



Strengthening international surveillance of vaccine safety

Covid-19 has exposed both the strengths and the limitations of our safety monitoring systems

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In a linked paper, Hippisley-Cox and colleagues (doi:10.1136/bmj.n1931) report a large self-controlled case series study from England assessing the risk of thrombocytopenia and thromboembolic events associated with a first dose of ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca) or BNT162b2 (Pfizer-BioNTech) mRNA vaccine against covid-19.¹ The main findings suggest increased risks of hospital admission or death from thrombocytopenia (incidence rate ratio 1.33, 95% confidence interval 1.19 to 1.47) and venous thromboembolic events (1.10, 1.02 to 1.18) 8-14 days after ChAdOx1 nCoV-19, and of arterial thromboembolic events (1.06, 1.01 to 1.10) 15-21 days after BNT162b2.

An important strength of this study is the large population covered using national covid-19 vaccination data linked to data for mortality, hospital admissions, and SARS-CoV-2 infections. Furthermore, the design controlled for time varying risk factors, and a range of sensitivity analyses—including one with a negative control outcome—showed the robustness of the findings for most outcomes.

This study is an example of active surveillance activities, complementing the passive surveillance that relies on spontaneous reporting of adverse events by vigilant clinicians and members of the public.² The increased rates of venous thromboembolic events and thrombocytopenia are compatible with case reports that initially signalled these adverse events related to ChAdOx1 nCoV-19³ and with a recent analysis of people who received ChAdOx1 nCoV-19 in Denmark and Norway.⁴ Although an increased risk of cerebral venous sinus thrombosis has been reported after BNT162b2,⁵ the finding needs further confirmation.

Importantly, the small absolute increase in rates of adverse events reported by Hippisley-Cox and colleagues should be considered in the context of the proven benefits of covid-19 vaccines and the risks of morbidity and mortality associated with SARS-CoV-2 infection. For most, benefits far outweigh the risk of these rare adverse events; however, this balance will vary across specific subgroups (for example, based on age) and will also vary with population infection rates.⁶ Therefore, the implications of these and other findings should be considered at the national level.

One interesting feature of Hippisley-Cox and colleagues' study is the analysis of adverse events after SARS-CoV-2 infection, confirming substantially higher and more prolonged risks after infection than after vaccination. This analysis included only vaccinated participants, and rates of these events would likely be higher in unvaccinated people with SARS-CoV-2 infection, again suggesting a net positive benefit-risk balance in favour of vaccination.

To quantify the public health impact of excess adverse events after vaccination, both Hippisley-Cox and colleagues' study and a Scandinavian study of ChAdOx1 nCoV-19⁴ relied on background rates of these events before the pandemic. Background rates are essential for the interpretation of signals of adverse events and have recently been provided across five European Union countries by the European Medicines Agency funded ACCESS (vACCine covid-19 monitoring readinESS) project.⁷ This project defined adverse events of special interest as those listed by the Safety Platform for Emergency Vaccines—an international collaboration on vaccine safety.⁸ However, additional harmonisation of codes to capture adverse events of special interest will be essential to allow comparisons across multiple databases and countries.

Continuous monitoring of vaccine safety using both passive and active surveillance, combined eventually with controlled observational studies, is critical to ensure the best, safest, and most rational use of covid-19 vaccines. The accelerated development and regulatory assessment as well as rapid deployment of vaccines have exposed both the strengths and the limitations of current safety monitoring systems. Rare adverse events such as thrombotic thrombocytopenia, cerebral venous sinus thrombosis, and myocarditis were initially detected by passive surveillance based on spontaneous reporting to regulatory agencies.^{3,9} Spontaneous reporting systems, however, are prone to underreporting and cannot be used to estimate rates of adverse events. Analyses of large routine healthcare databases complement passive surveillance, allowing estimation of risk among vaccinated people and comparison with unvaccinated groups.

To strengthen pharmacovigilance activities to inform and accelerate regulatory decision making, the many barriers to timely investigation of emerging concerns about drug safety must be overcome, including lags in data availability, delays in access to that data for researchers, and barriers to sharing data across countries. The EMA recently pledged to improve this situation in Europe through its Data Analysis and Real World Interrogation Network (Darwin EU) initiative, which aims to be fully operational by 2024.¹⁰ This mirrors the US Food and Drug Administration's sentinel system and the Canadian CNODES (Canadian Network for Observational Drug Effect Studies) initiative.^{11 12}

A massive effort is underway from regulatory agencies worldwide to accelerate the assessment of benefit-risk balance and harmonise protocols for evaluating the safety of covid-19 vaccines. This is crucial not only for the present and future safety of covid-19 vaccines,

but also will hopefully pave the way more broadly for future international harmonisation and collaboration in drug safety monitoring.

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Further details of The BMJ policy on financial interests is here: <https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf>.

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