symptoms (chills and fatigue) and one in gastrointestinal (nausea). As such, there are more suspected side effects in each category and overall, as compared to the number of reports received.
- The breakdown summary includes all suspected side effects as they are reported to the HPRA. This includes cases for which a diagnosis is reported as provisional, or for which there is more than one possible diagnosis at the time of reporting. In other cases, a diagnosis may not be available, and only signs and symptoms or laboratory test results are given. Reports are also received from members of the public, and the HPRA follows up to medically confirm these reports, where consent is provided and more information is required. For each report, all events are 'coded'[9] as suspected side effects in the national pharmacovigilance database using the exact information (verbatim) given in the report. The HPRA follows up with the reporter to collect any further information which may be relevant to the assessment of the case.
- The description of suspected side effects in this update, including the number and category, reflect 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 reports are further evaluated.
- Please refer to the section 'Understanding the data presented within this safety update' on page 3 with regard to further interpretation guidance. Background information on the evaluation of suspected side effect reports is available on page 16.

Of the 13,529 reports notified to the HPRA up to 03 August, just over 40% have been submitted to EMA's Eudravigilance database, and as such, additional anonymised information on these reports, is publicly available through the following link www.adrreports.eu. See page 16 for further details.

[9] *Medical Dictionary for Regulatory Activities (MedDRA) https://www.meddra.org/*

Suspected side effects to mRNA vaccines

A breakdown of suspected side effects described in the 7589 reports notified to the HPRA is provided below by category. Each report describes at least one suspected side effect for a vaccinated individual. Reports often describe several suspected side effects for an individual, including more than one in a specific category. As such, there are more suspected side effects in each category and overall, as compared to the number of reports received.

CATEGORY	NO. OF SUSPECTED SIDE EFFECTS
General symptoms and local reactions *e.g. chills, fatigue, 'flu-like' feeling, fever, injection site pain or swelling*	9175
Nervous system *e.g. dizziness, headache, lack of energy, pins & needles, fainting or feeling faint*	5144
Muscles, tissue, bones or joints *e.g. general muscular pain or weakness*	3507
Gastrointestinal *e.g. nausea, vomiting, diarrhoea*	2648
Skin *e.g. rash, itchy rash*	2102
Respiratory *e.g. cough, shortness of breath*	967
Reproductive system, obstetrics or gynaecology related *e.g. menstrual disturbance*	787
Behavioural, emotional and mental health *e.g. insomnia, trouble sleeping*	725
Blood and lymphatic system *e.g. swollen glands*	539
Social circumstances *e.g. need to rest in bed or take a break from normal daily activities*	493
Eye *e.g. eye pain, vision blurred*	479
Cardiac (heart) related *e.g. palpitations*	475
Abnormal clinical or laboratory result (i.e. where information is provided on results of relevant tests) *e.g. high temperature (via thermometer), increased heart rate or blood pressure (via BP monitor)*	435
Procedural issues and complications *e.g. injection site bruising*	420
Blood vessel related (i.e. veins/arteries) *e.g. pale complexion*	379
Infection *e.g. local or general such as influenza or cold sore*	353
Ear related e*.g. earache, tinnitus*	294
Metabolism and nutrition disorders *e.g. decreased appetite*	225
Immune system related *e.g. hypersensitivity, allergic reaction*	103
Kidney related *e.g. change in frequency of urination*	58
Liver related *e.g. jaundice*	13
Endocrine (hormone)	12
Cysts and polyps	7

Suspected side effects to adenoviral vector vaccines

A breakdown of suspected side effects described in the 5850 reports notified to the HPRA is provided below by category. Each report describes at least one suspected side effect for a vaccinated individual. Reports often describe several suspected side effects for an individual, including more than one in a specific category. As such, there are more suspected side effects in each category and overall, as compared to the number of reports received.

CATEGORY	NO. OF SUSPECTED SIDE EFFECTS
General symptoms and local reactions *e.g. chills, fatigue, 'flu-like' feeling, fever, injection site pain or swelling*	10333
Nervous system *e.g. dizziness, headache, lack of energy, pins & needles, fainting or feeling faint*	5265
Muscles, tissue, bones or joints *e.g. general muscular pain or weakness*	3683
Gastrointestinal *e.g. nausea, vomiting, diarrhoea*	2889
Skin *e.g. rash, itchy rash*	1578
Respiratory *e.g. cough, shortness of breath*	811
Behavioural, emotional and mental health *e.g. insomnia, trouble sleeping*	724
Social circumstances *e.g. need to rest in bed or take a break from normal daily activities*	566
Eye *e.g. eye pain, vision blurred*	439
Metabolism and nutrition disorders *e.g. decreased appetite*	437
Blood vessel related (i.e. veins/arteries) *e.g. pale complexion*	406
Abnormal clinical or laboratory result (i.e. where information is provided on results of relevant tests) *e.g. high temperature (via thermometer), increased heart rate or blood pressure (via BP monitor)*	366
Reproductive system, obstetrics or gynaecology related e.g. *menstruation disturbance*	364
Cardiac (heart) related *e.g. palpitations*	329
Ear related e*.g. earache, tinnitus*	322
Procedural issue or complications *e.g. injection site bruising*	306
Infection *e.g. local or general such as influenza or cold sore*	205
Blood and lymphatic system *e.g. swollen glands*	169
Kidney related *e.g. increased frequency of urination*	64
Immune system related *e.g. hypersensitivity, allergic reactions*	51
Liver related *e.g. jaundice*	8
Endocrine (hormone)	5
Cysts and polyps	<5

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. The EMA also publish regular safety updates for COVID 19 vaccines, as well as highlights from meetings of the EMA's 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.

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.