Follow-up of vaccine safety and lessons learned

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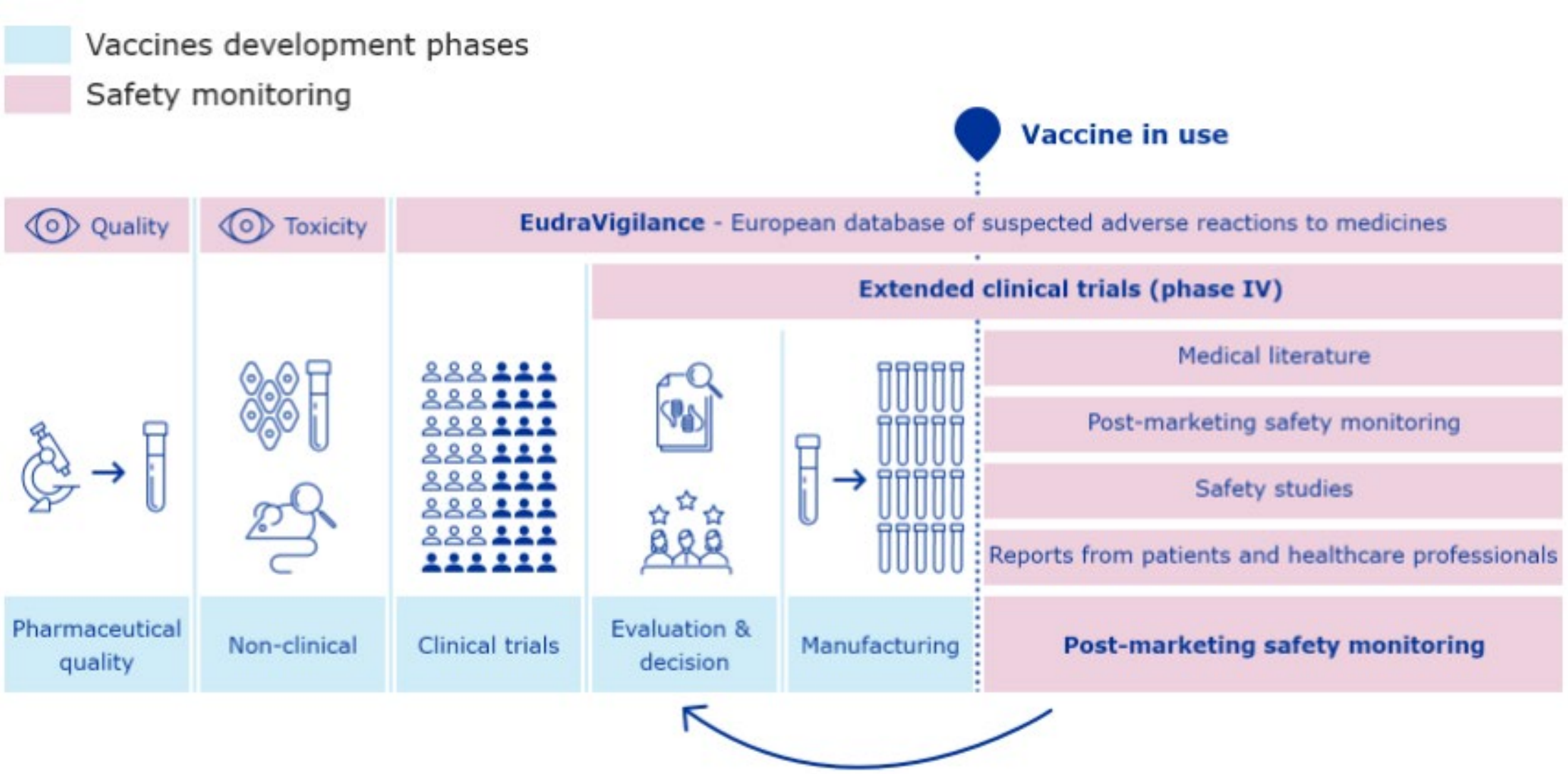
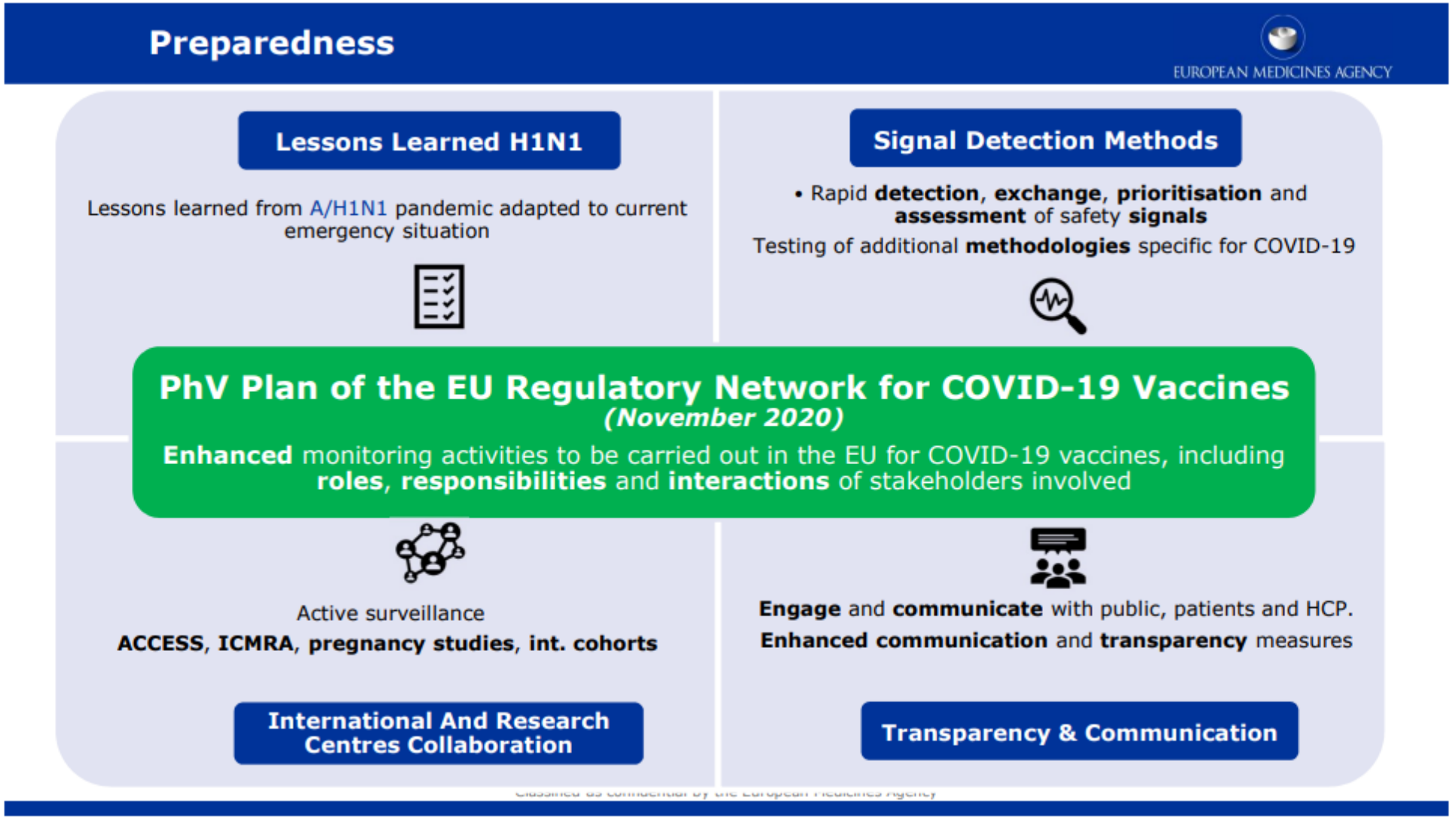
Follow-up of vaccine safety

