Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Vaccines

Minutes

Meeting 25, held 29 September 2021

COMMITTEE IN CONFIDENCE

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TGA Health Safety Regulation

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Item 3 Pharmacovigilance Issues

3.1 COVID-19 vaccine pharmacovigilance plan

Vaccine details

Sponsor	Active ingredient (Brandname)	Date of commencement of supply
s22 [redacted]		

Sponsor	Active ingredient (Brandname)	Date of commencement of supply
s22		

Documents submitted for ACV consideration

Delegate - Request for ACV advice, dated 24 September 2021
Attachment 1 – COVID-19 vaccine safety monitoring plan – February 2021
Attachment 2 – ACV 19 agenda paper 'Update on COVID-19 Vaccine Pharmacovigilance Plan' – February 2021
Attachment 3 - Sequential analysis for near real-time surveillance of COVID-19 vaccine safety: analysis plan and methods
Attachment 4 - Poisson Confidence interval and Chi-squared analysis
Attachment 5 - TGA COVID-19 vaccine Adverse Events of Special Interest (AESI) document

Overview of the Delegate of the Secretary of the Department of Health

Implementation of the COVID-19 Vaccine Pharmacovigilance Plan (the Plan) has included identification of AESI via use of a combination of weekly disproportionality analysis and comparison of observed AEFI reporting rates to background and expected rates.

The TGA has adopted the use of Proportional Reporting Ratio (PRR)[3] calculations for AEFI-vaccine pairs and revised the previous disproportionality analysis methods for COVID-19 vaccines to:

- increase the frequency of PRR analysis and reporting from bimonthly to weekly
- use PRR analysis by vaccine trade name rather than active ingredient
- use a lower threshold of a PRR >1 and case count ≥2 to identify vaccine-event pairs for assessment.

The current COVID-19 Vaccine Safety Monitoring Plan in Strategy 2.3 advises that the TGA will conduct enhanced cumulative data reviews for each COVID-19 vaccine to enable rapid analysis of AEFI rates to detect and confirm or disprove emerging COVID-19 safety signals. These methods include:

- access to Australian Immunisation Register (AIR) and vaccine distribution data for calculating COVID-19immunisation rates
- refined processes and statistical methods for analysing observed COVID-19 AEFI rates for detecting safety signals
- enhanced processes to determine if the frequency of particular AEFI are higher than expected

[3] Therapeutic product vigilance - September 2017
https://www.tga.gov.au/publication/therapeutic-product-vigilance

- processes for conducting subpopulation analyses to identify and investigate potential safety signals in at-risk populations.

From commencement of supply of COVID-19 vaccines six months ago, the TGA now has a better understanding of what information is available and reliable regarding COVID-19 vaccine adverse events and administered doses.

ACV Advice

1. **The Committee is requested to provide advice on section 2.3 of the Department of Health's COVID-19Vaccine Pharmacovigilance Plan, in particular, the proposed approach of weekly testing the association of AEFI reports by vaccine and doses administered using a Poisson confidence interval and a Chi-squared statistic and to implement weekly Maximised sequential probability ratio test (MaxSPRT).**

The ACV noted the value of descriptive analyses, such as time-to-onset. Rather than testing null hypothesis, a more qualitative approach was favoured, to consider international data and biological plausibility.

The ACV supported changes to the implementation of the COVID-19 Pharmacovigilance Plan section 2.3 to:

- reduce the frequency of DPAR to a 6-monthly basis
- make use of dosage information from the AIR for denominator-based signal analysis, and move to a weekly comparison of association of AEFI reports by vaccine and doses administered using a Poisson confidence interval and a Chi-squared statistic
- implement weekly Maximised sequential probability ratio test (MaxSPRT) analysis as per the MHRA and CDC model for AESI (immediately) and AEFI (in due course)
- as the appropriate comparator for each COVID-19 vaccine, use the other COVID-19 vaccines, noting residual confounding by age.

The ACV noted that the UK, Danish and Spanish databases to be used by the TGA for background rates will reflect local/regional approaches to diagnostic coding, especially for clinical events in patients not admitted to hospital and varying case definitions over time. Sensitivity analyses using non-Australian background rates would provide supportive evidence.

The ACV supported a focussed effort to access/obtain current Australian background rates, such as via hospital admission data, NPS and/or GP data.

Frequency of analyses should be risk assessed; new COVID-19 vaccines and new signals would require more frequent analyses.

The ACV noted that the previously-recognised delay in denominator data (doses administered) appears to now be adequately managed by the AIR. Median time to report cases is now of interest.

2. **The Committee is requested to provide advice on section 2.1 of the Department of Health's COVID-19 Vaccine Pharmacovigilance Plan, in particular, the proposed case definition for TTS and AESI changes.**

The ACV generally supported the new AESIs, additional AESI sub-categories, and refined MedDRA terms, as presented in the agenda paper, with the following amendments:

- retain viral meningitis (with aseptic meningitis)

- retain viral myocarditis/pericarditis (with myocarditis)
- add pericarditis
- review preference for 'multisystem inflammatory syndrome in children' (MIS-C) rather than 'Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2' (PIMS-TS)
- review preference for 'Vaccine-Associated Acute Respiratory Distress Syndrome' rather than 'Capillary leak syndrome'.

The ACV noted that the agenda paper did not include the extant or proposed revised case definition for TTS. Some members preferred the US CDC definition over the MHRA definition. It was noted that WHO, Brighton Collaboration and US CDC are each revising their case definitions and updated versions would be available shortly.

- Advice from the Thrombosis & Haemostasis society of Australia and New Zealand (THANZ) would contribute to the case definition. For example, whether/how to differentiate reports where PF4 is either negative or unavailable.
- Brighton Collaboration definition will likely suit low and middle income countries with limited technology for diagnostic work-up.
- Reporters should be encouraged/assisted to provide data required for each of these internationally used case definitions, such as the use of a standardised Case Report Form.
- The TGA advised that the next iteration of the TTS case definition would be provided to the ACV.

3. Other advice

The ACV had no objection to the use of similar statistical approaches for non-COVID-19 vaccines, except that:

- DPAR analysis should continue for vaccines without a reliable AIR denominator, such as Q fever and vaccines for outbound travellers[4]
- the appropriate comparators for non-covid vaccines are those used for the same disease or in the same patient population
- for seasonal influenza vaccines, and newly registered vaccines, there should continue to be frequent analysis.

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[4] AIR reporting is currently mandatory for COVID-19 vaccines, influenza vaccines and NIP vaccines.

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