HPRA Safety Update

COVID-19 Vaccines, Overview of National Reporting Experience
Publication date: 07 October 2021 (Update #12)

Highlights from this update:

- Up to 28 September, a total of 15,424 reports of suspected side effects were notified to the HPRA. The number of COVID-19 vaccines administered as of that date was reported as 7,207,797, including 235,521 administered as a single dose, 3,533,171 as a first dose, and 3,439,105 as a second dose.[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 01 October, the European Medicines Agency (EMA) published highlights from its monthly safety committee meeting, which included information on COVID-19 vaccines. On 06 October, 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. Topics of interest are summarised on page 7 of this update.

- The next HPRA safety update is due for publication on 4 November.

[1] *https://www.hse.ie/eng/services/news/newsfeatures/covid19-updates/vaccination-programme-dashboard-as-of-28-september-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

Number of reports received

Up to 28 September, the HPRA received 15,424 reports describing suspected side effects[2,3] in association with COVID-19 vaccines, as follows:

mRNA vaccines (Comirnaty® and Spikevax®)	9207
Adenoviral vector vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®)	6123
Brand unknown/not specified	94[4]

Doses administered by vaccine type, as of 28 September, were reported as follows:[1]

- mRNA vaccines: 5,213,092 Comirnaty®, 569,817 Spikevax®.
- Adenoviral vector vaccines: 1,189,367 Vaxzevria®, 235,521 COVID-19 Vaccine Janssen®.

Regularly reported suspected side effects

The most regularly reported suspected side effects notified to the HPRA include the following:[5]

mRNA vaccines (Comirnaty® and Spikevax®)
10% or more of reports describe side effects such as: ▪ Fever, tiredness ▪ Dizziness, headache ▪ Pain (non-specific) ▪ Nausea **1% to less than 10% of reports describe side effects such as:** ▪ Abdominal pain, diarrhoea, tingling sensation in mouth, vomiting ▪ Drowsy, fainting/feeling faint, migraine, numbness/reduced sensations, tingling/pins and needles/tremor ▪ Back pain, joint/limb pain, muscle pain/weakness/spasm/stiffness, neck pain ▪ Blurred vision ▪ Chest discomfort/pain, chills, 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, need to stay in bed) ▪ Enlarged lymph nodes ▪ Feeling anxious, insomnia/trouble sleeping

[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]Number of 'brand unknown' reports has decreased since the last safety update due to follow up information received from reporters who provided the brand name of the vaccine administered.

[5]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.

- 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

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 red/red rash, general rash, sweating/cold sweat, itching, itchy rash
- 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 vaccine, and are mild to moderate in nature.

In the reports evaluated which include information on outcome, approximately one fifth of 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 8.

A full breakdown of all suspected side effects described in reports is provided on page 14. Further information on how reports received by the HPRA are processed, including how safety signals are evaluated, is given on page 18.

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, including EMA recommendations

Topics of interest included in this update are listed below:

Common topics

- Menstrual disturbances
- Deaths following vaccination
- Allergic type reactions (also known as hypersensitivity)
- Systemic events

For mRNA vaccines (Comirnaty® and Spikevax®)

- Vaccination of adolescents (12 to 17 years)
- Myocarditis and pericarditis
- Other product information updates

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

- Immune thrombocytopenia (ITP)
- Venous thromboembolism (VTE) and COVID-19 Vaccine Janssen®
- Thrombosis with thrombocytopenia syndrome (TTS)
- Transverse myelitis and COVID-19 Vaccine Janssen®

COVID-19 vaccines - Common topics

Reports of menstrual disturbances

- Menstrual disturbances are one of the more regularly reported side effects to the HPRA (see pages 5 & 6). In the vast majority of caes, reports are received 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 that describe a bleeding event in a woman who is post menopausal have also been notified.
- The EMA's safety committee are reviewing reports of menstrual disturbances for all COVID-19 vaccines authorised in the EU. The review for Cormiranty®, Spikevax® and Vaxzevria® was recently completed, and in conclusion, no specific pattern of menstrual disturbances could be found, with no evidence of a causal association or link between menstrual disturbances and vaccination. The review of reports following vaccination with COVID-19 Vaccine Janssen® is ongoing however no causal association has been found so far.
- The EMA also highlighted that generally, menstrual disturbances are very common and can occur with or without an underlying medical condition. In about half of the cases reviewed, the patient's medical history or other medication being used provided a possible explanation for their symptom. The EMA outlined that menstrual disturbances may occur due to a wide range of reasons, including stress or tiredness and conditions such as fibroids and endometriosis. 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.

- Further information on the conclusion of the EMA review can be found in the recently published EMA safety update reports for mRNA vaccines (Comirnaty®, Spikevax®).