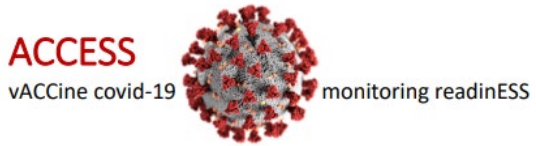
EMA – How vaccine safety is studied



EMA - Preparedness



EMA – ACCESS programme vACCine COVID-19 monitoring readinESS



- Funded by EMA: research to monitor safety, effectiveness and coverage of COVID-19 vaccines
- Public-academic partnership of 22 European research centres, led by Utrecht University
- Calculation of background rates for adverse events of special interest (AESI)
- Development of protocols for different studies: cohort event monitoring, safety signal evaluation, coverage and effectiveness studies - to be used by vaccine manufacturers or public entities (EMA, ECDC ...)

DAP: Alle | AESI: Guillain Barre Syndrome | Year: Alle | Age category: Alle

IR per 100,000 person-years

DAP	Body System	AESI	Year	Age category	IR	LL	UL
ES_BIFAP_PC	Autoimmune diseases	Guillain Barre Syndrome	2020	0-19	0,83	0,40	1,54
ES_BIFAP_PC	Autoimmune diseases	Guillain Barre Syndrome	2020	20-29	0,65	0,18	1,66
ES_BIFAP_PC	Autoimmune diseases	Guillain Barre Syndrome	2020	30-39	0,88	0,35	1,81
ES_BIFAP_PC	Autoimmune diseases	Guillain Barre Syndrome	2020	40-49	1,02	0,51	1,83
ES_BIFAP_PC	Autoimmune diseases	Guillain Barre Syndrome	2020	50-59	0,70	0,28	1,43
ES_BIFAP_PC	Autoimmune diseases	Guillain Barre Syndrome	2020	60-69	2,22	1,31	3,50

EMA – Preparedness

Routine	Additional (reduce timeframe and risk communication)
Risk management plan (RMP)	• Core RMP for COVID-19 vaccines • List of AESI • Traceability
Periodic safety update reports (PSURs)	• (Monthly) Summary Safety Reports
Post-authorisation safety studies (PASS)	• European infrastructure for monitoring COVID-19 treatments and vaccines (e.g. ACCESS, CONSIGN…) • Collecting exposure data to COVID-19 vaccines
Signal management	• Specific safety signal detection measures • Rapid signal outcomes and implementation (e.g. urgent confirmation, fast update of PI, etc.) + Extraordinary PRAC/CHMP meeting
Communication	• Exceptional transparency measures: EMA Press Conference, COVID-19 safety updates, Full RMP published, etc.

