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SCIENCE MEDICINES HEALTH

COVID-19 vaccines –
Updates, learnings and plans for pharmacovigilance

PCWP & HCPWP Joint Meeting
1-2 June 2022

Georgy Genov, Priya Bahri and Cosimo Zaccaria, European Medicines Agency

Strong surveillance of COVID-19 vaccines 2021 and 2022

- New strategies to help tailoring existing pharmacovigilance approaches
- Intense work by rapporteurs, the Pharmacovigilance Risk Assessment Committee (PRAC), and the EU regulatory network overall
- Close international collaboration
- Engagement with the public: stakeholder members in specific EMA Pandemic Task Force (ETF), 44 vaccine product safety updates in 2021 and monthly updates on all vaccine products in 2022, press conferences, public meetings, PCWP & HCPWP
- Some new risks and risk minimisation advice for early detection of adverse reactions and prevention of serious outcomes have been identified

Public COVID-19 vaccines safety updates – new format in 2022

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20 January 2022

COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)
COVID-19 Vaccine Janssen (Janssen-Cilag International NV)
Nuvaxovid (Novavax CZ, a.s.)
Spikevax (Moderna Biotech Spain, S.L.)
Vaxzevria (AstraZeneca AB)

The safety of authorised COVID-19 vaccines is continuously monitored and updated information is regularly provided to the public.

Safety updates outline the outcomes from assessments of emerging worldwide safety data carried out mainly by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (section 1). They also outline how safety is monitored and contain high-level information on suspected adverse reaction reports, which PRAC takes into account in its assessments (section 2).

This safety update follows the updates of 9 December 2021 and reflects the main assessment outcomes of the PRAC meeting held 10 to 13 January 2022.

EMA confirms that the benefits of all currently authorised COVID-19 vaccines continue to outweigh their side effects, given the risk of COVID-19 illness and related complications, including hospitalisation and death.

www.ema.europa.eu

Key messages from the latest safety assessments

COVID-19 Vaccine Janssen and Vaxzevria

- The product information will be updated to add transverse myelitis (inflammation in the spinal cord) as a side effect.
- Information on the known side effect of thrombosis with thrombocytopenia syndrome (TTS; blood clots with low blood platelets) will be updated in the product information.

Spikevax

- The product information will be updated to include paraesthesia (unusual feeling in the skin) as a rare side effect.

Comirnaty and Spikevax

- An assessment of whether vaccination can cause capillary leak syndrome (leakage of fluid from blood vessels) is ongoing.

1. Latest safety assessments

Comirnaty (BioNTech Manufacturing GmbH)

About 545 million doses of Comirnaty were administered in the EU/EEA between EU marketing authorisation on 21 December 2020 and 2 January 2022[1].

Capillary leak syndrome

Ongoing assessment

In January 2022, PRAC started an assessment of reports of capillary leak syndrome (CLS) in people vaccinated with Comirnaty. CLS is a disorder characterised by leakage of fluid from blood vessels causing tissue swelling

[1] The European Centre for Disease Prevention and Control (ECDC) collects these exposure data from EU Member States as well as from the additional countries of the European Economic Area (EEA) Norway, Iceland and Liechtenstein.

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and a fall in blood pressure. The investigations of whether Comirnaty can cause CLS will include an assessment of the most recent scientific literature.

Use of the vaccine in pregnancy

No sign of adverse outcomes

A review of several studies involving around 65,000 pregnancies at different stages did not find any sign of an increased risk of pregnancy complications, miscarriages, preterm births or adverse effects in the unborn babies following vaccination with the mRNA vaccines Comirnaty and Spikevax. The review was conducted by EMA's COVID-19 pandemic task force (ETF) and further information can be found in this EMA communication.

Information on how Comirnaty works is presented in the medicine overview (in all EU/EEA languages); full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages).

COVID-19 Vaccine Janssen (Janssen-Cilag International NV)

About 18,7 million doses of COVID-19 Vaccine Janssen were administered in the EU/EEA between EU marketing authorisation on 11 March 2021 and 2 January 2022[1].

