Monitoring of COVID-19 products: toolkit

PhV platform meeting 17/11/2021
Agnieszka Szmigiel, Emil Cochino
European Medicines Agency
11/03/2020 COVID-19 declared a pandemic

03/07/2020 MA 1st antiviral

21/12/2020 MA 1st COVID-19 vaccine
• EudraVigilance and signal management information day (24/11/2021)

• The impact of COVID-19 pandemic and the authorisation of COVID-19 vaccines on EudraVigilance in the context of signal detection and management

Monitoring, frequency, exchange of information

- **EU network**
  - PRAC:
    - monthly plenaries
    - additional TCs usually for organisational matters also used for product topics
    - *ad hoc* meetings
    - Signals validated by EU NCAs and EMA
  - **Regulatory submissions by the MAHs**
  - RWE studies in individual MSs or consortia (e.g. Nordic registries)

- **EV outputs**
  - Weekly reaction monitoring reports
  - Twice-weekly update for AESI
  - Observed to expected analysis using ACCESS generated background rates
  - **Literature**
    - Daily alerts
  - **International, e.g.**
    - WHO safety bulletins
Prioritisation of events for intensive monitoring

vTMEs: ascertainment of serious events that can be characterised via ICSRs

vaccine Targeted Medical Events (vTMEs): Dedicated list of MedDRA PTs mapped from list of adverse events of special interest (AESIs) for Covid-19 vaccines.

Objective: Facilitate assessment of events that warrant analysis irrespective of statistical criteria routinely used to prioritise signal review. Events subject to intensive monitoring.

Internal tool → subject to continuous review.
COVID-19 response: from early times to expanding vaccine safety surveillance

2020 ACCESS project

- Preparedness
  - Data sources
  - AESI background rates
  - Templates, feasibility

2021 'Early' safety study

- AESI incidence rates (primary data collection)
- Monitoring in EU healthcare databases
- Feb-Nov 2021

Ongoing + future studies

- Extended active surveillance and signal strengthening
- Framework for signal evaluation

Ongoing

- Large EU consortia with access to networks of data sources mapped to CDMs
- 5 to 10 EU databases in each study

Background incidence rates
- Signal evaluation
International collaborations for COVID-19 observational – selected studies

• European COVID-19 Observational Research Exchange (E-CORE)
  - Multinational collaboration for observational studies of COVID-19 medicines (drug use, safety, effectiveness): set of cohorts, common protocol and/or established CDM
  - Feasibility: pilot study of systemic glucocorticoids in hospital/ambulatory care using the OMOP CDM → identified challenges (sample size for rare outcomes, heterogeneity) and opportunities (network can be used for studying COVID-19 therapies in international setting)

• COVID-19 infectiOn aNd medicineS In pregnancy (CONSIGN)
  - Impact of COVID-19 treatments in pregnancy (ConcePTION, COVI-PREG, INOSS)
  - Meta-analysis: FDA adaptation of WP1 protocol (EHR/ConcePTION) within Sentinel, + non-EU regulators

• Natural history of coagulopathy and use of anti-thrombotic agents (COVID-19 patient cohort + vaccinated cohort)
  - Initiated by FDA as part of ICMRA WG on RWE: feasibility of joint protocol
  - EU study procured through EMA frameworks contracts with protocol adapted to OHDSI and EHDEN environments using the OMOP CDM
Observational COVID-19 research: EMA web-site

Monitoring of COVID-19 medicines

- Safety monitoring of COVID-19 vaccines in the EU (new)
- Natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients and COVID-19 vaccine recipients
- Early safety monitoring of COVID-19 vaccines
- Impact of COVID-19 infection and medicines in pregnancy
- Building a framework for the conduct of multicentre cohort studies on the use of medicines in COVID-19 patients
- Preparing an infrastructure for the monitoring of the coverage, safety and effectiveness of COVID-19 vaccines
Vaxzevria - Signal of Thrombosis with thrombocytopenia (TTS) - 1

Signal procedure → accelerated assessment, inclusion of an Ad Hoc Expert meeting, rapid implementation of Product information updates & dissemination of DHPCs

PRAC extraordnary meeting and the first PRAC recommendation (DLP 17 March 2021)

Dissemination of the first DHPC in the EU/EEA

22 March 2021

29 March 2021

Dissemination of the second DHPC in the EU/EEA

PRAC April plenary meeting and the second PRAC recommendation on Thromboembolic events with thrombocytopenia

Second communication:
Thromboembolic events with thrombocytopenia should be listed as very rare side effects of Vaxzevria. The reported cases were almost all in women under 60.

6 - 9 April 2021

7 April 2021

13 April 2021

First communication
No association with an increased overall risk of blood clotting disorders. There have been very rare cases of unusual Thromboembolic events with thrombocytopenia after vaccination. The reported cases were almost all in women under 55.


