Vaccines safety in adults
Experience and lessons learned
COVID-19 Vaccines

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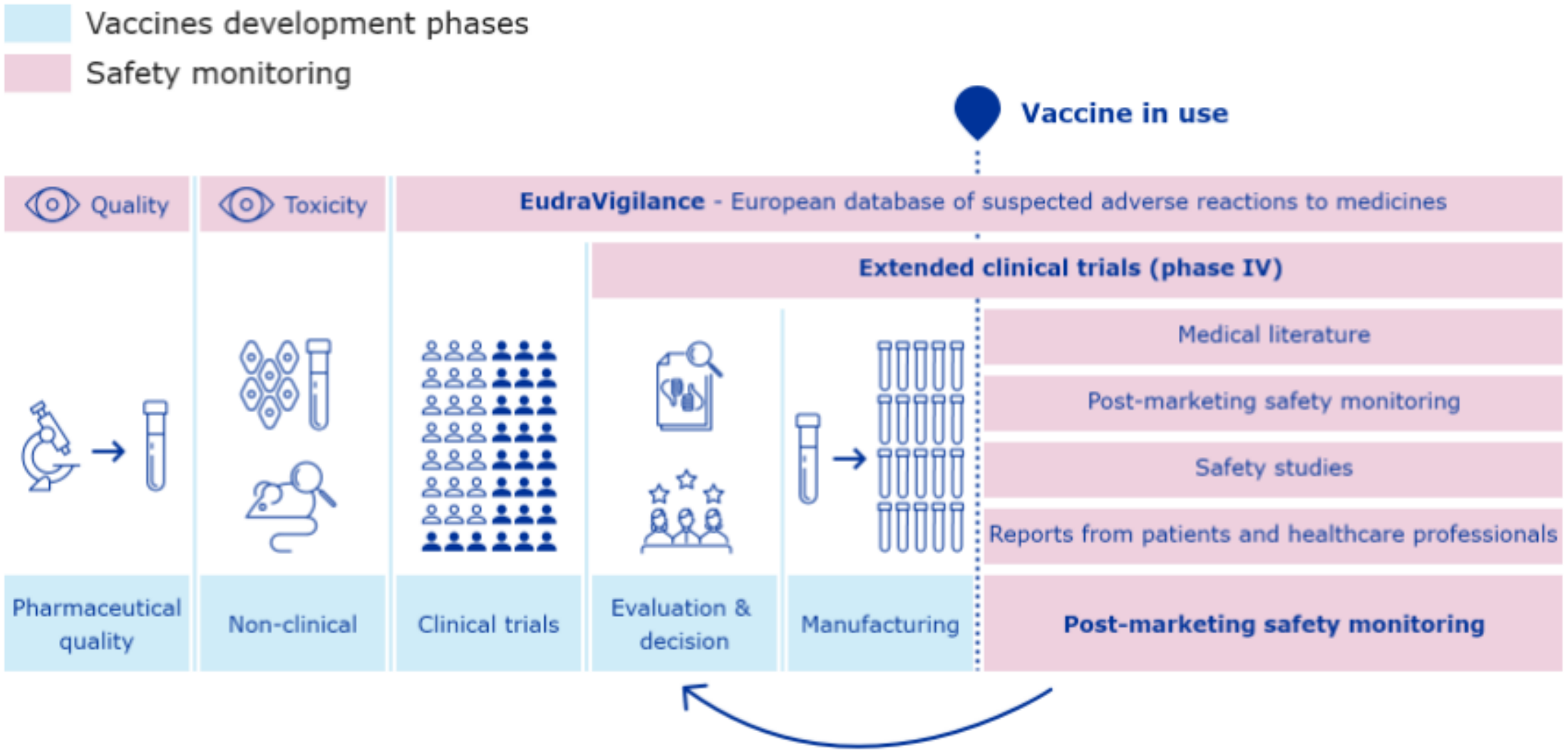
Questions?

- Who is responsible for the safety monitoring of vaccines for adults in the EU?
- How are suspected adverse events following immunization (AEFI) reported and assessed in the EU, and what actions are taken based on this reporting?
- How is safety information on vaccines communicated to health care professionals and the public in the EU, and what efforts are made to ensure transparency and public confidence?
- How can the methodologies developed for real-time safety monitoring of COVID-19 vaccines, including the integration of EudraVigilance data and real-world evidence, be applied, or adapted for the surveillance of other vaccines' safety in the European context?
- What can be done better in the future?
- And what lessons can we learn from specific examples?

