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CURRENT OPINION

Assessing the Safety of COVID-19 Vaccines: A Primer

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Abstract
Vaccines against COVID-19 are being developed at speeds not previously achieved. With this unprecedented effort comes challenges for post-marketing safety monitoring and challenges for vaccine safety communication. To deploy these new vaccines fast across diverse populations, it is vital that robust pharmacovigilance and active surveillance systems are in place. Not all countries have the capability or resources to undertake adequate surveillance and will rely on data from those who can. The tools exist to assess COVID-19 vaccines as they are deployed such as surveillance systems, administrative data and case definitions for adverse events of special interest. However, stitching these all together and using them effectively requires investment and collaboration. This paper provides a high-level overview of some of the facets of modern vaccine safety assessment and how they are, or can be, applied to COVID-19 vaccines.

Key Points

COVID-19 vaccines are being developed at an unprecedented speed leading to concerns about adequate safety assessments before deployment.

There are many entities tasked with assessing and monitoring vaccine safety at the global and national levels and prior experience in enhanced vaccine safety activities.

We have the tools to intensively monitor and assess the safety of COVID-19 vaccines as they are deployed, providing there is coordination and collaboration.

1 Introduction

An unprecedented commitment to developing and producing vaccines against SARS-CoV-2 in record time is underway and new candidates are entering clinical testing almost weekly. The speed at which development is unfolding has led to widespread concern among both health professionals and the public that vital steps may be skipped, in particular the assessment of safety.

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Vaccine development has traditionally been a long process taking an average of 10–15 years. The vaccine with the shortest timeline from antigen discovery to licensure is the mumps vaccine, which took 4 years. It is the high financial cost, particularly high-risk advanced clinical development, coupled with the investment in production facilities that has, in part, hampered nimble vaccine responses to emerging infectious diseases. However, recent developments in technology along with unprecedented collaboration and investment mean we may be able to escape the barriers of the past [1].

As well as the speed at which vaccine candidates were advanced, where possible the clinical development and regulatory phases are occurring alongside each other rather than sequentially [2]. This means that while all steps are adhered to, their timing can be expedited. The desperate need for an Ebola vaccine galvanised us, and in less than 12 months, 12 clinical trials ran the gamut from a "first in man" dosing study to a phase III efficacy trial [3]. This was achieved through successful collaborations and running these stages in parallel [4, 5]. However, while the pre-licensure clinical programme was executed in record time, fragile settings are often ill equipped for post-licensure safety surveillance.

2 Pre-Clinical: Assessment in Animal Models

Potential vaccine candidates need to be assessed in suitable animals for safety, immunogenicity and efficacy under challenge. Translating data from any single animal to humans can be problematic as the disease may not mimic human

infection accurately, and therefore fail to predict vaccine effects, positive or negative. The models for assessing SARS-CoV-2 vaccines include mouse (transgenic for the human ACE2 receptor), hamster, ferret and non-human primates, depending on what question is being asked [6]. Studies of earlier SARS vaccines in animals identified two potential safety issues; antibody-dependent enhancement and cellular immunopathology. These have not been observed in human studies but flag potential responses for close examination and highlight the importance of selecting vaccine approaches and adjuvants that drive desirable responses [7].

3 Pre-Licensure: Assessment in Humans

Clinical studies in humans generally follow three phases. Phase I with 10's (~ 30 to 50) of healthy volunteers assesses the safety, immunogenicity and dose ranging; phase II progresses to 100's of volunteers and assesses safety and immunogenicity; phase III includes 10,000's of volunteers and assesses safety and efficacy. Phase III is usually placebo-controlled studies and while safety continues to be studied efficacy will be assessed. Normally, these phases progress sequentially after careful assessment of results of each stage before moving to the next. In the case of COVID-19 vaccines, as with recent Ebola vaccines, these stages can be expedited without skipping anything thanks to investment and collaboration [2]. Each trial will have an independent drug safety monitoring board and ideally this group will have diverse expertise, including a biostatistician. For COVID-19 vaccines, it is recommended that there be persons with expertise in rare disease epidemiology. A meta-drug safety monitoring board has been established to ensure that high-level expertise is available to support all drug safety monitoring boards [8, 9].

