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Global covid-19 vaccine rollout and safety surveillance—how to keep pace

An agile internationally harmonised surveillance system is essential to maintain safety and trust in vaccines, argue **Vincent Lo Re and colleagues**

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The first vaccines against the novel pathogen SARS-CoV-2 were deployed just nine months after the covid-19 outbreak was declared a global pandemic. Several types of covid-19 vaccines have been developed using different platforms and adjuvants, including messenger RNA based vaccines, adenovirus based vector vaccines, and inactivated vaccines.[1] As of June 2021, 102 vaccines were under study in phase I-III trials, and 185 were under investigation in preclinical studies.[2]

Given the global impact of the pandemic, vaccine development received unprecedented public and political attention, resulting in accelerated regulatory review. However, there has been scepticism about the rigour of evidence supporting comprehensive benefit-risk assessments and concern that breakthroughs in vaccine development have not been accompanied by similar advances in systems to monitor adverse events or communicate safety signals among regulators, public health officials, and healthcare providers.[3-5] The limited human exposure and follow-up within the pivotal covid-19 vaccine trials, optimised to allow formal conclusions about efficacy, did not permit detection of rare adverse events (occurring in fewer than 1 in 10 000 people) after immunisation, particularly within subgroups under-represented in, or excluded from, those trials (such as pregnant women, children, and frail elderly or immunocompromised people).[6 7] Public apprehension about the safety of covid-19 vaccines has contributed to hesitancy to receive a vaccine.[8]

These concerns were heightened in February 2021, when cases of unusual blood clotting occurring after immunisation with the Oxford-AstraZeneca vaccine (ChAdOx1-S) were reported to regulatory agencies (box 1).[9] The timely detection of rare, serious events after covid-19 vaccination highlights the importance of robust safety surveillance systems. As countries roll out covid-19 vaccines to their populations, speed of safety assessments is crucial to ensure favourable benefit-risk profiles and preserve public trust. We highlight potential challenges in covid-19 vaccine global safety surveillance and suggest approaches to overcome them.

Box 1: Surveillance in action: thrombotic thrombocytopenia

Cases of moderate-to-severe thrombocytopenia and thrombotic complications at unusual sites (eg, cerebral venous thrombosis, splanchnic vein thrombosis) occurring 5-24 days after initial immunisation with the Oxford-AstraZeneca vaccine (ChAdOx1-S) were first reported to regulatory agencies in February 2021.[9-11] A population based cohort study from Denmark and Norway subsequently estimated an excess of 2.5 (95% confidence interval, 0.9 to 5.2) cases of cerebral venous thrombosis for every 100 000 people vaccinated.[12]

Analyses suggest that these events may be triggered by platelet activating antibodies and represent a rare vaccine related variant of spontaneous heparin induced thrombocytopenia. This is now referred to as vaccine induced immune thrombotic thrombocytopenia.[9-11]

Europe briefly suspended use of the AstraZeneca vaccine until the European Medicines Agency concluded that the benefit of its use exceeded the risks. National regulatory agencies conducted independent benefit-risk reviews of the vaccine and made country specific recommendations.

Several countries recommended that the vaccine be administered only to people above a particular age (range, 30-65 years).[13] Regulatory authorities in France and Sweden recommended that people younger than 55 years and 65 years, respectively, who had received a first dose of AstraZeneca vaccine receive a different vaccine for their second dose.[13] The UK announced that it would offer an alternative vaccine to people under 40 years of age.[14] Cameroon, Denmark, and Norway stopped using the vaccine altogether.[13]

Shortly after, cases of thrombotic thrombocytopenia were reported in people who had received the Ad26.COV2.S vaccine made by Janssen (Johnson and Johnson),[15] prompting a formal benefit-risk review by the US Food and Drug Administration and EMA. Both agencies concluded that the benefits outweighed the risks, and immunisation with this vaccine resumed. Denmark decided to exclude the Janssen vaccine from its immunisation programme.

These events interrupted covid-19 vaccine access, and publicity surrounding their investigation may have damaged the public's trust in these vaccines.