EMA –How vaccine safety is studied



Types of vaccines	DNA and RNA	Live attenuated	Inactivated	Subunit	Viral vector
					
How it works	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Advantages	Easy and quick to design.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Disadvantages	Never been done before. There are no licensed DNA or RNA vaccines currently in use.	May not be safe for those with compromised immune systems.	Not as effective as a live virus. Some previous inactivated vaccines have made the disease worse; safety for the novel coronavirus needs to be shown in clinical trials.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.
Existing examples	• None	• Measles, Mumps and Rubella • Chickenpox	• Polio	• Pertussis • Hepatitis C • Human Human papillomavirus (HPV)	• Ebola • Veterinary medicine
Group testing this approach for COVID-19	• Moderna (RNA) • Inovio (DNA)	• Codagenix • Indian Immunologicals Ltd.	• Sinovac • Sinopharm	• Novavax • AdaptVac	• University of Oxford & AstraZeneca • CanSino Biologics • Johnson & Johnson

Sources: CDC; NIAID; FDA

MICHELLE GUERRERO and JONATHAN WOSEN U-T

Overview of authorised COVID-19 vaccines

Vaccine	Platform*	Strain	Population ≥6 months	Population ≥5 years	Population ≥12 years	Population ≥18 years
Comirnaty (BioNTech)	mRNA	Original strain	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)***			✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Omicron XBB.1.5 variant (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
Spikevax (Moderna)	mRNA	Original strain	✓ 6 months to 5 years	✓ 6-11 years	✓	✓
		Original strain + Omicron BA.1 variant (adapted**)***		✓ 6-11 years	✓	✓
		Original strain + Omicron BA.4-5 variants (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
		Omicron XBB.1.5 variant (adapted**)	✓ 6 months to 4 years	✓ 5-11 years	✓	✓
Vaxzevria (AstraZeneca)	Adenoviral vector	Original strain				✓
Jcovden (Janssen)	Adenoviral vector	Original strain				✓
Nuvaxovid (Novavax)	Protein	Original strain			✓	✓
		Omicron XBB.1.5 variant (adapted**)			✓	✓
Bimervax (HIPRA Human Health S.L.U.)	Protein	Alpha + Beta variants***			✓ 16-18 years	✓

* Available platforms: See Figure 1 below

** Milestones for adapted vaccines: See Figure 2 below

*** Only used as boosters

EMA – Preparedness COVID-19 vaccines safety

- **COVID-19 vaccines to play a major role in the control of the pandemic**
- **limited number of selected participants included in the CTs (followed for a short duration and under controlled conditions)**
- **Rare and very rare side effects only emerge during real life use**
- **High volume of AE reports and other safety data expected**

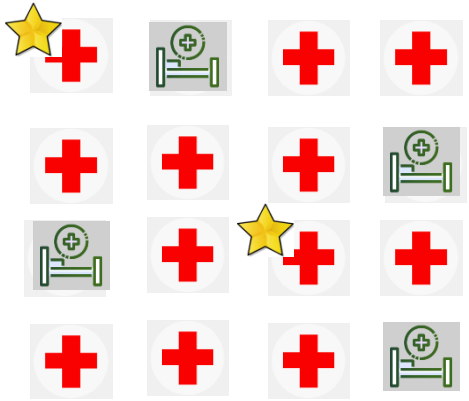
- **Prompt detection, evaluation, communication and high level of transparency will be key to protect public health and ensure public's trust**

The challenge of mass vaccination

Starting from high risk groups

~1 million vaccinations/day
=> 10 millions/day…

1 / 10.000
Rare events



100 events a day before we can react

How to be prepared?

Preparedness

EUROPEAN MEDICINES AGENCY

Lessons Learned H1N1

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

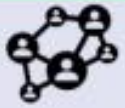
Signal Detection Methods

- Rapid **detection**, **exchange**, **prioritisation** and **assessment** of safety **signals**