4 Agencies and Entities Tasked with Assessing and Monitoring Vaccine Safety

4.1 World Health Organization Global Advisory Committee on Vaccine Safety

Established in 1999, this committee of 14 experts from all regions of the world meets twice a year (and when needed) to assess the safety of vaccines. They provide independent, authoritative, scientific advice to the World Health Organization (WHO) on vaccine safety issues of global or regional concern. In May 2020, the Committee focussed on COVID-19 and discussed potential safety issues that may arise with the new vaccines being developed and deployed under the emergency conditions. The Committee also considered the work being undertaken by the Coalition for Epidemic Preparedness Innovation-funded Safety Platform for Emergency vACcines (SPEAC), issues around pharmacovigilance preparedness, and safety communication at a time when vaccine hesitancy and misinformation are growing challenges. The key conclusions from this first meeting on COVID-19 vaccines was that post-licensure surveillance preparedness at both country and regional levels was urgent and that managing the 'infodemic' was critical, supporting the proposed approach and roadmap to COVID-19 vaccine benefit-risk communication [10].

4.2 World Health Organization Strategic Advisory Group of Experts

The Strategic Advisory Group of Experts is the principal advisory group to WHO for vaccines and immunisation. This 15-member group advises WHO on global policies and strategies, from vaccines and technology, research and development, to delivery of immunisation and its linkages with other health interventions. For vaccine safety, the Strategic Advisory Group of Experts takes the findings of the Global Advisory Committee on Vaccine Safety and makes recommendations. The Strategic Advisory Group of Experts are next meeting in October 2020 where COVID-19 vaccines will be considered and recommendations developed.

4.3 Brighton Collaboration

The Brighton Collaboration is an international collaboration launched in 1999 and tasked with developing definitions and guidelines for potential adverse events following immunisation [11]. Since 2019, the Brighton Collaboration have had a contract with the Coalition for Epidemic Preparedness Innovation to develop tools to guide developers, regulatory agencies and health authorities through safety evaluations of vaccines developed with new technologies. This is within the SPEAC project with the objective of harmonising safety assessments with standardised tools and definitions. Since COVID-19 emerged, they have increased their activities and are developing tools to help us assess COVID-19 vaccines. These tools include templates for the different vaccine platforms, and the development of adverse events of special interest (AESIs) likely to be pertinent to COVID-19 vaccines.

4.4 Standardised Templates and Adverse Events of Special Interest

The SPEAC working groups have developed templates that can be completed by vaccine developers/sponsors that describe the key considerations for risk benefit assessment. There are templates for viral vector vaccines [12], protein vaccines [13], nucleic acid vaccines [14] and AESIs [15].

An AESI is defined by the Council for International Organizations of Medical Sciences as:

> "An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted." [16]

The SPEAC project has developed a list of AESIs for COVID-19 vaccines based on: proven association with immunisation; proven association with a vaccine platform and/or adjuvant relevant to Coalition for Epidemic Preparedness Innovation vaccine development; theoretical concern based on immunopathogenesis; theoretical concern related to viral replication during wild-type disease; and theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms [16]. These events and the definitions and guidelines on collecting and reporting them will be invaluable to support active safety surveillance and phase IV studies.

4.5 Regulatory Agencies

Regulatory agencies are tasked with having authority over safety to protect consumers. Examples include the US Food and Drug Administration and the European Medicines Agency. Vaccines must be evaluated and approved by a national regulatory authority before they can be used. The US Food and Drug Administration has issued guidance for industry on the development and licensure of vaccines to prevent COVID-19. It outlines key considerations needed to satisfy the regulators in their assessment of these vaccines. This covers the chemistry, manufacturing, manufacturing facilities, non-clinical data such as toxicology studies and animal models, clinical trials and plans for post-licensure evaluation [17]. The European Medicines Agency has also issued similar guidance [18]. These guidelines will also serve as a useful framework for other nations in their decision making.

