Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Rapid evaluation of the safety of COVID-19 vaccines: how well have we done?

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The rapid development and deployment of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an unprecedented scientific achievement. Before the emergence of coronavirus disease 2019 (COVID-19), the usual time for taking a vaccine through the necessary preclinical and clinical evaluation phases was around 10 years. In previous pandemics involving novel influenza strains, vaccine development time could be shortened by building on licensed seasonal influenza vaccine technologies and preparing in advance a mockup dossier based on a putative pandemic strain.

However, when SARS-CoV-2 emerged, there were no licensed coronavirus vaccines because early attempts to develop vaccines against other highly pathogenic coronaviruses (e.g. SARS-CoV and Middle East respiratory syndrome coronavirus) were not pursued, with few reaching the clinical trial stage and concerns being raised from animal models about the potential for enhanced disease with some vaccine platforms. Unlike SARS-CoV and Middle East respiratory syndrome, for which transmission was successfully contained by stringent public health measures, the rapid pandemic spread of SARS-CoV-2 necessitated the urgent development and large-scale deployment of vaccines to mitigate its global impact.

Within a year of the emergence of the virus, COVID-19 vaccines based on novel technologies, such as mRNA platforms and adenovirus vectors, began to be rolled out in national immunization programmes worldwide after completing the preclinical and clinical trial phases required to secure an Emergency Use Authorization in record time. The efficacy trials of COVID-19 vaccines, although requiring tens of thousands of participants to demonstrate protection, had inadequate power to identify rare adverse events. Their detection therefore relied on having systems in place to monitor safety as the vaccines were deployed in the target populations. Although this is the case with all new vaccines, the novel technologies used to develop COVID-19 vaccines underlined the importance of having robust surveillance systems in place for rapidly evaluating vaccine safety.

Vaccine safety surveillance has two complementary components: an initial signal-generation step in which adverse events of interest are identified, followed by analytic epidemiological studies to assess the association with vaccination. Safety signals can be generated from pre-licensure trials or during vaccine implementation from reports of unexpected or rare clinical events that occur in temporal association with vaccination. In the study of Shasha et al. [1] provides a nice real-world example of this process. The authors used electronic records from the Meuhedet Health Maintenance Organisation (HMO) in Israel to investigate various safety signals raised for the BNT162b2 mRNA vaccine from pre-licensure trials and postmarketing case reports.

The Shasha et al. study showed no difference between a vaccinated and matched unvaccinated cohort in the incidence of Bell's palsy, consistent with the results of a case-control study from Hong Kong [2] and a matched cohort study from another Israeli HMO, Clalit [3]. However, a different analysis using the Clalit HMO dataset and a historical cohort as the comparator, rather than a contemporary matched unvaccinated cohort, showed a small excess of Bell's palsy cases within a month of receipt of the BNT162b2 vaccine. Using standardized incidence ratios stratified by age, sex, and dose, the study showed that the highest attributable risk (4.46 per 100 000) was in women aged ≥65 years after a first dose [4].

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The only outcome showing an association with vaccination in the study by Shasha et al. [1] was an excess of reports of numbness and tingling in BNT162b2 vaccinees mainly involving the face. This finding is difficult to interpret and warrants further investigation. There was no evidence of an elevated risk of herpes zoster in BNT162b2 recipients (relative risk: 1.07; 95% confidence interval, 0.85–1.35), although the Israeli Clalit HMO study found a marginally elevated relative risk of 1.43 (95% confidence interval, 1.20–1.73) [3]. Case reports of herpes zoster onset shortly after mRNA vaccination have led to speculation on the grounds of biological plausibility that such temporally coincident events are causally linked, but such isolated reports have no probative value by themselves. More epidemiological studies are needed to evaluate whether mRNA vaccines can trigger a herpes zoster episode.

Evidence on the risk of Guillain–Barré syndrome (GBS) after the BNT162b2 vaccine from the study by Shasha et al. [1] was inconclusive because the analysis was inadequately powered to exclude an elevated risk, and GBS was not included as an outcome in the other Israeli study using the Clalit HMO database [3]. Studies using health care databases in the United States and England, where the incidence of GBS after mRNA and adenovirus vectored vaccines could be compared, have shown an increased risk after both the AstraZeneca chimpanzee adenovirus vectored vaccine (ChAdOx1) and the Janssen human adenovirus 26 vectored vaccine (Ad.26.CoV-2-S), but not after the Pfizer BNT162b2 or Moderna mRNA-1272 vaccines [5,6].

As with all observational vaccine safety studies, those conducted for COVID-19 vaccines have the potential to give a biased result because individuals recommended for or who accept the offer of vaccination may differ from unvaccinated individuals with respect to the safety outcome under study. An obvious example is the risk of herpes zoster, which is highly age and comorbidity dependent, factors that are also included in deciding priority groups for vaccination. Use of a matched cohort or case-control design, and/or adjustment for the effect of confounding variables by multivariate regression analysis, can help control for such biases but is only able to control for those factors that are captured and measured in the dataset.

The self-controlled case series method is another way of controlling for individual-level confounders. This method assesses in a cohort of vaccinated individuals with the outcome event, the incidence of an event in a predefined postvaccination period compared with the incidence of the same event outside of the risk period [7]. Although the self-controlled case series method has been employed for assessing the risk of certain adverse events after COVID-19 vaccination [6], its use as a method for rapid investigation of safety signals has been limited by inadequate observation time to assess the baseline incidence in postvaccination periods after the putative risk period. When the period before COVID-19 vaccination is used to assess baseline incidence, this can result in bias if the event is considered a contraindication to, or a reason to recommend, vaccination [8]. Although the potential for unmeasured confounding inevitably remains in most observational safety studies of COVID-19 vaccines, when an elevated risk is shown for one vaccine but not another in the same study population (e.g. in those showing a risk of GBS with adenovirus vectored but not mRNA vaccines [5,6]), the results are more likely to be valid. Similarly, when elevated risks are shown for the same outcome with the same vaccine in different populations and with different study designs, the evidence for a causal association is strengthened.

Despite their limitations, the postmarketing safety surveillance systems in place in different countries have proven remarkably effective in identifying rare side effects associated with COVID-19 vaccines that could not be detected in clinical trials. Acute myocarditis after mRNA vaccines and thrombosis with thrombocytopenia after adenovirus vectored vaccines were rapidly identified as safety signals from passive reports from clinicians during the rollout of the vaccines. Prompt investigation of these safety signals by epidemiologists using electronic health records [8,9], accompanied by carefully documented case series by clinicians [10], has allowed informed decisions to be made about the risk–benefit of using these vaccines in different population groups. Of particular value have been studies that have compared the risk of vaccines with the risk of the same outcome if contracting SARS-CoV-2 infection [3,6]. Communication techniques that provide these risk–benefit analyses for the public in easily understandable and nonthreatening ways, such as those employed by the Winton Centre for Risk and Evidence Communication in the United Kingdom [11], can help mitigate any negative impact on vaccine coverage of emerging safety issues.

Much has been learned during the SARS-CoV-2 pandemic about how vaccine development and deployment can be accelerated without compromising patient safety. Devasting though the global impact of the SARS-CoV-2 pandemic has been, its scientific legacy is a range of new and proven vaccine technologies, together with an enhanced global infrastructure to support future vaccine safety surveillance efforts.

Transparency declaration

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