Testing of additional **methodologies** specific for COVID-19

PhV Plan of the EU Regulatory Network for COVID-19 Vaccines *(November 2020)*

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



Active surveillance

ACCESS, **ICMRA**, **pregnancy studies**, **int. cohorts**

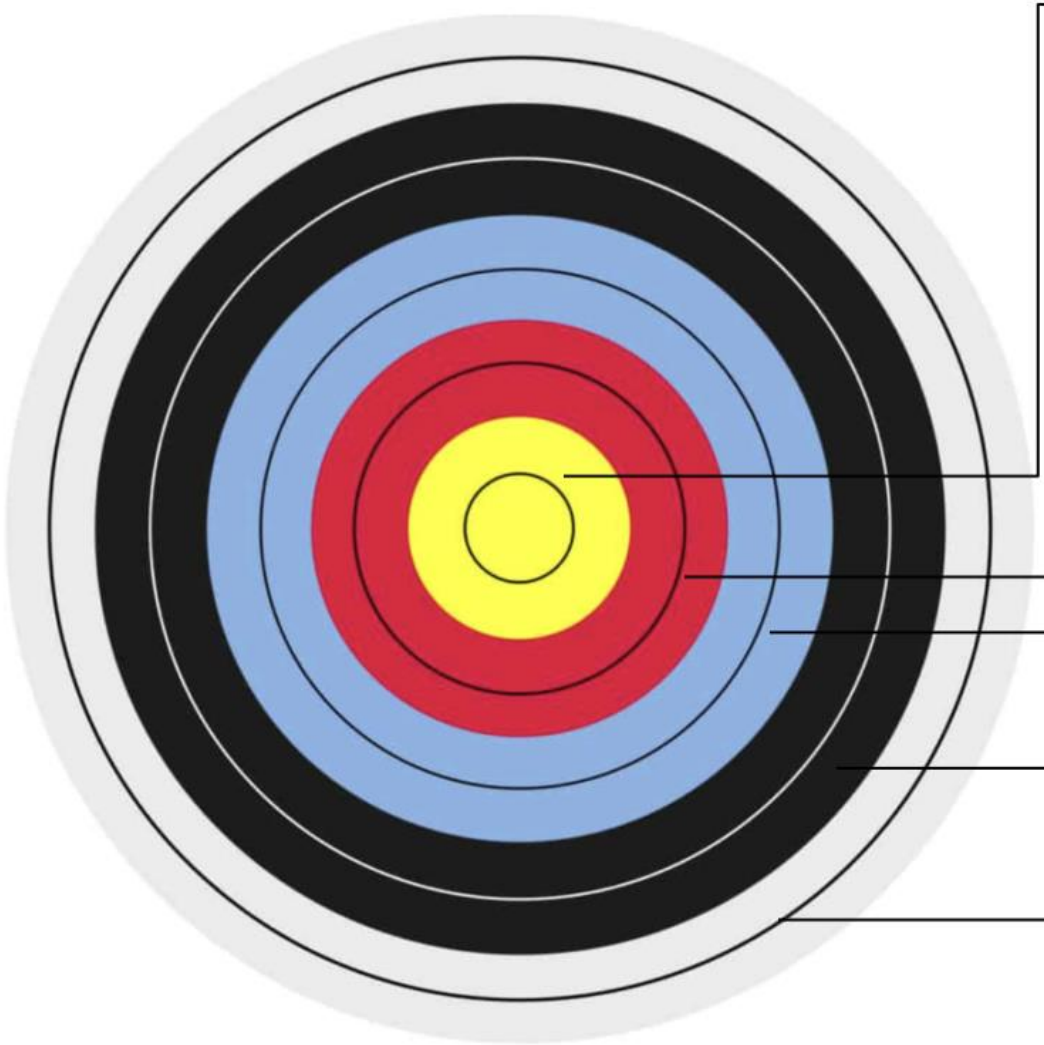
International And Research Centres Collaboration

Engage and **communicate** with public, patients and HCP.

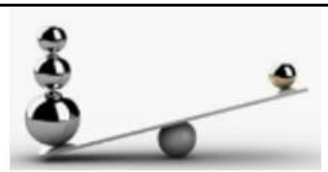
Enhanced communication and **transparency** measures

Transparency & Communication

EMA – Preparedness COVID-19 vaccines safety

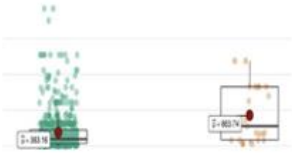


AdverseEventSpeciaInterest (AESI): high priority based on experience with similar vaccines in terms of manufacturing process, composition (e.g. adjuvants), immunogenicity and novelty. Potential risks that would need immediate investigation or regulatory action and could lead to a change in the benefit-risk balance or require prompt communication to the public



Observed vs Expected (OE) analysis based on background incidence rates

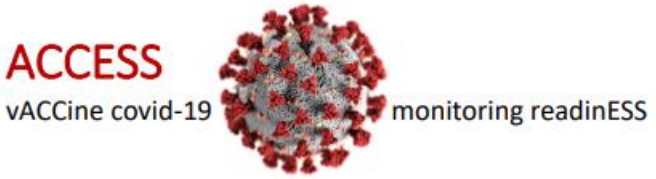
Imbalance Analysis: Adjusted Stastical Methods to compare competing vaccines



TimetoOnset: qualitative analysis based on the assumption that reporting trends may differ during vaccination

Combine all methods using specific features normally not available for routine PhV to optimise signal detection methods for a vaccination campaign against an epidemic

ACCESS program
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 the 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

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 & adults)
Acute cardiovascular injury(includes: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)
Myocarditis/pericarditis
Coagulation disorder (includes: thrombotic disorders, bleeding disorders)
Bleeding disorder
Anosmia, ageusia
Chilblain – like 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 immunization 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 immunization encompassing several different vaccines

