Vaccine safety: what systems are required to ensure public confidence in vaccines?

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No single surveillance system is perfect, but integrating data from multiple sources can provide comprehensive and reliable signal detection

Although phase 3 pre-licensing vaccine studies typically include tens of thousands of participants, they generally cannot detect rare adverse events following immunisation (AEFI). Further, participants in clinical trials are generally highly selected, and safety profiles may be different when programs are applied to broader populations. Robust systems for detecting AEFI (post-marketing surveillance) are therefore essential when large scale vaccination programs are implemented.

Each of the complementary safety surveillance systems in Australia has strengths and weaknesses. The states and territories and the Therapeutic Goods Administration (TGA) facilitate spontaneous reporting systems for drugs and vaccines to a central register of all reported events,[1,2] with subsequent follow-up of AEFI that may be of significance. Underreporting is a problem for all spontaneous reporting systems, although reporting rates are generally higher for the period soon after vaccination and for more severe events. Analytical techniques that correct for this problem, such as disproportionality analysis, can detect potential safety signals.[3]

The information reported by health care workers and vaccinated people is not always sufficient for a comprehensive assessment. Some surveillance systems nest clinical services within their structure so that clinical details can be collected at the time of assessment by expert clinicians.[4] Processes have been established for determining the nature of severe events of regulatory or public health significance.[5] For coronavirus disease 2019 (COVID-19) vaccines, the first cases in Australia of thrombocytopenia with thrombosis syndrome,[6] Guillain–Barre syndrome (with the AstraZeneca vaccine),[7] and myocarditis (with the Pfizer–BioNTech vaccine)[8] were all spontaneously reported by attentive health care professionals.

These spontaneous reporting systems are strengthened by networks of specialist vaccine safety clinics and regulators, inter-agency communications, and periodic safety update reports by vaccine manufacturers.

Recognising the gaps in spontaneous reporting systems, active surveillance systems such as AusVaxSafety actively solicit reports of adverse events in online questionnaires sent by text or email to vaccine recipients or their carers.[9] A follow-up questionnaire

is sent to those who report adverse events to elicit information about the AEFI and whether medical care was sought. As response rates generally decline time from vaccination, the system is better designed for detecting early events, especially the reactogenicity profile of vaccines in particular recipient subgroups (eg, by age group and in pregnant women).

In the study reported in this issue of the *MJA*,[10] Deng and colleagues analysed AusVaxSafety data for more than three million vaccination episodes. While the response rate to the survey was relatively high (63%), the authors may have overestimated the frequency of adverse events because non-responders are less likely to have experienced significant reactions. The authors forwarded electronic invitations three and eight days after vaccination. Large proportions of people reported adverse events during the three days following vaccination (22–55%, depending on vaccine and dose number), but typical events were local pain, fatigue, headache, and myalgia that resolved spontaneously within seven days; fewer than 1% of vaccine recipients sought medical advice about their symptoms.

What are the implications of these findings? First, in the context of safety reporting, the adverse event profile of COVID-19 vaccines is reassuring, with no major differences between the findings of post-marketing surveillance and previous clinical studies. The large numbers of participants surveyed by AusVaxSafety allows for reactogenicity profiles to be reported for specific subgroups, including specific age groups and Aboriginal and Torres Strait Islander people.

Second, the findings reinforce the need for ongoing surveillance with broader coverage and the ability to adapt quickly. AusVaxSafety is an established system that has collected data on several vaccines since 2014, including influenza, pertussis, herpes zoster, and human papillomavirus vaccines.[11,12] While their approach is relatively simple, its established platform and analytical methods enabled AusVaxSafety to rapidly commence surveillance of COVID-19 vaccines soon after they were deployed, allowing adverse event profiles to be characterised early.

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Third, the study by Deng and colleagues reinforces the need for local safety surveillance systems in Australia. Australian data contribute to the international body of evidence regarding vaccine safety, adds information on specific groups in our country (including Indigenous Australians), and permits comparisons between the vaccines used locally. Both the rapid establishment of reactogenicity profiles and the awareness that AEFI are actively being sought facilitates public confidence in vaccines.[10,13]

Fourth, safety surveillance can be further strengthened by linking data from different systems. Syndromic electronic systems analyse de-identified, near real-time health care data (eg, emergency department codes, telephone health line data, general practice data) to detect safety signals.[14] In the United States and Europe, linkage systems integrate information from vaccine registries linked to hospitalisation databases to determine whether specific post-vaccination events are clustered or more frequent than their background rates.[15,16] Data linkage systems can not only detect signals, but also validate or discount safety signals identified by other systems.