Transverse myelitis

Update to the product information

Following a previous assessment (see safety update for COVID-19 Vaccine Janssen of 6 October 2021), in January 2022 PRAC finalised the update of the product information on transverse myelitis (TM) as a side effect of COVID-19 Vaccine Janssen. TM is a neurological condition characterised by an inflammation in the spinal cord. The frequency category of this side effect will be 'unknown frequency', because it is generally difficult to robustly estimate side effect frequencies from cases of suspected side effects that have been reported by healthcare professionals or patients spontaneously. Further information can be found in the PRAC highlights of January 2022.

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People are advised to seek immediate medical attention if they develop weakness in the arms or legs, sensory symptoms (such as tingling, numbness, pain or loss of pain sensation) or problems with bladder or bowel function after vaccination.

Thrombosis with thrombocytopenia syndrome

Update to the product information

Following the last update to the product information regarding the very rare side effect of thrombosis (formation of blood clots in the blood vessels) with thrombocytopenia (low blood platelets) syndrome (TTS) (see safety update for COVID-19 Vaccine Janssen of 11 May 2021), in January 2022 PRAC concluded that the product information should be updated further. This update will remove the current statement that reported TTS cases occurred mostly in women, since the sex imbalance seems smaller than previously observed. The observed cases occurred within the first three weeks following vaccination, mostly in individuals under 60 years of age.

Reminder: People are advised to seek immediate medical attention if they experience severe or persistent headaches, seizures (fits), mental status changes or blurred vision, unexpected bleeding, unexpected skin bruising beyond the site of vaccination which appears days after vaccination, or pinpoint round spots beyond the site of vaccination, or develop shortness of breath, chest pain, leg pain, leg swelling, or persistent abdominal pain (see product information).

Information on how COVID-19 Vaccine Janssen works is presented in the medicine overview (in all EU/EEA languages); full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages). The product information will be updated in accordance with the latest safety assessment outcomes.

Nuvaxovid (Novavax CZ, a.s.)

Reminders: The administration of Vaxzevria is contraindicated in individuals who have experienced TTS following vaccination with this vaccine.

People should seek immediate medical attention if they develop shortness of breath, chest pain, leg swelling, leg pain or persistent abdominal pain following vaccination, or experience after a few days following vaccination severe or persistent headaches, blurred vision, confusion or seizures (fits), or unexplained bleeding or skin bruising or pinpoint round spots beyond the site of vaccination which appears after a few days (see product information).

Transverse myelitis

Update to the product information

In January 2022, PRAC concluded that transverse myelitis (TM) should be added to the product information as a side effect of Vaxzevria. TM is a neurological condition characterised by an inflammation in the spinal cord. The frequency category of this side effect will be 'unknown frequency', because it is generally difficult to robustly estimate side effect frequencies from cases of suspected side effects that have been reported by healthcare professionals or patients spontaneously. Further information can be found in the PRAC highlights of January 2022.

People are advised to seek immediate medical attention if they develop weakness in the arms or legs, sensory symptoms (such as tingling, numbness, pain or loss of pain sensation) or problems with bladder or bowel function after vaccination.

Information on how Vaxzevria works is presented in the medicine overview (in all EU/EEA languages); full information on the vaccine, including all identified side effects and advice on how to use it, is available in the product information (in all EU/EEA languages). The product information will be updated in accordance with the latest safety assessment outcomes.

2. How safety is monitored

Before COVID-19 vaccines were granted EU marketing authorisation, the efficacy and safety of the vaccines were assessed in pre-clinical studies and large clinical trials.

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All relevant new information emerging worldwide on the vaccines since marketing authorisation is collected and promptly assessed. This is in line with the pharmacovigilance plan for COVID-19 vaccines of the EU regulatory network (comprising the regulatory bodies of the EU Member States, EMA and the European Commission).

EMA's detailed assessments take into account all available data from all sources to draw robust conclusions on the safety of the vaccines. These data include clinical trial results, reports of suspected side effects, epidemiological studies monitoring the safety of the vaccine, toxicological investigations and any other relevant information.