Ad hoc Expert meeting
To discuss hypothesis, pathophysiological mechanisms, and possible underlying risk factors, gaps in knowledge and additional studies

Update EV search DL 22/3/21

24 March 2021

11/12 March 2021

18 March 2021

22 March 2021

29 March 2021

Thrombotic Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sarvoll, M.D., Annika E. Michelisen, Ph.D., Ludwig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skatte, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Tom Solomon, M.D., Marcel Levi, M.D., David Goldblatt, M.D., Ph.D., Pavel Kotoucek, M.D., William Thomas, M.D., and William Lester, M.D.
COVID-19 vaccines, remdesivir – signal outcomes

Signal outcomes for Covid-19 vaccines and remdesivir

Based on 21 signal procedures
Submission of safety variations (signal context)

- Standard variations after signal procedures -> submission 2 months post publication dates
- COVID-19 vaccines variations -> submission within 1-2 weeks
  - High level of urgency -> within days after PRAC meeting

**Expected publication dates of PRAC recommendations on safety signals**

When PRAC has recommended a product information update, marketing authorisation holders (MAHs) are expected to submit the requested variation according to the timeline specified in the PRAC recommendation. This timeline is calculated from the date of publication of the PRAC recommendation. Expected dates of publication can be found below. The actual date of publication is always mentioned on the EMA website just below the published document.

This timetable may be subject to revision.

<table>
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<tr>
<th>PRAC dates</th>
<th>Expected publication dates of PRAC recommendations on safety signals</th>
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<td>5 January 2022</td>
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EMA provided comprehensive guidance as early as data allowed it

- GVP guidance and RMP templates
- Info on infection and candidate vaccines limited at start of pandemic
- Recurrent topics in Scientific Advice requests = basis for picking up areas that could benefit from further scientific and procedural guidance
- EMA guidance to ensure common approach to:
  - Safety concerns
  - Adverse Events of Special Interest (AESI)
  - Traceability tools
  - Routine activities
  - PM safety surveillance
  - Safety monitoring for vaccines developed for variants
Essential tool for vaccines safety monitoring

• Envisaged as a light and flexible procedure, meant to pick up new safety topics and signals;

• However, more and more safety topics were picked up for follow-up in MSSRs (e.g. with cumulative reviews, and risk/benefit considerations)

• “Normal” timetables (30+14 or 60+14 days) cannot apply:
  – 5 working days for the primary assessment; EU Member States (MS) commenting within 48 hours; updated report, PRAC discussion and adoption in another 48 hours.

• Despite all challenges -> high quality reports from assessment teams; a good amount of high quality and focused MS comments
  – Picked up the need for starting cumulative reviews, signals, referral, product information changes with warnings that led to changes in vaccination policies in various EU Member States

• Further feedback from MAHs and trade associations received and under consideration
MSSR – where to? and next steps

Product specific recommendations on:

- Content: what topics to be added; what topics can be monitored with other tools (e.g. PSURs)
- Frequency: e.g. bi-monthly SSRs for Comirnaty and Vaxzevria
- DLP: potential option to adjust DLP +/- submission date in bi-monthly timetables to give more time to both MAH and Rapporteurs

Common recommendations applicable to all vaccines:

- Identify and remove topics that were a greater concern at the beginning of the pandemic but for which PRAC is reassured are either not a concern, or considers can be monitored using other pharmacovigilance tools (e.g. some identified and potential risks and missing info, some AESIs, most of special situations and populations)
- Further consider frequency changes while keeping alignment for timetables, to leverage the PRAC plenary discussions
- Develop and publish criteria for stopping the MSSR requirements for vaccines
- Keep the focus on new populations added to the label

Unknowns (being actively discussed): MSSR requirements for antivirals, for new vaccines, etc.
Unprecedented public engagement

- Rapid implementation of **Product information updates**;
- Dissemination of **Dear Healthcare Professional Communications**;
- **Stand alone Public Health Communication & PRAC Highlights** published on EMA website;
- **EMA Press Conference**:
  - Ad-hoc
  - Routine
- **Public stakeholder meetings**
- **Covid-19 vaccines** safety updates:
  - Monthly aligned with MSSR and ad-hoc when needed
    - Meaningful communication to the public, journalists and specialist stakeholders
    - 40 issued so far

26/10/2021

EMA will hold a fourth public stakeholder meeting on 25 November to provide an update on COVID-19 vaccines and therapeutics in the EU

Public stakeholder meeting on COVID-19 vaccines and therapeutics in the EU
Key messages

• COVID-19 continues to be a major public health challenge

• Pharmacovigilance activates to be prioritised in order to manage large volume of data without the quality being compromised

• Need for timely, high-quality, fit-for-purpose RWE, with focus on strengthening all steps of evidence generation and appraisal

• Large healthcare databases from several MSs can be used and rapid analyses are possible, but challenges still exist

• International collaboration is key to share information, data, experience, and leverage this knowledge to develop a global public health strategy

• Regulators and companies need to rise to the challenge and demonstrate to have systems in place to rapidly detect any safety issues and minimise serious risks to patients

• Timely exchange of information and transparency critical to build trust among stakeholders
Thank you for your attention

Any questions?

Further information

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