Current approaches to monitoring vaccine safety

Safety of vaccines after licensing should ideally be monitored by a combination of passive and active surveillance.[16 17] Passive vaccine safety surveillance systems rely on spontaneous reporting of adverse events by vaccine manufacturers, healthcare providers, care givers, or patients. Reports are submitted to national regulatory authorities through systems such as the EMA's EudraVigilance and US's Vaccine Adverse Event Reporting System. Regulators review their accuracy and completeness and evaluate them to detect safety signals. Spontaneous reports can inform hypotheses regarding causal associations between vaccines and adverse events.

The complementary active vaccine safety surveillance systems seek to determine as completely as possible

the number of vaccine related events in a population. This information is critical during vaccine rollout, as is now exemplified in the realignment of target groups for the AstraZeneca vaccine.[18] Traditionally, these systems have been based on reports from hospitals or clinics, but electronic healthcare databases provide population based data on a much larger scale.[12] Such databases facilitate determination of the risk of particular adverse events in cohorts of vaccinated people and whether rates exceed those among unvaccinated comparator groups, at least until the majority of the population has received the vaccine. Thus, they allow for the conduct of formal controlled studies (phase IV studies) that permit causal inferences about vaccine related adverse events and effectiveness to recalibrate benefit-risk assessments. Together, passive and active surveillance systems and their expansion into controlled observational studies represent the pillars of monitoring vaccine safety after deployment.

Challenges surrounding covid-19 vaccine safety surveillance

Global assessment of covid-19 vaccine safety faces several challenges. Firstly, there is substantial heterogeneity in vaccine safety monitoring across countries.[4] Many low and middle income countries have had challenges in establishing and maintaining passive and active vaccine safety surveillance systems.[19] These include low participation in spontaneous reporting and limited resources for investigation and communication of safety signals.[20] Follow-up with patients who experience adverse events after covid-19 vaccination (or their care givers or healthcare providers) to collect clinical information has been uncommon, even in high income countries.[21] Moreover, in many countries, limited collaboration between national regulatory authorities and immunisation programmes prevents assessment of vaccine related events by regulators.

Low and middle income countries often lack electronic healthcare data or the pharmacoepidemiological expertise to permit active vaccine surveillance using large, validated data sources. Data from surveillance programmes in high income countries may not be able to detect adverse events that affect particular ethnic subgroups or have specific genetic, environmental, or socioeconomic patterns that occur in lower income countries.

Secondly, passive surveillance systems globally will find it difficult to use traditional approaches to the analysis of spontaneously reported adverse events because of the unprecedented rapid rollout of different covid-19 vaccines and intense scrutiny of their safety. While this scrutiny may have qualitative value, quantitative assessments will be challenging because signal identification in these systems relies on comparisons against "expected" rates (eg, for other vaccines). Reports may not include details about vaccine type or immunisation date,[22] which may further impede safety monitoring.

Thirdly, even for countries with well established infrastructure for real world data, such as access to electronic health record or administrative databases, the rapid and simultaneous release of multiple covid-19 vaccines poses challenges to population based ascertainment of vaccine exposure and adverse events. Since some people are being vaccinated outside of healthcare settings and without reimbursement by health plans, documentation may not be available within electronic healthcare databases.[23] This will lead to incomplete digital tracking of vaccine administration, missed opportunities to capture important vaccine safety outcomes, and misclassification when establishing exposure groups for controlled comparisons.

Different vaccines will have different event profiles, requiring careful tracking of product detail and lot numbers.[24] Vaccine registries, which may provide such information locally, may not be linked to healthcare databases. The possibility that individuals will receive different vaccines for the two doses (eg, AstraZeneca for first dose and Pfizer for second dose) will make it more difficult to identify which vaccine may have caused an adverse event. Any lags in availability of analysable data because systems are not set up for data linkage and extraction will delay assessment of rates of vaccine related adverse events.

A final, but extremely important, challenge to covid-19 vaccine safety is the need for global coordination of monitoring, evaluation, and communication of adverse events.[25] This includes not only coordination of passive surveillance efforts but also standardised data collection of safety and effectiveness endpoints for phase IV studies. Country specific usage patterns and population specific adverse events will require identification and broad communication. As a practical example, international travellers may present for urgent care after pre-travel covid-19 vaccination, requiring clinical understanding of vaccine safety at the global level.