Summary safety reports

The pharmacovigilance plan for COVID-19 vaccines includes monthly summary safety reports (MSSRs) which are compiled by the marketing authorisation holders to support timely and continuous benefit-risk evaluations for COVID-19 vaccines used during the pandemic. MSSRs are intended to be compiled for at least the first six months of marketing. After the first six months, summary safety reports may cover time periods longer than a month or not be necessary anymore. MSSRs/ summary safety reports complement the submission of periodic safety update reports (PSURs).

Case reports of suspected side effects

Collecting reports of medical events and problems that occur following the use of a medicine, and therefore might be side effects, is one of the pillars of the EU safety monitoring system.

Healthcare professionals and vaccinated individuals are encouraged to report to their national competent authorities all suspected side effects individuals may have experienced after receiving a vaccine even if it is unclear whether the vaccine was the cause. For more information on how to report, including the importance of detailing the vaccine product name and the batch, see Reporting suspected side effects.

These spontaneous reports are collected in EudraVigilance, the EU database used for monitoring and analysing suspected side effects. Publicly available information can be accessed via EudraVigilance – European database of suspected drug reaction reports (in all EU/EEA languages).

As of 2 January 2022, EudraVigilance contained:

- for Comirnaty: a total of 532,530 cases of suspected side effects spontaneously reported from EU/EEA countries; 6,490 of these reported a

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Spontaneously reported suspected adverse reaction cases

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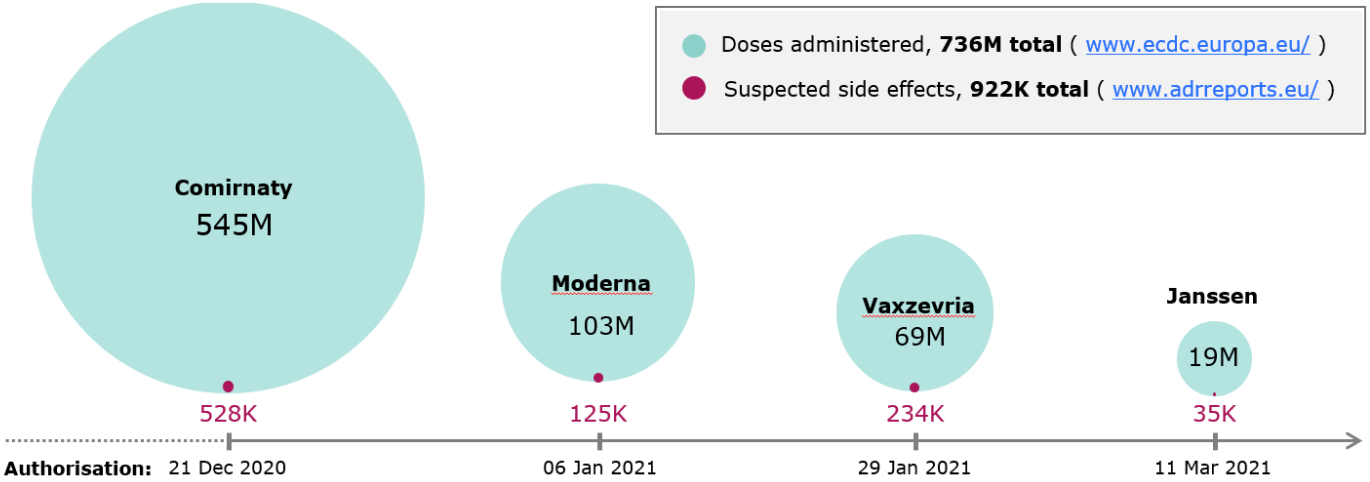
EudraVigilance on 2 January 2022:

More reports received with 4 vaccines than all other centrally authorised products in 1 year

European Economic Area (EEA)