EMA - Core risk management plan (RMP)

EMA/PRAC/73244/2022
8 February 2022

Consideration on core requirements for RMPs of COVID-19 vaccines
coreRMP19 guidance v3.0

coreRMP19

Lesson learned: guidance early and comprehensive

- GVP and RMP templates
- Info on infection and candidates vaccines limited at start of pandemic
- Recurrent topics in Scientific Advice
- PRAC stepped up with common approach to:
  - Safety concerns
  - AESI
  - Traceability tools
  - Routine activities
  - PM safety surveillance

Adverse Events of Special Interest (AESI) SPEAC/Brighton – WHO/GACVS

AESI included because they are seen with COVID-19 disease [3,4]
Acute respiratory distress syndrome
Multisystem inflammatory syndrome (children and adults)
Acute cardiovascular injury (including: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)
Myocarditis/pericarditis
Coagulation disorder (including: thrombotic disorders, bleeding disorders)
Bleeding disorder
Anosmia, ageusia
Chilblain (for example: lesions)
Erythema multiforme
Single Organ Cutaneous Vasculitis
Acute kidney injury
Acute liver injury
Acute pancreatitis
Rhabdomyolysis
Subacute thyroiditis
AESI included because they have a proven or theoretical association with immunisation in general
Anaphylaxis [1,2]
Thrombocytopenia[1,2,3,4]
Generalized convulsion[1,2]
Acute disseminated encephalomyelitis[4]
Guillain Barré Syndrome[3,4]
AESI included because they have a proven or theoretical association with specific vaccine platform(s)
Acute aseptic arthritis
Aseptic meningitis
Encephalitis/Encephalomyelitis
Idiopathic Peripheral Facial Nerve Palsy
Vaccine associated enhanced disease[1,2,5]

1. Proven association with immunisation involving several different vaccines
2. Proven association with vaccine that could theoretically apply to novel COVID-19 vaccines
3. Theoretical concern based on wild type disease immunopathogenesis
4. Theoretical concern related to viral replication during wild type disease
5. Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform

EMA – Reports of suspected side effects: signals

Comirnaty
(BioNTech and Pfizer)

Status as of 03/04/2022

625,000,000

Doses given to people in the EU/EEA

699,605*

Reports of suspected side effects in the EU/EEA (see www.adrreports.eu)

Spikevax
(Moderna)

Status as of 03/04/2022

155,000,000

Doses given to people in the EU/EEA

193,037*

Reports of suspected side effects in the EU/EEA (see www.adrreports.eu)

Vaxzevria
(AstraZeneca)

Status as of 03/04/2022

69,000,000

Doses given to people in the EU/EEA

266,091*

Reports of suspected side effects in the EU/EEA (see www.adrreports.eu)

COVID-19 Vaccine Janssen

Status as of 03/04/2022

19,300,000

Doses given to people in the EU/EEA

45,947*

Reports of suspected side effects in the EU/EEA (see www.adrreports.eu)

EudraVigilance screened weekly through statistical reports in 2021:

- 992 potential signals related to COVID-19 vaccines reviewed
- 21 signals validated at EU level related to COVID-19 vaccines – further investigated

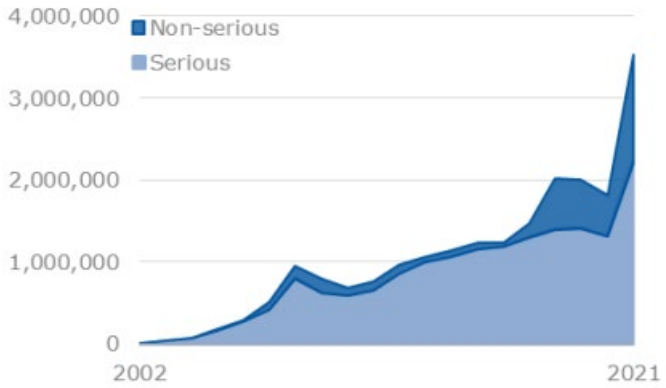


Figure 6. Number of ADR reports processed per year in EVPM.

EMA – Outcome 2021

Outcome of MSSR/signals/PSURs: updates of PI/SmPC, DHPC, RMP, Safety Updates, PRAC highlights, press communications …

March	April	May	June	July
• **Vaxzevria**: TTS, Anaphylaxis • **Comirnaty**: Diarrhoea and vomiting, extensive swelling of the vaccinated limb	• **Vaxzevria**: TTS • **Janssen**: TTS • **Comirnaty**: Hypersensitivity reactions	• **Comirnaty**: facial swelling • **Spikevax**: Diarrhoea and delayed injection site reactions • **Janssen**: TTS • **Vaxzevria**: TTS, urticaria and angioedema	• **Vaxzevria**: capillary leak syndrome (CLS)	• **Comirnaty**: Myocarditis, pericarditis • **Spikevax**: Myocarditis, Pericarditis • **Vaxzevria**: Guillain-Barré Syndrome (GBS) • **Janssen**: CLS