Both system types are being developed in some Australian states, but require further work.[14] Clinical networks, such as the national Adverse Events Following Immunisation Clinical Assessment Network (AEFI-CAN), can also facilitate timely assessment of potential safety signals, such as suspected anaphylaxis events following human papillomavirus vaccination, whereby most vaccine recipients who reported adverse events could subsequently be re-vaccinated without further allergic events.[17]

Finally, ongoing post-marketing safety surveillance is needed even for vaccines with an established safety history. Many systems were developed in the aftermath of reports of severe febrile convulsions in children who received the 2010 seasonal formulation of the Fluvax Junior vaccine, after years of unproblematic annual use. These events were reported to then available surveillance systems by Western Australian emergency department staff, but it was clear that complementary systems were needed to detect such events earlier.[1,14]

Our ultimate goal must be an integrated safety system that exploits the strengths of each contributing system. None is perfect, but together they can provide comprehensive signal detection mechanisms, with the capacity to validate and investigate potential signals, and to confidently rule out spurious signals and avoid scares.

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1 Gold MS, Effler P, Kelly H, et al. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. *Med J Aust* 2010; 193: 492-493. https://www.mja.com.au/journal/2010/193/9/febrile-convulsions-after-2010-seasonal-trivalent-influenza-vaccine-implications

2 Martin JH, Lucas C. Reporting adverse drug events to the Therapeutic Goods Administration. *Aust Prescr* 2021; 44: 2-3.

3 Clothier HJ, Lawrie J, Russell MA, et al. Early signal detection of adverse events following influenza vaccination using proportional reporting ratio, Victoria, Australia. *PLoS One* 2019; 14: e0224702.

4 Clothier HJ, Crawford NW, Russell M, et al. Evaluation of "SAEFVIC", a pharmacovigilance surveillance scheme for the spontaneous reporting of adverse events following immunisation in Victoria, Australia. *Drug Saf* 2017; 40: 483-495.

5 World Health Organization. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. 2nd edition, 2019 update. https://www.who.int/publications/i/item/9789241516990 (viewed June 2022).

6 Hocking J, Chunilal SD, Chen VM, et al. The first known case of vaccine-induced thrombotic thrombocytopenia in Australia. *Med J Aust* 2021; 215: 19-20.e1. https://www.mja.com.au/journal/2021/215/1/first-known-case-vaccine-induced-thrombotic-thrombocytopenia-australia

7 Osowicki J, Morgan H, Harris A, et al. Guillain–Barre syndrome in an Australian state using both mRNA and adenovirus-vector SARS-CoV-2 vaccines. *Ann Neurol* 2021; 90: 856-858.

8 Wong J, Sharma S, Yao JV, et al. COVID-19 mRNA vaccine (Comirnaty)-induced myocarditis. *Med J Aust* 2022; 216: 122-123. https://www.mja.com.au/journal/2022/216/3/covid-19-mrna-vaccine-comirnaty-induced-myocarditis

9 Cashman P, Macartney K, Khandaker G, et al. Participant-centred active surveillance of adverse events following immunisation: a narrative review. *Int Health* 2017; 9: 164-176.

10 Deng L, Glover C, Dymock M, et al. The short term safety of COVID-19 vaccines in Australia: AusVaxSafety active surveillance, February – August 2021. *Med J Aust* 2022; 217: 000-000.

11 Pillsbury AJ, Glover C, Jacoby P, et al. Active surveillance of 2017 seasonal influenza vaccine safety: an observational cohort study of individuals aged 6 months and older in Australia. *BMJ Open* 2018; 8: e023263.

12 Phillips A, Carlson S, Danchin M, et al. From program suspension to the pandemic: a qualitative examination of Australia's vaccine pharmacovigilance system over 10 years. *Vaccine* 2021; 39: 5968-5981.

13 King C, Leask J. The impact of a vaccine scare on parental views, trust and information needs: a qualitative study in Sydney, Australia. *BMC Public Health* 2017; 17: 106.

14 Mesfin YM, Cheng AC, Enticott J, et al. Post-vaccination healthcare attendance rate as a proxy measure for syndromic surveillance of adverse events following immunisation. *Aust N Z J Public Health* 2021; 45: 101-107.

15 Mesfin YM, Cheng A, Lawrie J, Buttery J. Use of routinely collected electronic healthcare data for postlicensure vaccine safety signal detection: a systematic review. *BMJ Glob Health* 2019; 4: e001065.

16 Lai LY, Arshad F, Areia C, et al. Current approaches to vaccine safety using observational data: a rationale for the EUMAEUS (Evaluating Use of Methods for Adverse Events Under Surveillance-for Vaccines) study design. *Front Pharmacol* 2022; 13: 837632.

17 Crawford NW, Hodgson K, Gold M, et al; AEFI-CAN network. Adverse events following HPV immunization in Australia: establishment of a clinical network. *Hum Vaccin Immunother* 2016; 12: 2662-2665. ■