Worldwide

#CASES

1,485,040

Healthcare Professional	482,006
Non HCP	862,349

Spontaneously reported suspected adverse reaction cases

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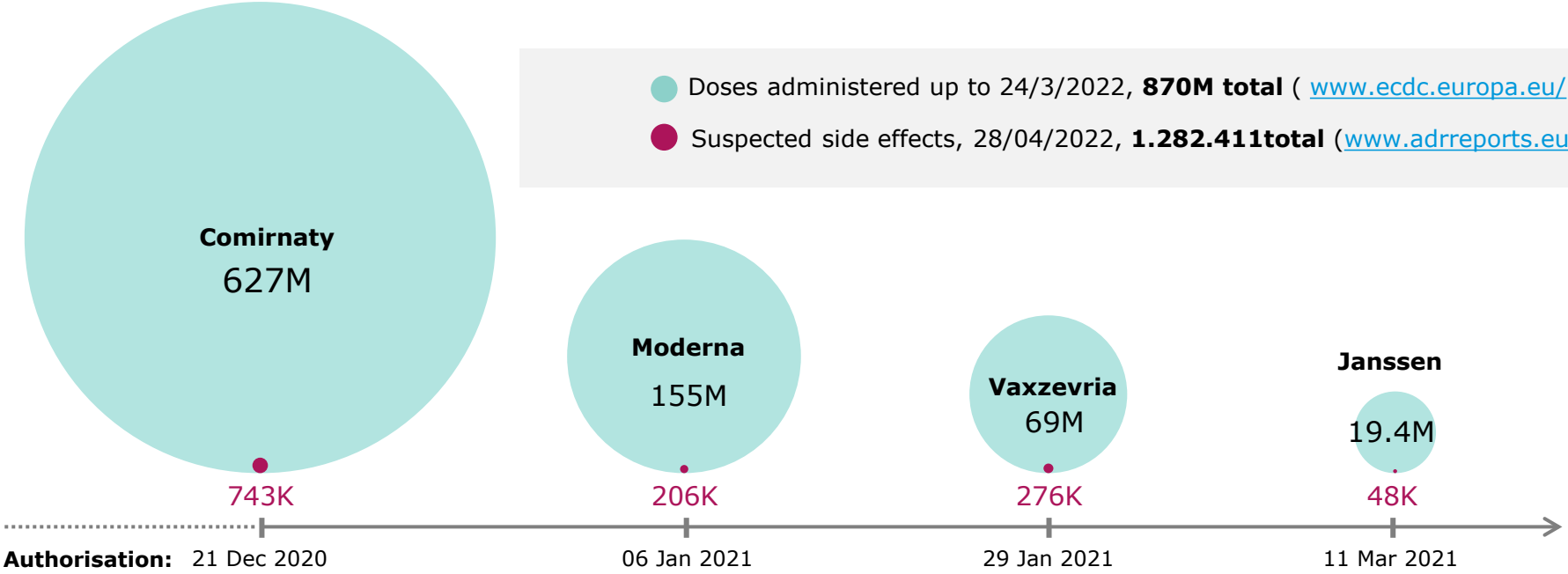
EudraVigilance on 24 April 2022:

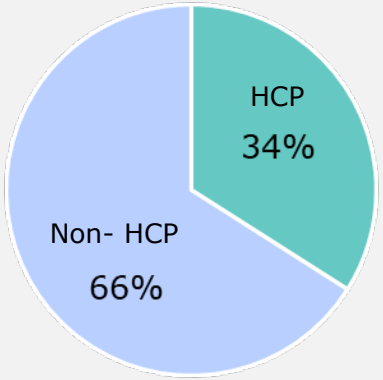
Numbers of **suspected** side effects need to be put into context of **how many** people have been vaccinated and **how long** the vaccine has been on the market.



- **Anyone** can report a suspected side effect to their national authority or the vaccine manufacturer
- Consult the appropriate authority from the list of national medicines regulatory authorities in the EEA for information on how to report a side effect
- Reports are sent to **EudraVigilance, the European database** of suspected side effects

Who has reported?