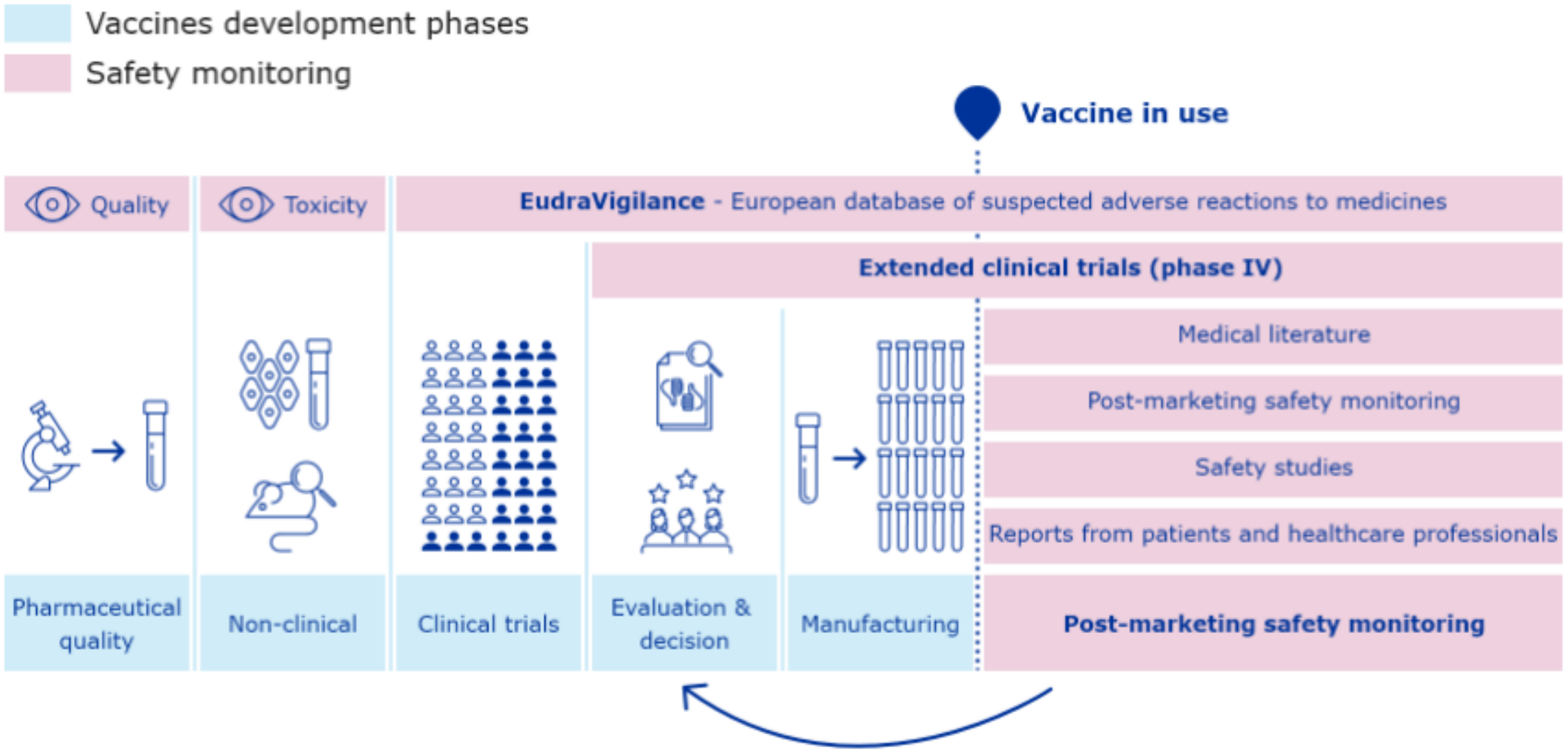
2 Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines

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 –How vaccine safety is studied



EMA – Preparedness

Routine	Additional (Reduce time-frame + 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
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Communication	• Exceptional transparency measures: EMA Press Conference, COVID-19 safety updates, Full RMP published, etc.

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 trough statistical reports – in 2021:

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

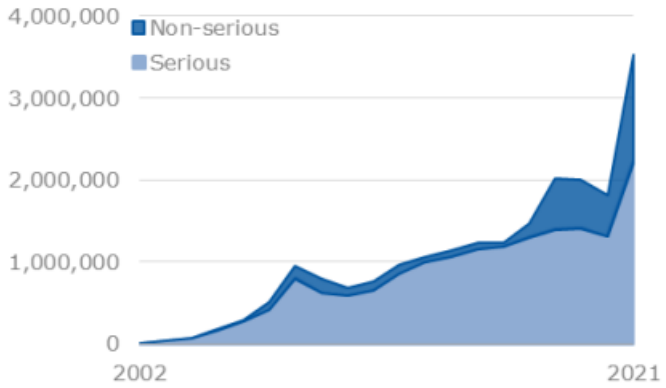


Figure 6. Number of ADR reports processed per year in EVPM.

EMA – Outcome 2021

Outcome of MSSR/Signals/PSURs: Updates of PI/SmPC, DHPC, RMP, Safety Updates, PRAC highlights, press communications etc.