Making vaccine safety surveillance work

The global deployment of covid-19 vaccines affords an unprecedented opportunity for innovation in post-licensing vaccine safety assessment. National regulatory authorities could collaborate on the development of "master protocols" that detail approaches to capture vaccine administration within healthcare databases or vaccine registries with linkage to electronic health records; ascertain events of interest after vaccination using prespecified algorithms; and identify subgroups that were under-represented in trials.[26]

Such protocols would help overcome challenges related to the heterogeneity in vaccine safety monitoring across countries by promoting harmonisation of pharmacoepidemiological designs, data, and safety endpoints across countries. They would also allow assessment of the heterogeneity of safety signals across different settings and subgroups. Protocols to harmonise safety evaluations of covid-19 vaccines have been developed by the US Food and Drug Administration's Center for Biologics Evaluation and Research,[26] the Safety Platform for Emergency Vaccines funded by the Coalition for Epidemic Preparedness Innovations,[27] the Vaccine Covid-19 Monitoring Readiness (ACCESS) programme funded by the EMA (which uses the list of adverse events provided by the Safety Platform for Emergency Vaccines),[28] and the Japanese Society for Pharmacoepidemiology,[29] but broader collaboration between national regulatory authorities is needed.

The massive rollout of covid-19 vaccines also offers an opportunity to enhance active vaccine safety surveillance systems. This could help overcome existing barriers in ascertaining vaccine exposure and adverse events on a population level. Ideally, these systems should use databases that can be accessed in near real time to identify large numbers of individuals who have been vaccinated, ascertain the vaccine and lot number administered, and detect adverse events using validated coding algorithms, such as those developed by the Brighton Collaboration.[30] These systems could address concerns regarding cases of Bell's palsy observed in phase III trials of the messenger RNA based vaccines developed by Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273)[31] by comparing incidence of this outcome against background rates in the general population and matched non-vaccinated comparison groups.

Settings that have not yet established such systems could invest in infrastructure to electronically record covid-19 vaccinations and

diagnoses of relevant events. This has been done in Vietnam to monitor events after measles vaccination[32] and in Guatemala to assess the safety of the DTP-HepB-Hib vaccine.[33] Moreover, the creation of databases across regions and countries could increase sample size and diversity, enhance detection of rare acute and delayed onset events, allow adequately powered comparative vaccine safety studies, and promote collaborations and communication. This will enable regulators to determine the causes of adverse events more quickly and definitively. As mRNA based vaccines are a new technology, such databases will be especially important for evaluating their long term safety. The Vaccine Safety Datalink in the US and European Accelerated Development of Vaccine Benefit-Risk Collaboration are two examples of collaborations that successfully established distributed systems based on electronic medical records for rapid monitoring of vaccine safety.[34 35] In Europe, the ACCESS programme recently published background incidence of events of interest to facilitate comparisons between those who have and have not had covid-19 vaccines.[36]

Since many countries are initially vaccinating healthcare and other essential workers,[37] registries of these workers could be developed and linked to electronic health data to assess rates of vaccine related events. In addition, use of novel data collection methods, such as smartphone based surveys like V-safe in the US,[38] V-Watch in Taiwan,[39] and WEB-RADR in Europe,[40] could enhance capture of covid-19 vaccination and related adverse events, although these systems have not identified any adverse events related to covid-19 vaccines so far.

Finally, national regulatory authorities should foster close collaborations with their regional and national immunisation programmes to ensure timely dissemination of information about safety signals and changes to vaccine recommendations. They should also establish collaborations across regions to promote sharing of vaccine safety data, including potential signals for which causality cannot be established.

Failure to keep pace with vaccine rollout and overcome the challenges to global surveillance of vaccine safety could lead to delays in determining important alterations in the benefit-risk profiles of covid-19 vaccines. This could erode public confidence in vaccination programmes and have grave public health consequences.

Key messages

- The development of rare, serious adverse events after covid-19 vaccination highlights the critical importance of robust vaccine safety surveillance systems
- The widespread rollout of covid-19 vaccines creates an opportunity for international harmonisation of pharmacoepidemiological designs, data, and safety endpoints
- Enhanced active vaccine safety surveillance systems could overcome existing barriers in ascertaining vaccine exposure and adverse events at a population level
- National regulatory authorities should establish formal collaborations across regions to promote sharing of safety data

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