Reports of deaths following COVID-19 vaccination

- A total of 90 reports have been received describing an individual who was known to have been vaccinated and subsequently passed away. Of these, 79 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. 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 regarding reports of death was not identified from 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 global data.

Reports of allergic type reactions (also known as hypersensitivity)

- Allergic type reactions are known side effects of both mRNA and 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 however, some reports do not contain sufficient detail for classification purposes.[6] Of the reports reviewed, 12 cases associated with an mRNA vaccine and a small number[7] of cases associated with an adenoviral vector vaccine are currently classified as anaphylaxis. In some cases the individual concerned had recovered at the time of reporting 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

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[6] *Reports classified using Brighton Collaboration case definition for anaphylaxis https://brightoncollaboration.us/category/pubstools/case-definitions/. Some reports contain limited information and therefore it is not possible to classify according to the Brighton Collaboration case definition. In these case, the HPRA follows up with the reporter for the missing information.*

[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

- In the reports received, reporters sometimes comment on the impact of expected systemic events following vaccination on their normal daily activities (1% to less than 10% of reports). Reporters have described a need to take time off work or to rest in bed, typically for a short period.
- Systemic events can feel 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.[8]
- 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.[9]
- The product information (package leaflet) for Comirnaty®, Spikevax®, 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.

mRNA vaccines (Comirnaty® and Spikevax®)

Vaccination of adolescents (12 to 17 years)

- As the national vaccination programme continues, the HPRA are closely monitoring any reports of suspected side effects received in adolescents aged 12 to 17 years.
- As of 28 September, the HPRA has received 168 reports of suspected side effects following vaccination of an adolescent with an mRNA vaccine. A breakdown of all suspected side effects by type, reported in those aged 12 to 17 years is available on page 16. Overall, the reports received are consistent with the types of reports received for adults, with most being mild to moderate in nature.

Reports of myocarditis and pericarditis

- Myocarditis and pericarditis, which are inflammatory conditions of the heart, are possible side effects of Comirnaty® and Spikevax®. Cases that have been 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

[8] *European Public Assessment Report (EPAR) for Comirnaty® available from the EMA website https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty*
[9] *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*

which can occur in unvaccinated people, for example, when myocarditis or pericarditis develop after a viral infection, or due to an immune disorder.

- Current advise is that those vaccinated should 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® and Spikevax®, as of 28 September, the HPRA received a total of 80 reports describing suspected side effects of myocarditis (25 reports), pericarditis (33 reports) or a combination of both (22 reports). Of these, 70 occurred following vaccination with Comirnaty® and 10 following Spikevax®. In relation to dose, 36 cases occurred after the first dose and 41 after the second dose (information not reported for three cases), with most occurring within 14 days of vaccination. Suspected cases were reported in 57 males and 23 females, with a median age of 35 years (range 12 to 81). In five cases, the report concerned an adolescent (aged 12 to 17 years).
- 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 the cases, the individuals were still recovering or had ongoing symptoms at the time of initial reporting.
- The EMA's safety committee continues to closely monitor any emerging data to further characterise the frequency and nature of the risk of myocarditis and pericarditis following an mRNA vaccine and to determine whether there is a need to update the current advice in the product information for the vaccines. Current advise for healthcare professionals on this topic is available from the HPRA website here.
- 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.

Other product information updates for mRNA vaccines

- **Comirnaty® and Spikevax®: EMA's safety committee have recommended that** product information is updated to include erythema multiforme as a new potential side effect of both vaccines. Up to 28 September, the HPRA has received a small number[7] of reports of this nature following administration of Comirnaty®. Erythema multiforme is a skin reaction where red spots or patches, which have a dark red centre surrounded by paler red rings, that may look like a target or ''bulls-eye'', appear on the skin, Most cases of erythema multiforme are mild and recover without treatment. The frequency (how often these effects may occur) of erythema multiforme following vaccination is as of yet unknown.
- **Comirnaty®: EMA's safety committee have recommended that** product information is updated to include the following as new potential side effects:
    - paraesthesia (tingling/pins and needles)
    - hypoaesthesia (numbness/reduced sensations in the skin)
    - asthenia (weakness/lack of energy or strength)
    - lethargy (tiredness)
    - decreased appetite
    - nocturnal hyperhidrosis (sweating especially at nighttime)

- These types of events have been notified to the HPRA, including as some of the more regularly reported side effects (see pages 5 & 6). Up to 28 September, the HPRA received, 419 reports of tingling/pins and needles, 321 reports of numbness/reduced sensations in the skin, 459 reports describing weakness, 128 reports of decreased appetite and 207 reports of hyperhidrosis following administration of Comirnaty®.