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

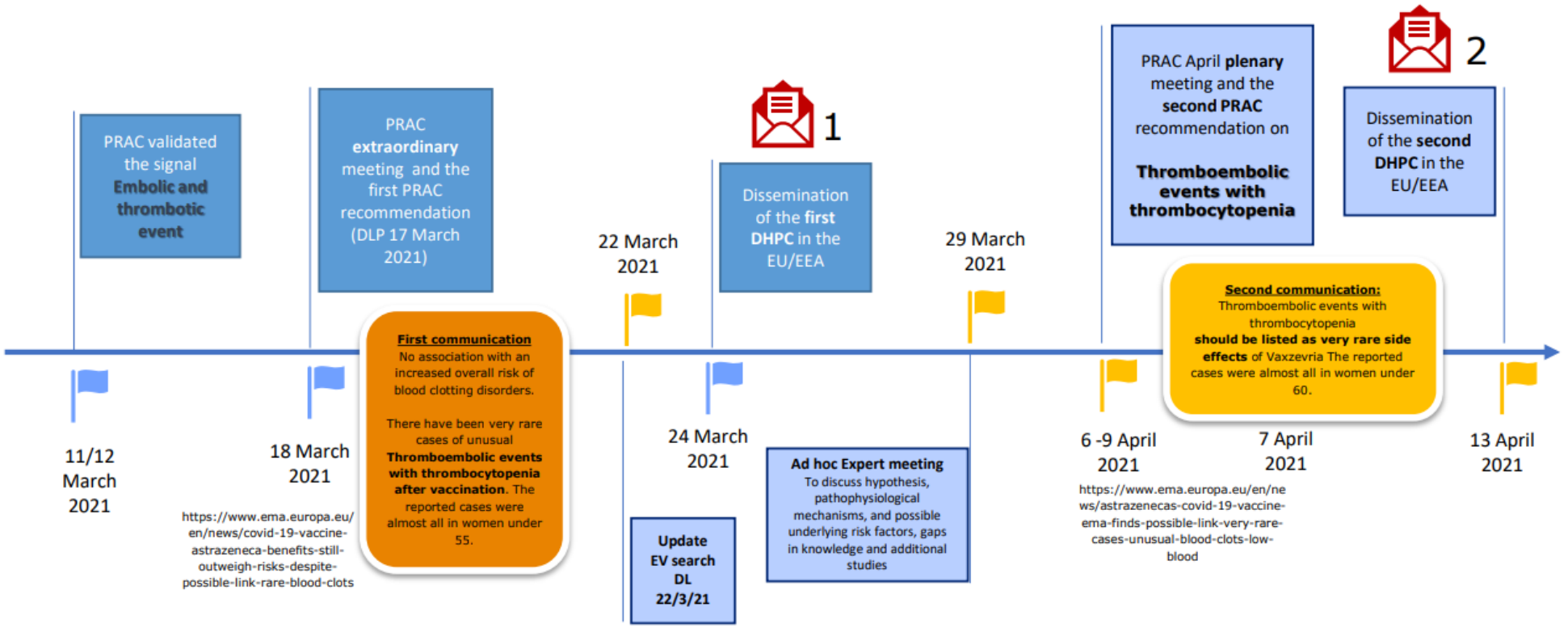
EMA - Signals

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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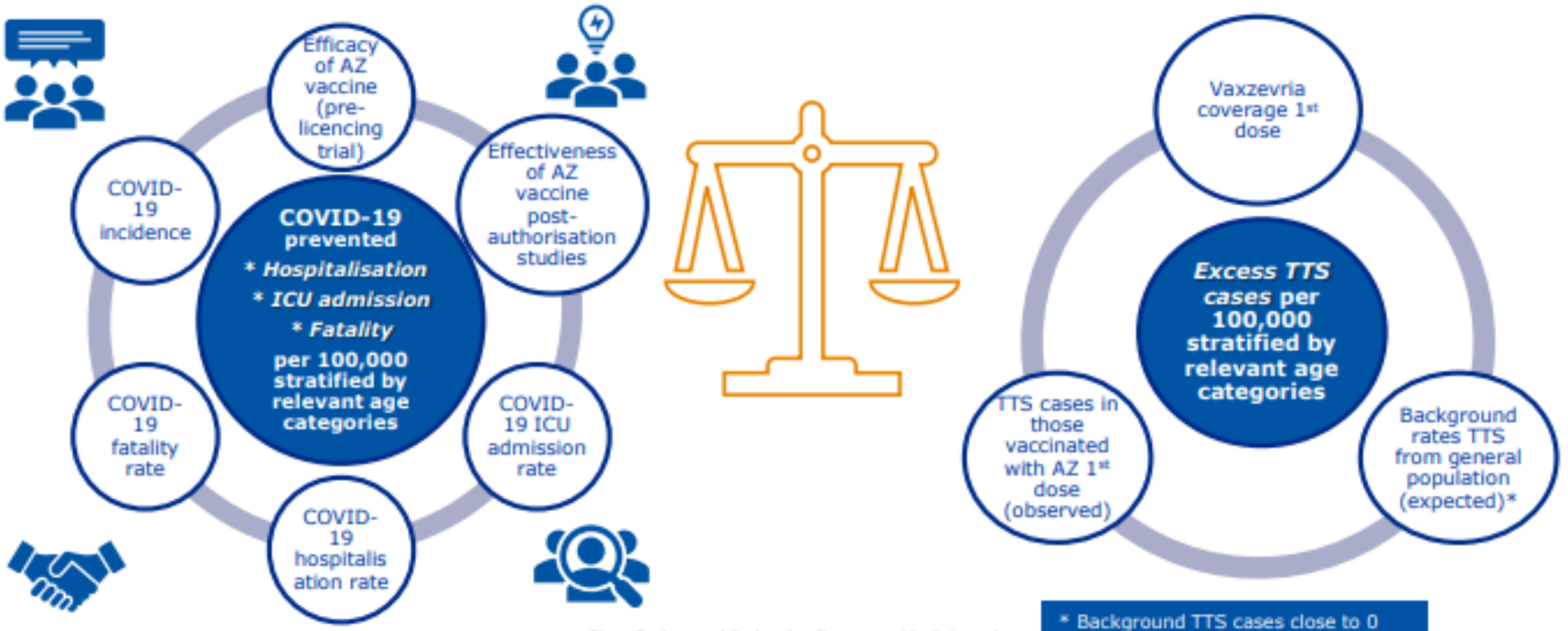
EMA - Signals