August	September	October	November	December
• **Janssen**: GBS, immune thrombocytopenia (ITP), dizziness and tinnitus	• **Vaxzevria**: GBS • **Janssen**: Lymphadenopathy, paraesthesia, hypoesthesia, tinnitus, diarrhoea and vomiting	• **Janssen**: VTE, ITP, TTS • **Vaxzevria**: ITP • **Comirnaty**: Erythema multiforme, Paraesthesia and hypoesthesia • **Spikevax**: Erythema multiforme	• **Vaxzevria**: CVST without thrombocytopenia	• **Comirnaty**: Myocarditis, Pericarditis • **Spikevax**: Myocarditis, Pericarditis • **Janssen**: Cutaneous small vessel vasculitis

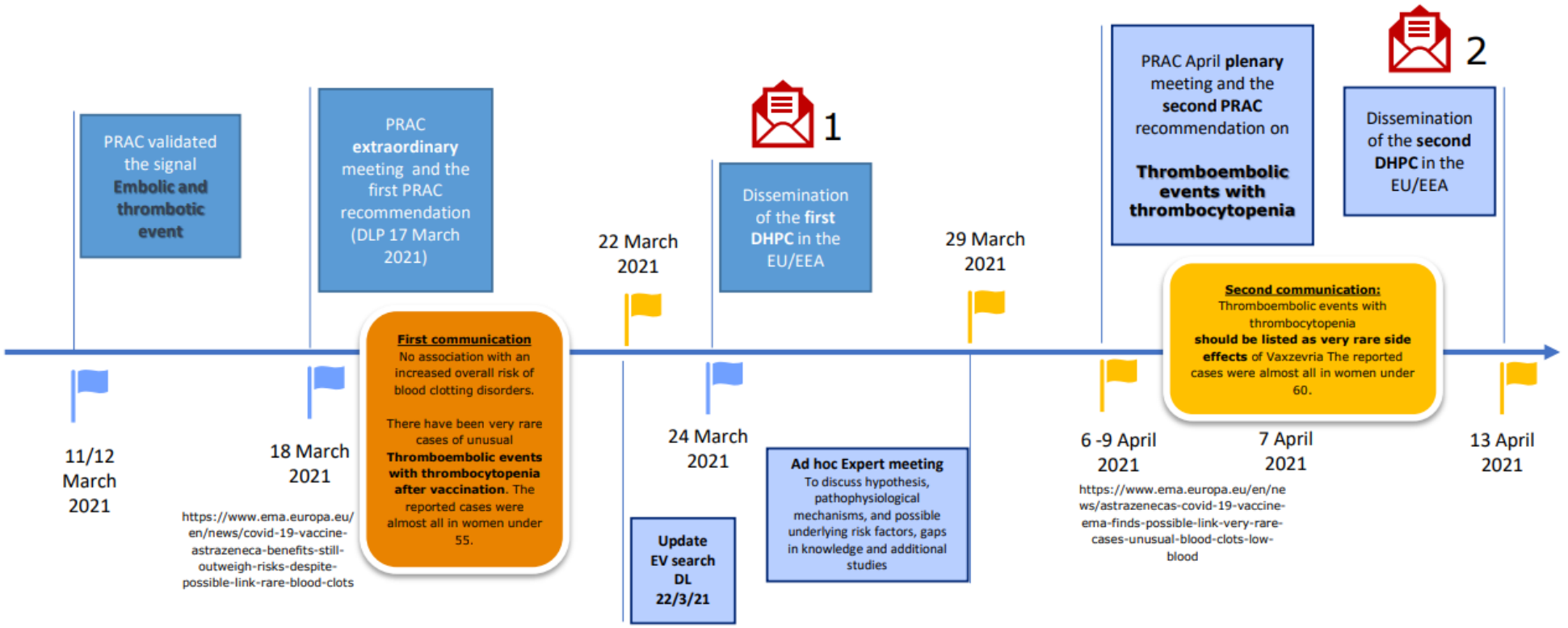
EMA - Signals

Example as PRAC rapporteur for Vaxzevria

EU regulatory network/PRAC: robust and agile system in place

EUROPEAN MEDICINES AGENCY

Exceptional EMA and Network Effort to rapidly detect, minimise, conclude and communicate on serious risks such as TTS