Status as of 28.04.2022 – European Economic Area (EEA)



#Cases
1,282,411

Healthcare professionals (**392.703 reports**)

Non-healthcare professionals (**764.523 reports**)

Source: EudraVigilance

Risk minimisation advice added from 2021 to February 2022

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Anaphylaxis

- Don't vaccinate if allergic against ingredient
- Talk to your doctor about past allergies to vaccines
- 15 min observation time
- Equipment
- Go to a doctor immediately if swelling, rash, nausea, stomach pain, breathing difficulties or fainting occurs

Comirnaty

Spikevax

Myo/pericarditis

- Go to a doctor immediately if breathlessness, strong heartbeat or chest pain occurs

Vaxzevria

Janssen

Capillary leak syndrome

- Don't vaccinate if CLS history
- Go to a doctor immediately if arms and legs swelling, sudden weigh gain or feeling faint occurs
- Intensive care

Vaxzevria

Janssen

TTS

- Don't vaccinate if TTS history after COVID-19 vaccine
- Go to a doctor immediately if breathlessness, chest pain, leg swelling/pain, persistent abdominal pain, severe or persistent headaches, blurred vision, confusion, seizures or skin bruising occurs
- Investigate thrombocytopenia (within three weeks after vaccination) for thrombosis; investigate thrombosis for thrombocytopenia
- Special care

Janssen

Vaxzevria

Venous thrombo-embolism

Cerebral blood clots

- Advice as for TTS

Vaxzevria

Janssen

Immune thrombocytopenia

- If ITP history, consider if to vaccinate and monitor platelets after vaccination
- Go to a doctor immediately if unexplained bleeding, skin bruising or pinpoint round spots beyond site of vaccination occur

Vaxzevria

Janssen

Guillain-Barré syndrome

- Tell your doctor before vaccination if GBS history after Vaxzevria (Vaxzevria package leaflet only)
- Go to a doctor immediately if weakness/paralysis in arms and legs, which can progress to chest and face, occurs

Vaxzevria

Janssen

Transverse myelitis

- Tell your doctor before vaccination if TM history after Vaxzevria (Vaxzevria package leaflet only)
- Go to a doctor immediately if weakness/paralysis in arms and legs, sensory symptoms or problem of bladder or bowel function occur

General

- Talk to your doctor before vaccination about existing severe illness, current severe infection with high fever, existing weakened immune system, bleeding problems, fainting after previous needle injection, vaccination anxiety

Please see full product information

New risk minimisation advice from March to May 2022

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17 March 2022

COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)
COVID-19 Vaccine Janssen (Janssen-Cilag International NV)
Nuvaxovid (Novavax CZ, a.s.)
Spikevax (Moderna Biotech Spain, S.L.)
Vaxzevria (AstraZeneca AB)

Key messages from the latest safety assessments

COVID-19 Vaccine Janssen

PRAC recommends updating the product information to include cutaneous small vessel vasculitis (inflammation of blood vessels in the skin) as a new side effect of COVID-19 Vaccine Janssen.

Spikevax

PRAC recommends updating the product information with a warning to reflect the potential of flare-ups of capillary leak syndrome (leakage of fluid from blood vessels) following vaccination with Spikevax, in patients who have a medical history of this extremely rare condition.

A few cases of capillary leak syndrome (CLS) flare-up (causing fluid leakage from small blood vessels (capillaries) resulting in rapid swelling of the arms and legs, sudden weight gain and feeling faint, low blood pressure) have been reported following vaccination with Spikevax. If you have previously had episodes of CLS, talk to a doctor before you are given Spikevax.

13 April 2022

COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)
COVID-19 Vaccine Janssen (Janssen-Cilag International NV)
Nuvaxovid (Novavax CZ, a.s.)
Spikevax (Moderna Biotech Spain, S.L.)
Vaxzevria (AstraZeneca AB)

Key messages from the latest safety assessments

No updates to the product information are currently recommended for any of the authorised COVID-19 vaccines.

Comirnaty

Capillary leak syndrome (CLS)

No update to the product information required

An assessment of whether vaccination with Comirnaty can cause capillary leak syndrome (CLS) has been completed. PRAC has concluded that there are currently insufficient data to support an update of the product information.

Auto-immune hepatitis (AIH)

No evidence for a causal relationship with Comirnaty or Spikevax

12 May 2022

COVID-19 vaccines safety update

Comirnaty (BioNTech Manufacturing GmbH)
Jcovden (previously COVID-19 Vaccine Janssen) (Janssen-Cilag International NV)
Nuvaxovid (Novavax CZ, a.s.)
Spikevax (Moderna Biotech Spain, S.L.)
Vaxzevria (AstraZeneca AB)

Key messages from the latest safety assessments

No updates to the product information for any of the authorised COVID-19 vaccines are currently warranted.