Example as PRAC Rapporteur for Vaxzevria

EUROPEAN MEDICINES AGENCY

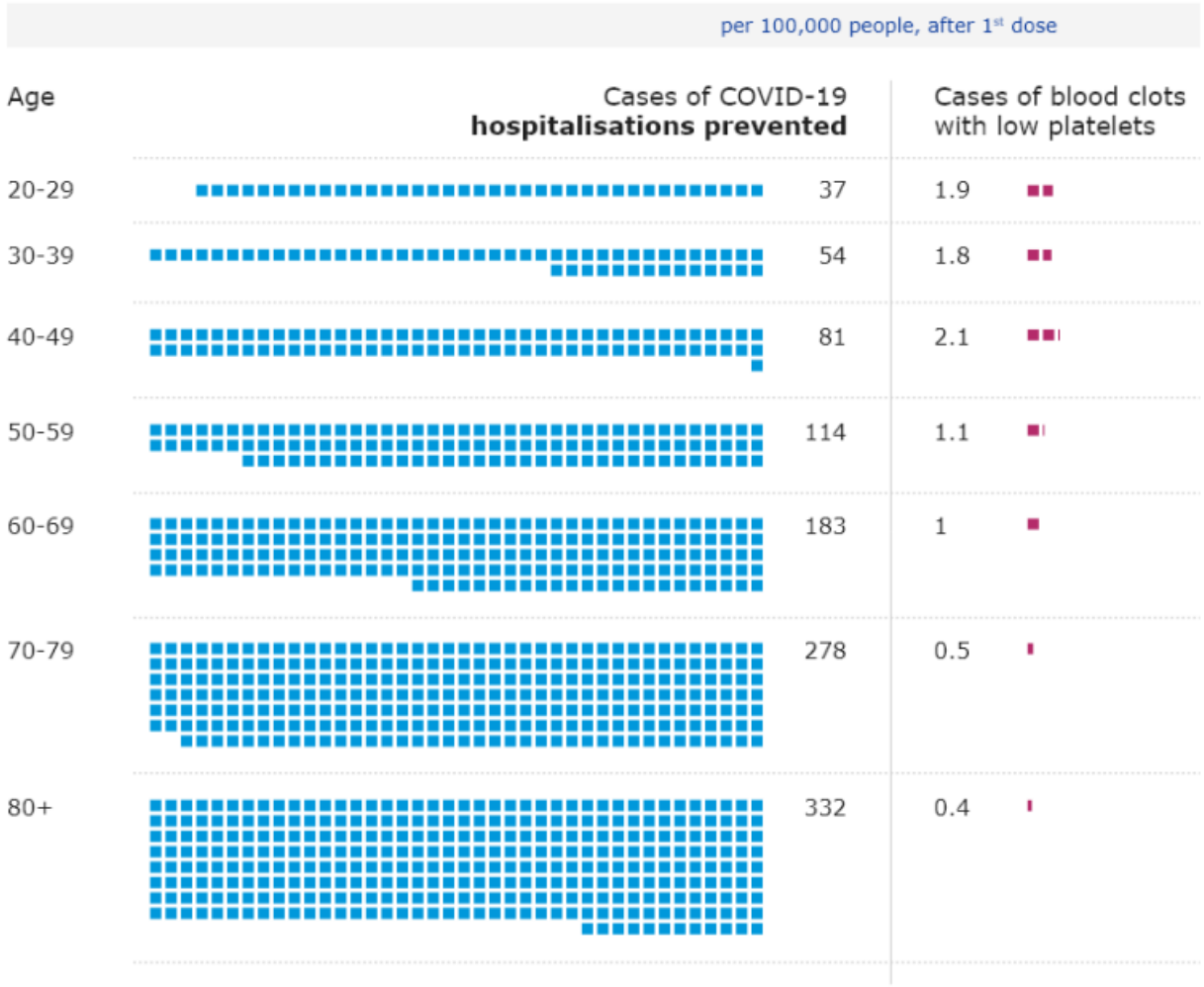
Benefits of having AZ vaccine versus potential risks associated with AZ vaccine by relevant risk factors: contextualisation exercise (EU/EEA)



* Background TTS cases close to 0

EMA Communication - Visual benefit risk contextualisation

Medium infection rate*



* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

- To support national decisions on roll out of vaccine
- 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 rates
- Member States can take different actions depending on pandemic situation, vaccine availability etc.