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EMA - Signals

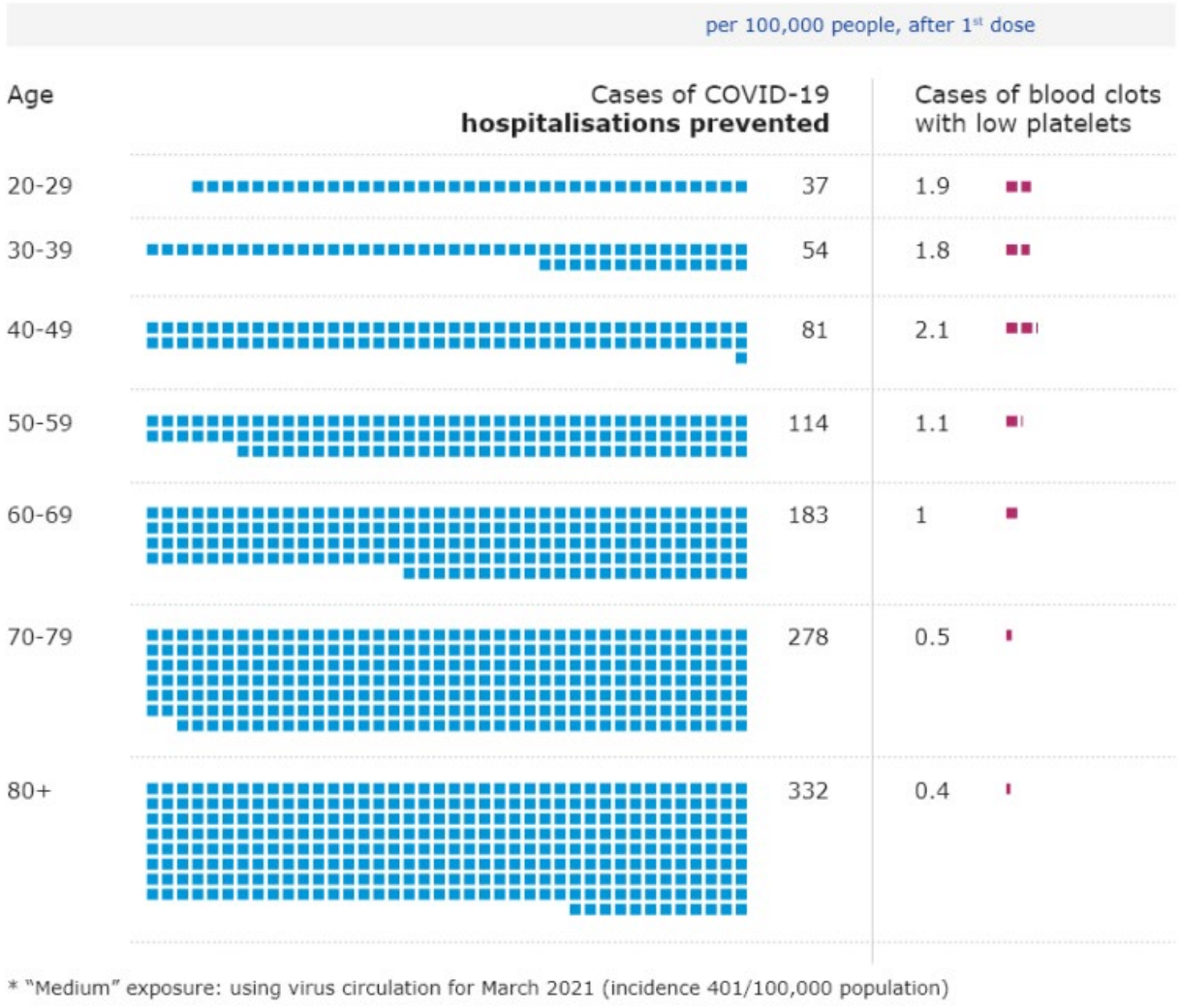
Example as PRAC rapporteur for Vaxzevria

EUROPEAN MEDICINES AGENCY

Benefits of having AZ vaccine versus potential risks associated with AZ vaccine by relevant risk factors: contextualisation exercise (EU/EEA)

EMA Communication - Visual benefit risk contextualisation

Medium infection rate*



- To support national decisions on vaccine rollout
- Analysis for different age groups, different levels of infection rate and outcomes (hospitalisations, ICU admissions, deaths due to COVID-19)
- Benefits of vaccination increase with increasing age and infection rate
- Member states can take different actions depending on pandemic situation, vaccine availability, etc.

Follow-up of vaccine safety

Belgium – Vaccinovigilance Plan (November 2020)

Activity	Objectives
Spontaneous reporting integrated in: - **VaccinNet+** - **eForms** - **Hospital**	• Facilitate an easy and fast access to the system of spontaneous reporting • Standardise spontaneous reports • Reduce workload • Improve the rate of spontaneous reporting
ACCESS project – active vigilance (EMA, NL coordination)	• Measure the frequency of solicited and unsolicited adverse events following vaccination in a cohort of vaccinated persons via a web application
ACCESS project – background incidence rates (EMA)	• Compare the number of reported cases of an AESI with the number of expected cases (observed vs. expected analysis)
Experts panel	• Rapidly investigate unusual medical cases identified in Belgium and assess their possible causal relationship with the vaccine • Participate in the evaluation of safety signals at EU level
Vaccine breakthrough cases (LinkVac - Sciensano)	• Investigate confirmed cases of COVID-19 infection with a history of vaccination