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. Very low levels of blood platelets can be associated with bleeding and serious health problems.
- The EMA's safety committee has completed a review of cases of ITP reported in individuals who received Vaxzevria® or COVID-19 Janssen®. Following this review, the product information for both vaccines will be revised to include the following advice:
    - ITP will be listed as a possible side effect. This follows reports of very rare cases, usually within 4 weeks of vaccination, including some with very low platelet levels, bleeding or a fatal outcome. Some cases occurred in individuals who had a history of ITP, prior to being vaccinated.
    - Healthcare professionals are advised that in individuals with a history of a low platelet count disorder (e.g. ITP), the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination.
    - Those vaccinated are reminded to seek immediate medical attention if following vaccination they experience any unexplained bleeding, bruising or petechiae (pinpoint, round spots that appear on the skin) beyond the site of vaccination.
- A communication will be issued to healthcare professionals to raise awareness of the risk of ITP. Healthcare professional are reminded that in patients presenting with low platelets following vaccination, a diagnosis of thrombosis with thrombocytopenia syndrome (TTS) should also be considered (see page 12)
- As of 28 September, the HPRA has received five reports of ITP which occurred in individuals following vaccination with Vaxzevria®. No reports have been received in association with COVID-19 Vaccine Janssen®. In some cases the individual concerned had a history of ITP or another relevant underlying condition. In all cases, ITP was reported to have occurred within 1-3 weeks post vaccination and all individuals were treated in hospital.
- Further information is available from the EMA safety update reports for Vaxzevria® and COVID-19 Vaccine Janssen®.

Reports of venous thromboembolism (VTE) and COVID-19 Vaccine Janssen®

- Venous thromboembolism (VTE) is a condition in which a blood clot forms in a deep vein, usually in a leg, arm or groin and may travel to the lungs causing a blockage of the blood supply, which can have potential life-threatening consequences. VTE includes 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).

- Following a review of all available data, including from clinical trials, EMAs safety committee has concluded that there is a reasonable possibility that VTE may be linked to vaccination with COVID-19 Vaccine Janssen, and product information will be revised as follows:
    - Product information will highlight that cases of VTE have been observed rarely following vaccination with COVID-19 Vaccine Janssen®, and that the risk of VTE should be considered for individuals with increased risk factors for thromboembolism (blood clotting).
    - Those vaccinated are advised to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain following vaccination.
- A communication will be issued to healthcare professionals to raise awareness of the risk of VTE. Healthcare professional are reminded that in patients presenting with thrombosis following vaccination, a diagnosis of thrombosis with thrombocytopenia syndrome (TTS) should also be considered (see section below on page 12)
- To 28 September, the HPRA has received 12 reports describing a blood clotting event following vaccination with COVID-19 Vaccine Janssen®. The 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). The median age of individuals who experienced a blood clotting event was 40 (age range 19 to 66 years). In the majority of the cases, the individuals were still recovering or had ongoing symptoms at the time of initial reporting. A small number of additional cases of blood clotting, which occurred together with low blood platelets, have been received and are described under the TTS section below (see page 12).
- All reports of clotting events 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.
- Further details on the EMA safety committee review of the risk of VTE for COVID-19 Vaccine Janssen is available here.

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) together with thrombocytopenia (very low platelet levels).
- 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 28 September, the HPRA has received nine reports that are suspected cases of TTS, and which mostly 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® or single dose of COVID-19 Vaccine Janssen®. 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 42 (age range, 21 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.

Reports of transverse myelitis and Covid-19 Vaccine Janssen®

- Transverse myelitis is a rare disorder caused by inflammation to the spinal cord, which interrupts communication between nerve cells in the spinal cord and the rest of the body, and can result in altered sensations, bladder and bowel dysfunction, pain and weakness. The underlying cause is often unknown but may be related to an immune system disorder or an infection.
- Transverse myelitis has been reported very rarely following vaccination with Covid-19 Vaccine Janssen® and the EMA's safety committee has recommended that product information be updated to include transverse myelitis as a potential side effect. The exact frequency (how often these effects may occur) of transverse myelitis following vaccination is as of yet unknown.
- Up to 28 September, the HPRA received a small number[7] of reports of transverse myelitis following COVID-19 vaccination. However none were associated with COVID-19 Vaccine Janssen®.

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'[10] 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 18.

Of the 15,424 reports notified to the HPRA up to 28 September, 55% have now 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 18 for further details.