Challenges & lessons learned Scientific level

- 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)
- New approaches for **signal detection/management** needed

Drug Safety
https://doi.org/10.1007/s40264-024-01422-8

CURRENT OPINION

Lessons Learned on Observed-to-Expected Analysis Using Spontaneous Reports During Mass Vaccination

María Gordillo-Marañón[1,2] · Gianmario Candore[3] · Karin Hedenmalm[1] · Kate Browne[4] · Robert Flynn[1,5] · Loris Piccolo[1] · Aniello Santoro[6] · Cosimo Zaccaria[6] · Xavier Kurz[1]

Accepted: 7 March 2024

Belgium – Vaccinovigilance Plan (November 2020)

Activity	Objectives
Spontaneous reporting integrated in : - VaccinNet+ - eForms - Hospital	• To facilitate an easy and quick access to the spontaneous reporting system • To standardise spontaneous reports • To reduce workload • To improve the rate of spontaneous reporting
ACCESS project – active vigilance (EMA, NL coordination)	• To measure the frequency of solicited and unsolicited adverse events following vaccination in a cohort of **vaccinated subjects** via a web application
ACCESS project – background incidence rates (EMA)	• To compare the number of reported cases of an AESI with the number of expected cases (Observed vs Expected analysis)
Experts panel	• To rapidly investigate unusual medical cases identified in Belgium and assess their possible causal relationship with the vaccine • To participate in the evaluation of safety signals at the EU level
Vaccine breakthrough cases (LinkVac - Sciensano)	• To investigate confirmed cases of COVID-19 infection with a history of vaccination

EMA – Game changer: BIG DATA

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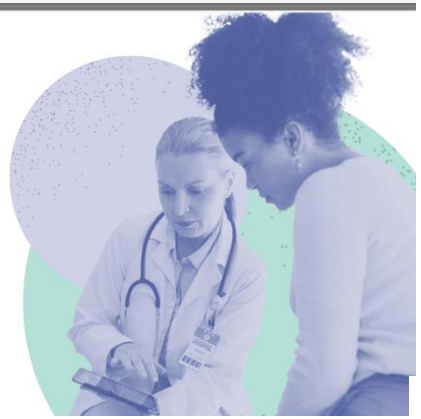
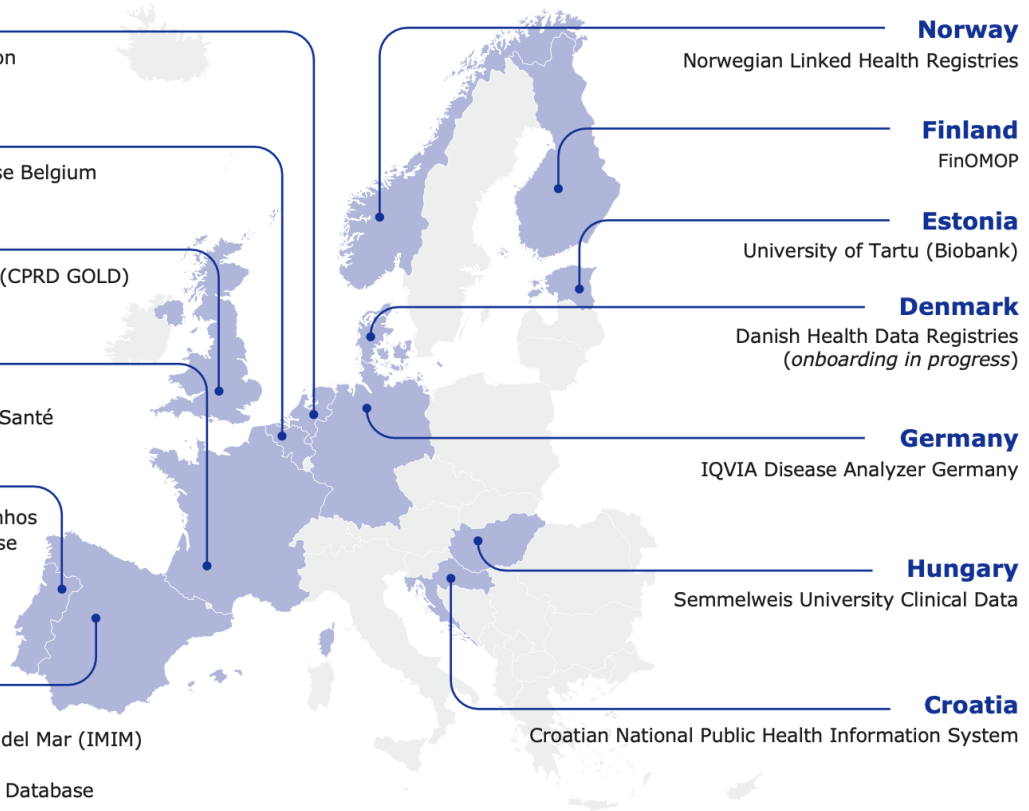
EMA – Game changer: BIG DATA: DARWIN EU®

2 YEARS OF EXPERIENCE

DARWIN EU®: Making health data count

DARWIN EU® (Data Analysis and Real-World Interrogation Network) generates real-world evidence (RWE) to support EMA committees and national regulators in the EU in making more data-driven decisions on medicines. RWE comes from the analysis of real-world data, health data collected in routine care settings. It complements data from clinical trials.