Belgium – Experts panel

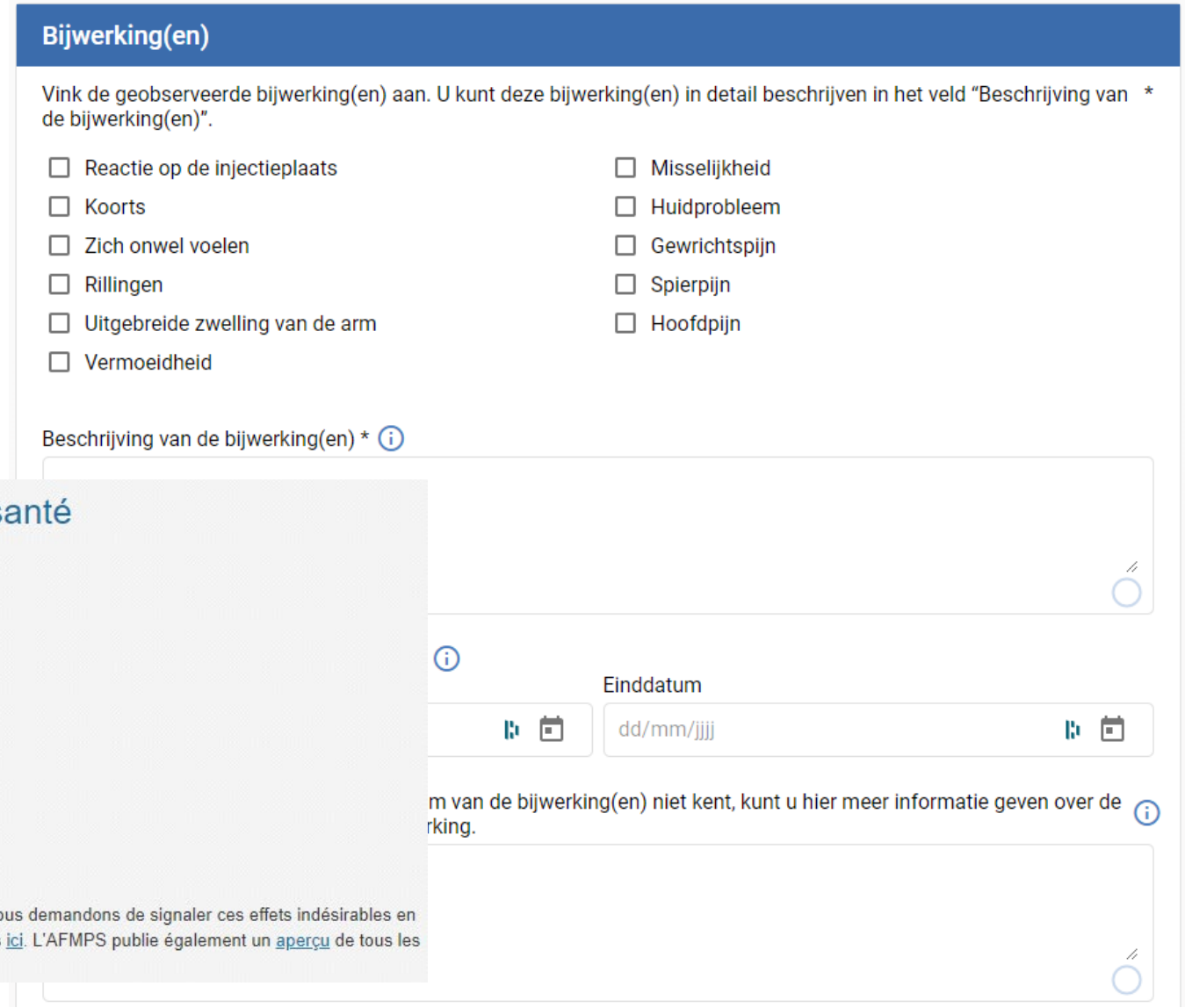
Proposed and consulted domains of expertise

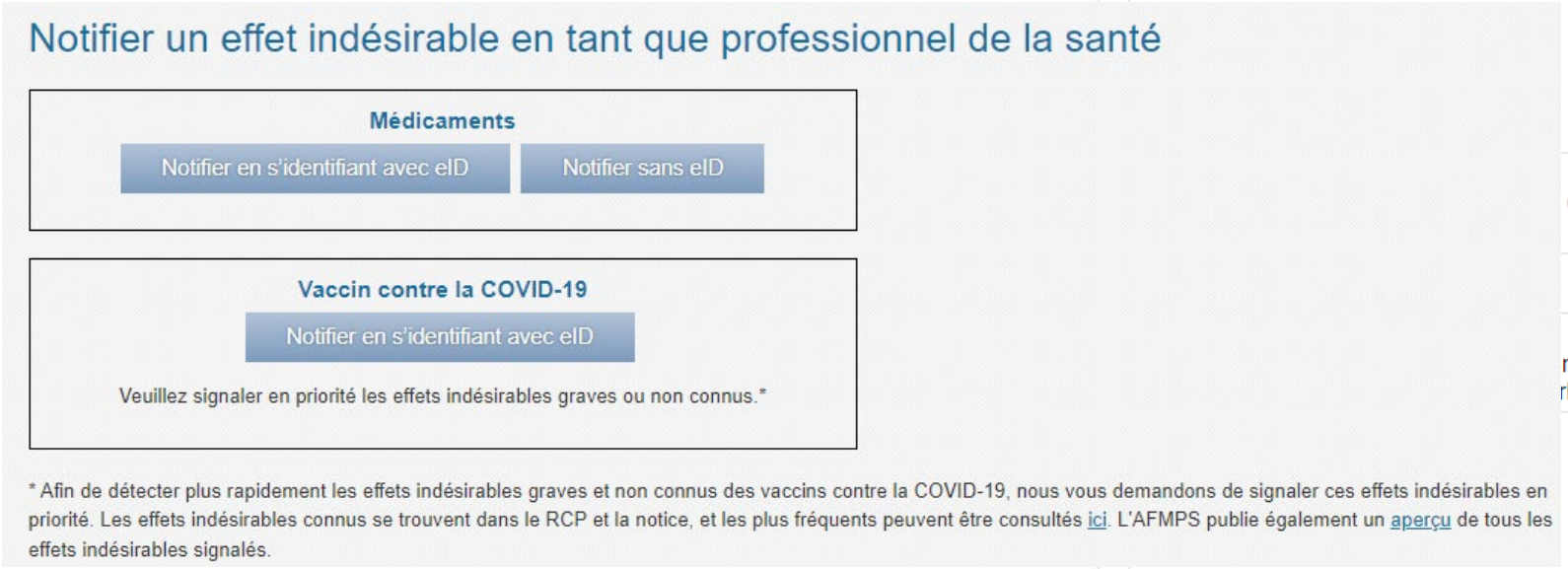
1. Neurology (adult)
2. Radiology / Neuroradiology
3. Pneumology
4. Haematology (coagulation disorders)
5. Infectious diseases
6. Immunology (AID)
7. Rheumatology
8. Cardiology
9. Gynaecology
10. Neonatology
11. Geriatrics
12. Endocrinology
13. Ophthalmology
14. Otorhinolaryngology
15. Dermatology
16. Intensive care specialist
17. Anatomopathologist
18. Hepatology
19. Nephrology
20. Psychiatry
21. Virology