Ongoing investigations whether causally related:

- Short-lived menstrual disorders for Comiranty and Spikevax, after previous reviews for COVID-19 vaccines have not evidenced such disorders
- Myocardial infarction for Vaxzevria and Jcovden
- Thrombosis and pulmonary embolism for Vaxzevria
- Corneal graft rejection (CGR) for Comirnaty, Spikevax and Vaxzevria

Continuous pharmacovigilance improvement cycle

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Lessons Learned H1N1

Lessons learned from A/H1N1 pandemic adapted to current emergency situation

Signal Detection Methods

- Rapid **detection**, **exchange**, **prioritisation** and **assessment** of safety **signals**
- Testing of **new methodologies** specific for COVID-19

COVID-19 Vaccines Monitoring Preparedness Plan

Enhanced monitoring activities to be carried out in the EU for COVID-19 vaccines, including **roles**, **responsibilities** and **interactions** of stakeholders involved

- Active surveillance of **vulnerable populations**:
- Active data collection on **rare** and **severe** risks
- **ACCESS**, **ICMRA**, **pregnancy studies**, **int. cohorts**

International And Research Centres Collaboration

- **Engage** and **communicate** with public, patients and HCP.
- **Enhanced communication** and **transparency** measures

Transparency & Communication

Crisis for innovation, efficiency and preparedness

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Pandemic has been a powerful booster for developing tools, methods, risk communication and international collaboration → Maintain momentum!

Tools and methods for adhoc analysis, visualisation, prioritisation and contextualisation of large volumes of spontaneous reports

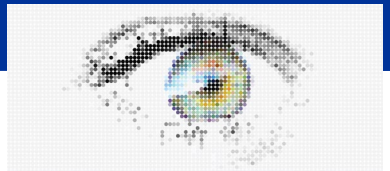
Development of standardised case definitions for new clinical entities

Flexible and tailored (e.g. sex, age, dose) regulatory procedures for accelerated assessment with near “real-time” information

Enhanced collaboration amongst international regulators, learned societies and consortia leveraging experience

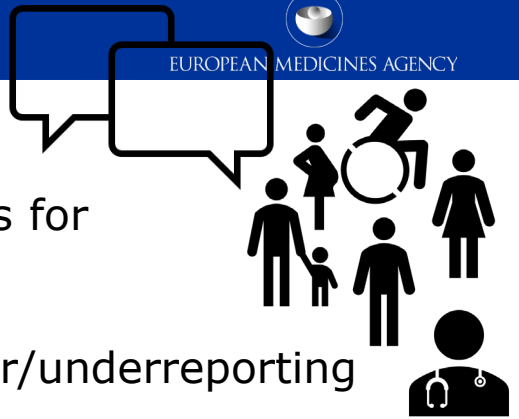
Diverse range of channels for risk communication and engagement of broad range of stakeholders in timely manner

Plans for safety surveillance



- Measure possible masking effects
- Explore case adjudication using machine learning and neuro-linguistic programming
- Refine methods and guidance overall

Plans for pharmacovigilance engagement



- SARS-CoV-2 pandemic augmented needs and opportunities for pharmacovigilance engagement
- Reporting of suspected adverse reactions – differential over/underreporting
- Fact-checking workshop with journalists regarding COVID-19 vaccines
- Re-start with new experiences plans at EMA for enhancing engagement of the Pharmacovigilance Risk Assessment Committee (PRAC), e.g.
  - Study on integration of risk minimisation measures (RMM) in clinical guidelines with examples for 5 major disease areas
  - Pilot start in July 2022 for the PRAC Risk Minimisation Alliance (PRISMA) for informal input to PRAC regarding the implementability of RMM options for widely used products with significant preventable risk to support patient safety
  - Reflection paper on digital support tool to RMM to be drafted in 2022/23 by a multistakeholder working group

Thank you

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