The Netherlands
Integrated Primary Care Information
Netherlands Cancer Registry

Belgium
IQVIA Longitudinal Patient Database Belgium

United Kingdom
Clinical Practice Research Datalink (CPRD GOLD)
UK BioBank

France
Bordeaux University Hospital
Système National des Données de Santé

Portugal
Unidade Local de Saúde de Matosinhos
Egas Moniz Health Alliance DataBase

Spain
SIDIAP
Parc Salut Mar Barcelona, Hospital del Mar (IMIM)
BIFAP
Valencia Health System Integrated Database

Norway
Norwegian Linked Health Registries

Finland
FinOMOP

Estonia
University of Tartu (Biobank)

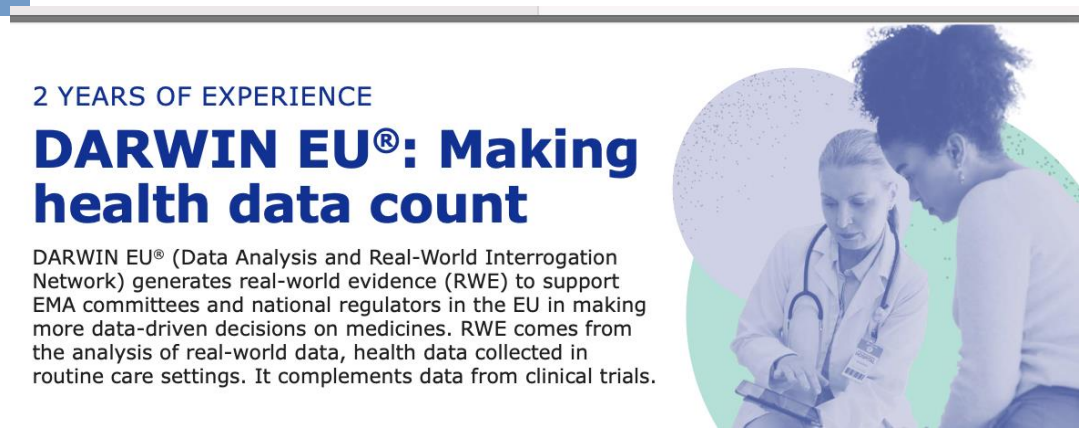
Denmark
Danish Health Data Registries
(*onboarding in progress*)

Germany
IQVIA Disease Analyzer Germany

Hungary
Semmelweis University Clinical Data

Croatia
Croatian National Public Health Information System

EMA – Game changer: BIG DATA: DARWIN EU®



Effectiveness of COVID-19 vaccines against severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection?

Background incidence rates of selected vaccine adverse events of special interest (**AESIs**) in Europe?

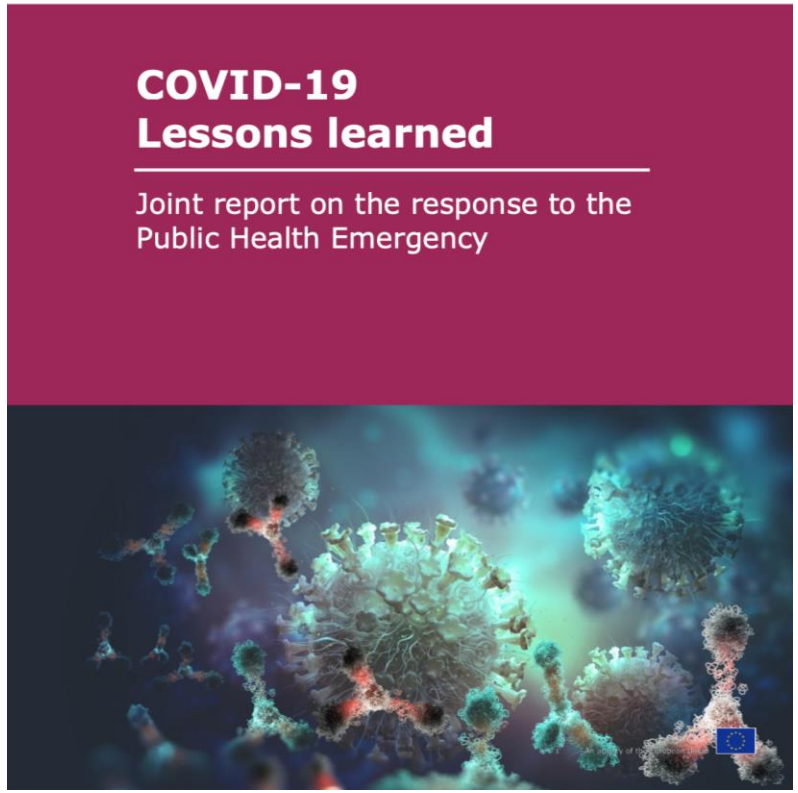
Effectiveness of Human Papillomavirus Vaccines (**HPV**) to prevent cervical cancer in women?

Age-specific incidence rates of **RSV**-related disease in Europe?

Challenges & lessons learned

HMA Heads of Medicines Agencies

EMA EUROPEAN MEDICINES AGENCY



Summary of areas for improvement

- Enable large clinical studies that can provide timely and meaningful results.
- Extend development and access of real-world data sources with relevant and granular information, improve IT systems for processing these data, and strengthen network of expertise.
- Reserve resource-intensive additional measures to the most promising medicines.
- Continue to invest in improving resourcing within the EMRN and developing more streamlined processes to deal with the increased workload.
- Earlier medicines availability might be supported by the introduction of an EU level mechanism such as the proposed TEMA.
- Build on communication and engagement approaches developed during COVID-19, work further on establishing collaborations on infodemic management and prepare a strategy to address mis- and disinformation.
- Reinforce cooperation with other partners, e.g., NITAGs.

Any question?