Belgium – Spontaneous reporting for COVID-19 vaccines

www.notifieruneffetindesirable.be
www.eenbijwerkingmelden.be

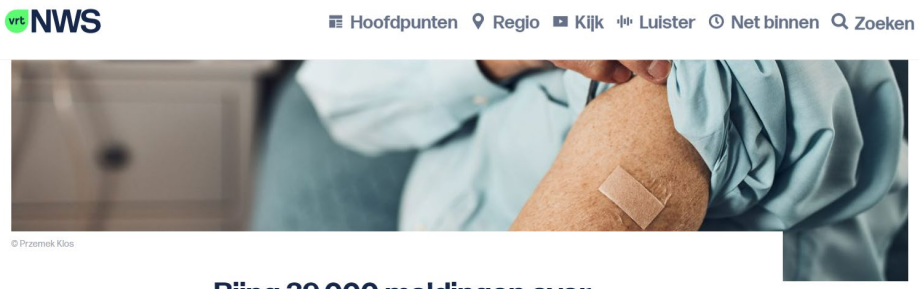
Accessible via the FAMHP website, VaccinNet+, hospital form (breakthrough cases)





Belgium – COVID-19 vaccines safety communication

- Questions and answers on COVID-19 vaccines (FAMHP website)
- Weekly communication of reported adverse effects (ADR), now monthly reporting
- Press/social media



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Effets secondaires: le covid a accentué la transparence de la pharmacovigilance

Après la mise sur le marché d'un médicament ou d'un vaccin, les effets indésirables sont enregistrés par les organismes nationaux et à l'échelon européen où ils sont scrutés à la loupe. Ce n'est pas nouveau. Mais la transparence totale l'est un peu plus.

Coronavirus : aperçu mensuel des effets indésirables des vaccins contre la COVID-19 du 28 avril 2022

Date: 28/04/2022

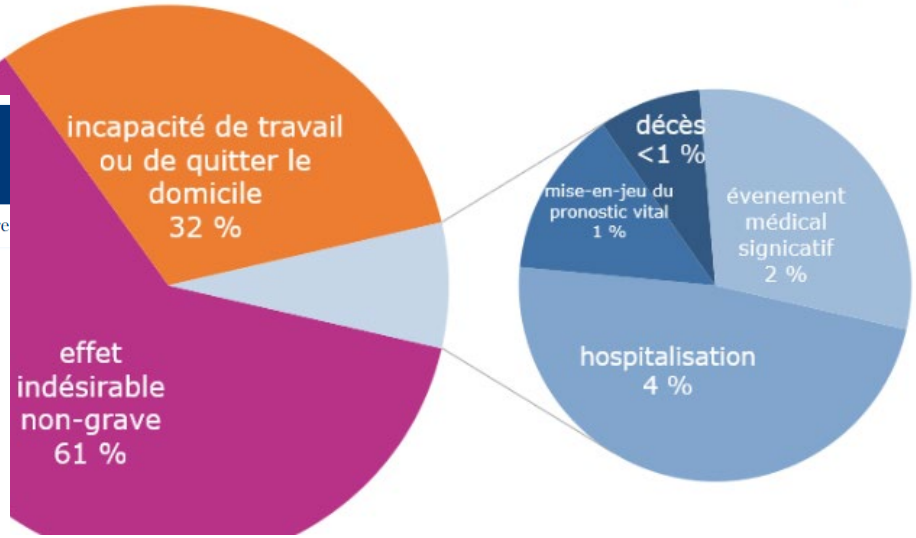
L'AFMPS publie un aperçu cumulatif des effets indésirables signalés suite à l'administration d'un vaccin contre la COVID-19 en Belgique. Les nouvelles informations proviennent de l'Agence européenne des médicaments (EMA) ou d'autres sources officielles. En étant totalement transparente, l'AFMPS vise à accroître la confiance dans les vaccins contre la COVID-19. Le prochain bulletin est prévu le 2 juin 2022.

