Safety of vaccines: Lessons learned

WHO, R&D Blueprint, 25 October, 2021

Marco Cavaleri, Head of Biological Health Threats and Vaccine Strategy, European Medicines Agency
COVID-19 vaccines approved in the EU

4 vaccines **authorised in the EU**

- Approval via Conditional Marketing Authorisation based on RCTs recruiting several thousands subjects

- Rare adverse reactions with frequency lower than 1 in 10,000 could not be determined pre-approval and required post-authorisation monitoring via active and passive surveillance

- **No significant safety concerns were emerging at time of approval**

  - **Comirnaty (BioNTech/Pfizer)**: 21 Dec
  - **COVID-19 Vaccine Moderna**: 6 Jan
  - **COVID-19 Vaccine AstraZeneca**: 29 Jan
  - **COVID-19 Vaccine Janssen**: 11 Mar
More reports received with 4 vaccines than all other Centrally authorised products in 1 year

Represented data received in EudraVigilance (EVDAS) as of 6th Oct 2021
- Cases picked up initially in unusual location (e.g. CVST, Splanchnic Thrombosis, DIC)
- Cases in EV appear similar to HIT-like syndrome
- New clinical entity was identified Thrombosis Thrombocytopenia Syndrome (TTS) = platelets count decreased + thromboembolism
- Frequency: about 1/100,000 vaccinees
- Same risk was confirmed also for Janssen
- Second doses did not show same size of the risk
- Continuous monitoring of the new cases + frequency
- Further research to characterise TTS and pathophysiology
Temporary pause of vaccination programme

Requirement for “real time” data concerning safety monitoring to ensure appropriate decision making → inform policy makers/public health agencies.

• Temporary pause in vaccination programme in several EEA countries (e.g. NL, IE, DK etc.) → pending outcome of extraordinary PRAC on 18\textsuperscript{th} March.

• Resumed use of Vaxzevria\textregistered within the vaccination programme on the 18\textsuperscript{th} March but subsequently imposed restrictions concerning use of COVID-19 non-replicant adenovirus vector-based vaccines:
  • Twelve EU/EEA countries based their recommendation on information concerning benefit risk contextualization provided by EMA within the context of Article 5(3) procedure (as reported to ECDC (12 May 2021))
**Risk contextualisation of vaccination with Vaxzevria**

### Medium infection rate*

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases of COVID-19 ICU admissions prevented</th>
<th>Cases of blood clots with low platelets</th>
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<tbody>
<tr>
<td>20-29</td>
<td>3</td>
<td>1.9</td>
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<tr>
<td>30-39</td>
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<td>1.8</td>
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<td>10</td>
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<td>50-59</td>
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<td>1.1</td>
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<tr>
<td>60-69</td>
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<td>39</td>
<td>0.5</td>
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<tr>
<td>80+</td>
<td>29</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)
# Risk contextualisation of vaccination with Vaxzevria

## Medium infection rate

<table>
<thead>
<tr>
<th>Age</th>
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<th>Cases of blood clots with low platelets</th>
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<tbody>
<tr>
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</tbody>
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Challenges

- Background rates ≠ predefined AESI → need for rapid generation for new signals.
- Readiness/limitations of EHRs (impact of lagtime on data availability, outcome ascertainment, linkage to hospital data).
- Case definitions, phenotypes for case finding.
- Pharmacogenomic & lab data → availability & validity.
- Quantifying associations: appropriate adjustments (risk factor data), design to allow measure of AR.
- Risk periods (TTO from spontaneous reports, biological plausibility).
- Impact of pandemic on healthcare systems.

Learnings

- Primary data collection using modern tools for prospective monitoring (apps) allowing near-real time surveillance.
- Value of large healthcare databases (sample size, hospital data, federated networks, common data models, rapid analyses possible).
- Value of EMA framework contracts.
- Consortia with demonstrated capacity/expertise.
- International collaborations with other regulators.
- Mechanistic studies to elucidate pathophysiology.
Research questions mirror the deployment of the vaccination campaigns and the accumulating post-authorisation experience.

- **Effectiveness, duration of protection/waning immunity**
- **Variants of concern**
- **Transmission**
  - Special populations
  - Co-administration
  - Boosters
- **Heterologous vaccination**
- **Anaphylaxis**
- **Capillary leak**
- **Myocarditis pericarditis**
- **GBS**
- **TE events/TTS**

**Dec. 2020**
- Pfizer
- Moderna
- AZ
- J&J

**Sept. 2021**
- More (“traditional”) vaccines to become authorised

**More signals**
- Continuous surveillance

- **Variants of concern**
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Further information
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