[10] *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 9207 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	Suspected side effects
General symptoms and local reactions *e.g. chills, fatigue, 'flu-like' feeling, fever, injection site pain or swelling*	10854
Nervous system *e.g. dizziness, headache, lack of energy, pins & needles, fainting or feeling faint*	6176
Muscles, tissue, bones or joints *e.g. general muscular pain or weakness*	4242
Gastrointestinal *e.g. nausea, vomiting, diarrhoea*	3109
Skin *e.g. rash, itchy rash*	2469
Reproductive system, obstetrics or gynaecology related *e.g. menstrual disturbance*	1444
Respiratory *e.g. cough, shortness of breath*	1266
Behavioural, emotional and mental health *e.g. insomnia, trouble sleeping*	987
Cardiac (heart) related *e.g. palpitations*	732
Social circumstances *e.g. need to rest in bed or take a break from normal daily activities*	714
Eye *e.g. eye pain, vision blurred*	649
Blood and lymphatic system *e.g. swollen glands*	643
Procedural issues and complications *e.g. injection site bruising*	569
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)*	545
Blood vessel related (i.e. veins/arteries) *e.g. pale complexion*	462
Infection *e.g. local or general such as influenza or cold sore*	449
Ear related e*.g. earache, tinnitus*	394
Metabolism and nutrition disorders *e.g. decreased appetite*	269
Immune system related *e.g. hypersensitivity, allergic reaction*	132
Kidney related *e.g. change in frequency of urination*	85
Endocrine (hormone) *e.g. thyroid function change*	20
Liver related *e.g. jaundice*	18
Cysts and polyps *e.g. benign skin growth*	9

Suspected side effects to adenoviral vector vaccines

A breakdown of suspected side effects described in the 6123 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	Suspected side effects
General symptoms and local reactions *e.g. chills, fatigue, 'flu-like' feeling, fever, injection site pain or swelling*	10622
Nervous system *e.g. dizziness, headache, lack of energy, pins & needles, fainting or feeling faint*	5506
Muscles, tissue, bones or joints *e.g. general muscular pain or weakness*	3844
Gastrointestinal *e.g. nausea, vomiting, diarrhoea*	2949
Skin *e.g. rash, itchy rash*	1641
Respiratory *e.g. cough, shortness of breath*	885
Behavioural, emotional and mental health *e.g. insomnia, trouble sleeping*	778
Social circumstances *e.g. need to rest in bed or take a break from normal daily activities*	613
Eye *e.g. eye pain, vision blurred*	467
Metabolism and nutrition disorders *e.g. decreased appetite*	461
Reproductive system, obstetrics or gynaecology related e.g. *menstruation disturbance*	458
Blood vessel related (i.e. veins/arteries) *e.g. pale complexion*	430
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)*	388
Cardiac (heart) related *e.g. palpitations*	354
Ear related e*.g. earache, tinnitus*	341
Procedural issue or complications *e.g. injection site bruising*	338
Infection *e.g. local or general such as influenza or cold sore*	237
Blood and lymphatic system *e.g. swollen glands*	175
Kidney related *e.g. increased frequency of urination*	69
Immune system related *e.g. hypersensitivity, allergic reactions*	53
Liver related *e.g. jaundice*	9
Endocrine (hormone) *e.g. thyroid function change*	5
Cysts and polyps	<5

Suspected side effects in adolescents (aged 12 to 17 years)

A breakdown of suspected side effects described in the 168 reports notified to the HPRA concerning adolescents aged 12 to 17 years 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	Suspected side effects
General symptoms and local reactions *e.g. tiredness, weakness, chest pain, feeling hot*	149
Nervous system *e.g. dizziness, headache, fainting or feeling faint*	117
Gastrointestinal *e.g. nausea, vomiting, abdominal pain*	83
Muscles, tissue, bones or joints *e.g. limb,muscle,joint pain*	48
Skin *e.g. rash, sweating*	33
Respiratory *e.g. shortness of breath, nose bleed*	30
Cardiac (heart) related *e.g. palpitations/racing heart*	22
Behavioural, emotional and mental health *e.g. trouble sleeping*	20
Social circumstances *e.g. need to rest in bed or take a break from normal daily activities*	15
Blood vessel related (i.e. veins/arteries) *e.g. pale complexion*	14
Eye *e.g. vision blurred*	13
Blood and lymphatic system *e.g. swollen glands*	9
Infection *e.g. chest infection*	9
Reproductive system, obstetrics or gynaecology related *e.g. menstruation disturbance*	9
Procedural issue or complications *e.g. fall*	7
Metabolism and nutrition disorders *e.g. decreased appetite*	7
Abnormal clinical or laboratory result (i.e. where information is provided on results of relevant tests) *e.g. changes in heart rate*	6
Ear related	<5
Immune system related	<5
Kidney related	<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.