Notifications en Belgique : chiffres-clés jusqu'au 25.04.2022 inclus

Il est important d'interpréter correctement les chiffres de cet aperçu.

- 9 227 907 personnes ont reçu au moins une dose d'un vaccin contre la COVID-19.
  Au total, 25 056 689 doses d'un vaccin contre la COVID-19 ont été administrées.
- 38 507 rapports d'effets indésirables ont été notifiés via le formulaire de notification en ligne.

Distribution des cas reçus via le formulaire de notification en ligne COVID-19 en fonction des critères de gravité.



Follow-up of vaccine safety

Challenges: EMA Workload indicator highlights

- **ADR reports from EEA** at an all-time high: 480K reports (quarterly average in 2021: 436 K) – 70 % for COVID-19 vaccines
- **ADR reports from non-EEA**: still high at 383K reports (quarterly average in 2021: 445K) – 20 % for COVID-19 vaccines
- **ADR reports recoded in EV by EMA** still high: almost 64K (12K reports quarterly before vaccines) – approximately 30 % for COVID-19 vaccines
- **Reporting from patients** increased by 151 % compared to Q1 2021
- **Continued high number of hits on adrreports.eu**: 6.1 million in Q1 (in the range of 2.5 million per year before the pandemic)

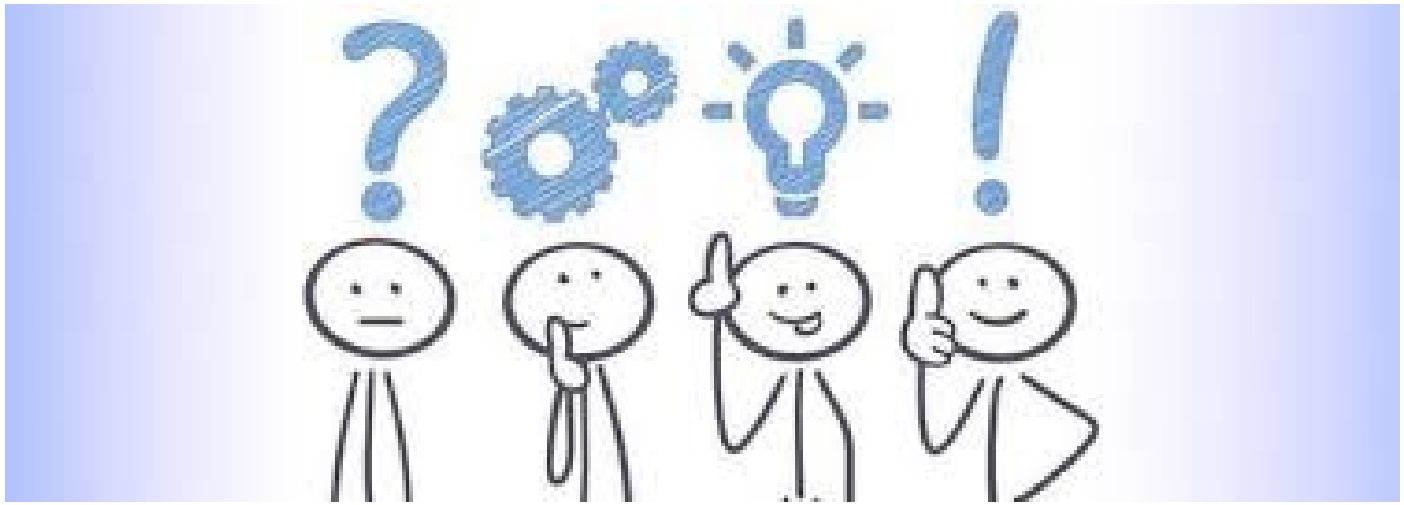
Challenges and lessons learned - Scientific level

- Rapidly growing number of cases –backlog processing ongoing (national level, MAHs)
- Information received through different channels (not reported to EudraVigilance)
- Often incomplete information from spontaneous case reports: importance of quality over quantity
- Incomplete information on exposure and disease burden - needed for O/E analysis and sub-analysis by age group and gender
- Importance of background incidence rates (but not possible for all topics)
- Future COVID-19 vaccines: different roll-out
- Safety of mixed use of different platforms
- New approaches for signal management needed (e.g. corneal graft rejection)
- Off-label use in different MS (second dose of booster, different age-groups, etc.)

Challenges and lessons learned - Regulatory and communication level

- National positions on vaccination policy before completion of scientific assessment
- External confusion about the role of regulators and other bodies
- Importance of traceability
- Early guidance (e.g. coreRMP)
- Measures to focus resources on COVID-19-related assessments
- Collaboration and exchanges at national/international level
- Communication: balance increased public interest and need to protect confidential information; avoid promotional activities

Any questions?



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