4.6 Country-Level Pharmacovigilance Systems and Passive Surveillance

Most countries have a passive surveillance system for recording and reporting on adverse events following immunisation and in turn report to the WHO pharmacovigilance centre in Uppsala, Sweden. The WHO Global Vaccine Safety Blueprint I considers a minimum reporting rate of 10 per 100,000 population for functional adverse events following an immunisation surveillance system [19]. In 2017, 114 countries met or exceeded this objective [20]. However, while safety capacity has improved in many low-and middle-income countries, others still face challenges with low detection rates and reporting, the investigation of safety signals, lack of epidemiological tools for active surveillance, challenges at the national regulatory authority level, and a lack of information sharing between countries. When optimised, these systems have demonstrated their value in detecting unexpected or rare events but limitations such as the lack of a denominator and reliance on voluntary reports mean they cannot be relied on for detection and they cannot be used for causality assessment. There are also significant deficiencies in global-level reporting with over half of the total reports in 2017 received from the USA, UK, France, China and the Republic of Korea [21]. Many reports are not timely with an average of 2.4 years between event onset and report date. These limitations will clearly limit or prevent the generation of COVID-19 vaccine-related safety signals in most countries.

4.7 Active Safety Surveillance and Phase IV Studies

Some countries have systems that can monitor events in at least some of their population in near real time and map to vaccine exposure. A larger number of countries can assess potential safety events retrospectively. Examples of advanced systems include the US Vaccine Safety Datalink [22, 23] and the European ADVANCE [24]. The ADVANCE project has led to a sustainability project called VAC4EU, which will support the European Medicines Agency-funded COVID-19 vaccine monitoring programme called ACCESS. While these systems have demonstrated their ability to undertake robust assessments, they are not globally representative, are restricted to locally used vaccines, and the population sizes under observation lack the power to assess very rare events such as Guillain–Barre Syndrome. These limitations can be overcome through global collaboration [25].

Distributed networks allow individual countries (or sites) to collaborate. These collaborations pull multiple countries together to conduct studies on huge numbers of people using administrative data and can compare the risks for very rare events between vaccinated and unvaccinated people. Such collaborations have occurred in the past, pooled data from

several countries were used to assess measles-containing vaccines and aseptic meningitis and idiopathic thrombocytopenic purpura [26, 27], rotavirus vaccines and intussusception [28], and the pandemic influenza vaccine and Guillain–Barre syndrome and narcolepsy [29]. However, all these studies were ad hoc, with no sustainable network in place. The capacity exists globally to assess vaccine safety. The development of this capacity is critical for the ongoing assessment of COVID-19 vaccine safety but as yet lacks investment [25].

5 Challenges and Solutions for the Safe and Responsible Deployment of COVID-19 Vaccines

Too few countries have high functioning pharmacovigilance systems, and far fewer are able to undertake robust signal verification and post-licensure studies on safety. These countries will need to rely on data generated by those who do have the capability, perhaps placing some further ethical obligations on those countries who can, rather than rely on the predominant data contributions from Europe and the USA.

Adverse events will coincide temporally with vaccine administration [30]. Prior to the use of COVID-19 vaccines, it is important to understand the background rates of conditions that may be temporally associated with vaccine administration to be able to assess observed rates vs the expected rates [31]. For most events, these rates are unknown and to further complicate matters the rates of many events, such as multiple sclerosis, vary by sex and geography [32, 33]. Developing background rates for COVID-19 vaccine AESIs for as many populations as possible is a matter of urgency.

Deploying any new vaccine based on data from expedited clinical trials into a population without a functioning safety monitoring system in place is reckless and irresponsible given the tools that are available. While there are international collaborations aimed at supporting coordinated efforts in COVID-19 vaccine safety assessments, vaccine nationalism and a lack of a globally coordinated vaccine safety effort could limit the potential in this space. Furthermore, deployment of vaccines before the successful completion of robust clinical programmes could threaten not only public confidence in COVID-19 vaccines but also immunisation programmes in general.

While the clinical testing of COVID-19 vaccines can be done robustly and assessment by regulatory agencies can be stringent, the vaccines are likely to be used under emergency conditions and the follow-up time from the trials will be minimal. Under such conditions, it is vital that the products are monitored (in near real time) for rare adverse events until risks can be either quantified or excluded (see Box for a case study). Only a few countries have the capability to conduct this monitoring [34] and even fewer are prepared with systems at the ready and baseline rates of AESIs established. There is an urgency to support as many sites as possible to prepare in collaboration with each other to actively monitor COVID-19 vaccines as they are deployed using common protocols so that data may be pooled, and rare events assessed in diverse populations.

We have the tools to intensively monitor the safety of COVID-19 vaccines. While billions are being spent on the development and scale manufacturing of vaccines that have yet to demonstrate efficacy, with the exception of the European Union, there is limited investment in the post-licensure phase yet, which is inexpensive in comparison. Failure to assess these vaccines for safety to our full ability is wrong. As we well know from extensive experience, vaccine safety issues can threaten not only the success of any COVID-19 vaccine programme but also routine immunisation programmes. It is vital we get this right and we have the tools and the expertise to do so and to do it well.

5.1 Rolling Out a Vaccine with Limited Clinical Data Case Study: The New Zealand MeNZB Vaccine

During the 1990s and into the 2000s, New Zealand had a devastating meningococcal B disease epidemic. There was no suitable existing vaccine available, so a tailor-made outer-membrane vesicle vaccine was developed through a collaboration (New Zealand Government, University of Auckland, Norwegian Institute of Public Health, The Institute of Environmental and Research, and industry). It was tested in New Zealand in phase I, II and IIb trials then rolled out to the highest risk members of the New Zealand population after only a few thousand people had received the vaccines (for meningococcal vaccines, immunogenicity bridging data may be used for licensure as phase III trials are not feasible because of the rarity of the disease outcome).

To do this safely, a multi-faceted, intensive, post-licensure safety surveillance strategy was implemented [35]. All people in the age group receiving the vaccine who went to hospital were assessed for their vaccine exposure [35]. Additionally, a proportion of primary care practices provided data on visits so that exposure to the vaccine could be assessed [36]. Weekly screening occurred against background rates (observed vs expected). An electronic national immunisation register made comparisons between vaccinated and unvaccinated people possible to detect any safety signals. This happened in near real time and provided high-quality data that provided reassurance about the vaccine's safety profile. Since this occurred in 2004–6, information technology has progressed, as have methodologies in pharmacoepidemiology, which make such systems cheaper and more feasible to implement.

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References

1. Brende B, Farrar J, Gashumba D, Moedas C, Mundel T, Shiozaki Y, et al. CEPI: a new global R&D organisation for epidemic preparedness and response. Lancet. 2017;389(10066):233–5.
2. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med. 2020;382(21):1969–73.
3. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015;386(9996):857–66.
4. Wolf J, Bruno S, Eichberg M, Jannat R, Rudo S, VanRheenen S, et al. Applying lessons from the Ebola vaccine experience for SARS-CoV-2 and other epidemic pathogens. NPJ Vaccines. 2020;5:51.
5. Henao-Restrepo AM, Preziosi M-P, Wood D, Moorthy V, Kieny MP. On a path to accelerate access to Ebola vaccines: the WHO's research and development efforts during the 2014–2016 Ebola epidemic in West Africa. Curr Opin Virol. 2016;17:138–44.
6. Lakdawala SS, Menachery VD. The search for a COVID-19 animal model. Science. 2020;368(6494):942–3. https://doi.org/10.1126/science.abc6141.
7. Lambert P-H, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT, et al. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 2020;38(31):4783–91.
8. Petkova E, Antman EM, Troxel AB. Pooling data from individual clinical trials in the COVID-19 era. JAMA. 2020;324(6):543–5.
9. Brighton Collaboration. SPEAC. 2020. https://brightoncollaboration.us/speac/. Accessed 17 Aug 2020.
10. World Health Organization. Global Advisory Committee on Vaccine Safety, 27–28 May 2020. Wkly Epidemiol Rec. 2020;28(95):325–36.
11. Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine. 2002;21(3–4):298–302.
12. Clarke DK, Hendry RM, Singh V, Rose JK, Seligman SJ, Klug B, et al. Live virus vaccines based on a vesicular stomatitis virus (VSV) backbone: standardized template with key considerations for a risk/benefit assessment. Vaccine. 2016;34(51):6597–609.
13. Kochhar S, Kim D, Excler J-L, Condit RC, Robertson JS, Drew S, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines. Vaccine. 2020;38(35):5734–9.
14. Kim D, Robertson JS, Excler J-L, Condit RC, Fast PE, Gurwith M, et al. The Brighton collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines. Vaccine. 2020;38(34):5556–61.
15. Law B, Sturkenboom M. D2. 3 Priority list of adverse events of special interest: COVID-19. The Brighton Collaboration. https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf.
16. Council for International Organizations of Medical Sciences. The development safety update report (DSUR): harmonizing the format and content for periodic safety reporting during clinical trials: report of CIOMS Working Group VII. Geneva: Council for International Organizations of Medical Sciences; 2006.
17. Federal Drug Administration. Development and licensure of vaccines to prevent COVID-19: guidance for industry. In: U.S. Department of Health and Human Services, editor. Rockfield, Maryland: Federal Drug Administration, Centre for Biologics Evaluation and Research; 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.
18. European Medicines Agency. Guidance for medicine developers and companies on COVID-19. European Medicines Agency, Amsterdam, The Netherlands. 2020. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-medicine-developers-companies-covid-19. Accessed 17 Aug 2020.
19. World Health Organization. Global vaccine safety blueprint. In: Department of Immunization VaB, editor. Geneva: Quality, Safety and Standards Unit of the Department of Immunization, Vaccines and Biologicals; 2012.
20. World Health Organization. Global vaccine action plan: monitoring, evaluation & accountability. Secretariat Annual Report 2018. Geneva: World Health Organization; 2018.
21. Anonymous. VigiBase now contains around 17 million ADR reports. React Wkly. 2018;1700(1):3. https://doi.org/10.1007/s40278-018-45575-x.
22. Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States. Pediatrics. 1997;99(6):765–73.
23. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014;32(42):5390–8.
24. Bollaerts K, De Smedt T, McGee C, Emborg H-D, Villa M, Alexandridou M, et al. ADVANCE: towards near real-time monitoring of vaccination coverage, benefits and risks using European electronic health record databases. Vaccine. 2019;S0264-410X(19)31051-5.
25. Petousis-Harris H, Dodd CN. Progress toward a global vaccine data network. Pediatr Infect Dis J. 2020. https://doi.org/10.1097/INF.0000000000002785.
26. Guillard-Maure C, Elango V, Black S, Perez-Vilar S, Castro JL, Bravo-Alcántara P, et al. Operational lessons learned in conducting a multi-country collaboration for vaccine safety signal verification and hypothesis testing: the global vaccine safety multi country collaboration initiative. Vaccine. 2018;36(3):355–62. https://doi.org/10.1016/j.vaccine.2017.07.085.
27. Perez-Vilar S, Weibel D, Sturkenboom M, Black S, Maure C, Castro JL, et al. Enhancing global vaccine pharmacovigilance: proof-of-concept study on aseptic meningitis and immune

thrombocytopenic purpura following measles-mumps containing vaccination. Vaccine. 2018;36(3):347–54.
28. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of intussusception after monovalent rotavirus vaccination in Africa. N Engl J Med. 2018;378(16):1521–8.
29. Weibel D, Sturkenboom M, Black S, de Ridder M, Dodd C, Bonhoeffer J, et al. Narcolepsy and adjuvanted pandemic influenza A (H1N1) 2009 vaccines multi-country assessment. Vaccine. 2018;36(41):6202–11.
30. Siegrist C-A, Lewis EM, Eskola J, Evans SJ, Black SB. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. Pediatr Infect Dis J. 2007;26(11):979–84.
31. Black S, Eskola J, Siegrist C-A, Halsey N, MacDonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009;374(9707):2115–22.
32. Ebers GC, Sadovnick AD. The geographic distribution of multiple sclerosis: a review. Neuroepidemiology. 1993;12(1):1–5.
33. Ebers GC. Environmental factors and multiple sclerosis. Lancet Neurol. 2008;7(3):268–77.
34. Donahue JG, Kieke BA, Lewis EM, Weintraub ES, Hanson KE, McClure DL, et al. Near real-time surveillance to assess the safety of the 9-valent human papillomavirus vaccine. Pediatrics. 2019;144(6):e20191808.
35. McNicholas A, Galloway Y, Stehr-Green P, Reid S, Radke S, Sexton K, et al. Post-marketing safety monitoring of a new group B meningococcal vaccine in New Zealand, 2004–2006. Hum Vaccin. 2007;3(5):196–204.
36. Tatley MV, Kunac DL, McNicholas A, Zhou L, Ballantyne S, Ashton J, et al. The Intensive Vaccines Monitoring Programme (IVMP): an electronic system to monitor vaccine safety in New Zealand. Vaccine. 2008;26(22):2746–52.