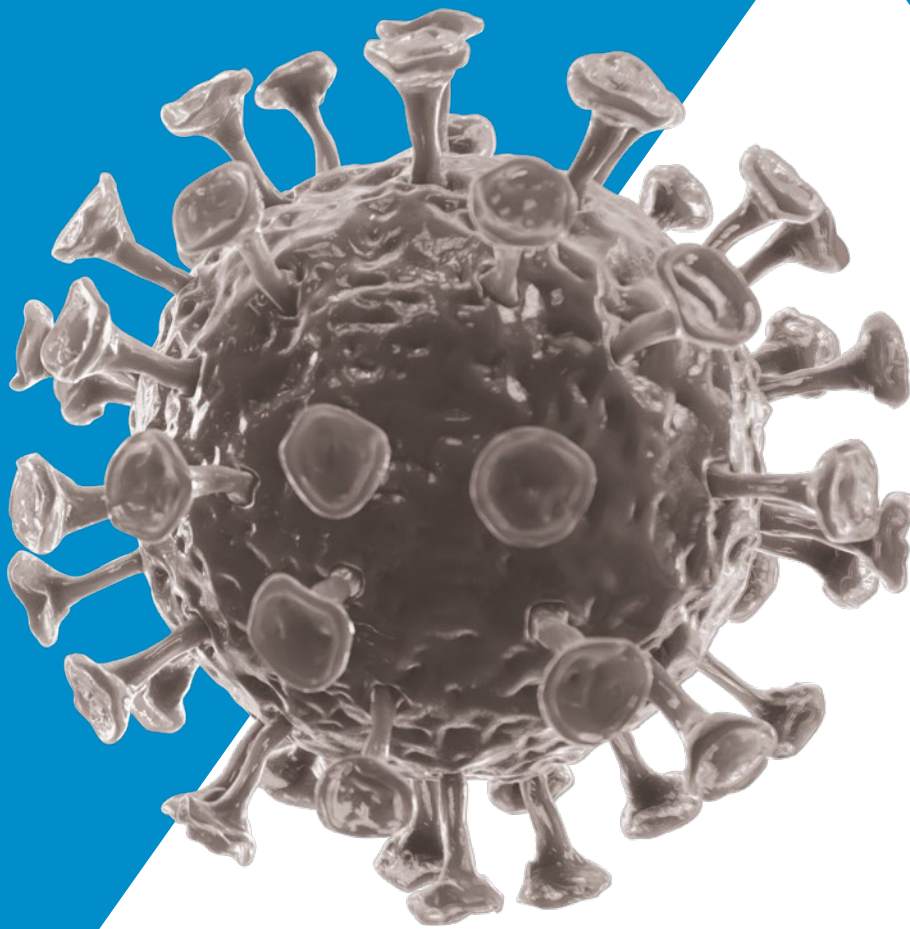


COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL



EXECUTIVE SUMMARY



World Health
Organization

Covid-19 vaccines: safety surveillance manual

ISBN 978-92-4-001828-0 (electronic version)

ISBN 978-92-4-001829-7 (print version)

© World Health Organization 2020

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Covid-19 vaccines: safety surveillance manual. Geneva: World Health Organization; 2020. Licence: [CC BY-NC-SA 3.0 IGO](#).

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Design and Layout: Agence Gardeners

1. Background

On 30 January 2020, World Health Organization (WHO) declared that the outbreak due to a novel coronavirus, SARS-CoV-2, also known as COVID-19, was a public health emergency of international concern. By 12 March 2020, due to its rapid global spread, the outbreak was declared a pandemic. The pandemic has already caused millions of deaths and disrupted the lives of billions more.

The 42nd Global Advisory Committee on Vaccine Safety (GACVS) meeting on 27–28 May 2020 recommended that, before COVID-19 vaccines are introduced, infrastructure and capacity for surveillance of the safety of COVID-19 vaccines should be in place in all countries and existing infrastructure be reactivated and engaged. This will require local, national, regional and global collaboration. Countries should include preparedness plans for COVID-19 vaccine safety in their overall plans for COVID-19 vaccine introduction, building on WHO guidance. This COVID-19 vaccine safety surveillance manual was developed through the contributions of GACVS members and several international experts. The manual incorporates current and available information that is critical for all stakeholders before, during and after the introduction of COVID-19 vaccines.

2. Lessons learnt about vaccine safety surveillance from the past

Key lessons about vaccine safety surveillance learnt from the past when new vaccines were introduced in response to pandemic and epidemic emergencies have been taken into consideration for the development of this manual. For example, the 2009 H1N1 influenza pandemic demonstrated that few countries had a pandemic preparedness plan that comprehensively addressed vaccine deployment and monitoring of adverse events. Data from the American spontaneous reporting system, Vaccine Adverse Event Reporting System (VAERS), showed that the adverse event profile for the 2009-H1N1 vaccines was consistent with that of seasonal influenza vaccines, but with a higher reporting rate. However, many other countries were unable to provide timely information leading to lack of confidence in H1N1 vaccination which was challenging for vaccine uptake and communication. The 2014-2016 Ebola epidemic that affected countries in West Africa led to accelerated development of vaccines and therapeutics. The African Vaccine Regulatory Forum (AVAREF), a regional network of regulators and ethics committees, working closely with regulators from other parts of the world, participated in the review of clinical trial protocols and results, joint monitoring of trials and joint authorization and deployment of vaccines. This model can be used to guide

pharmacovigilance reliance for the deployment of COVID-19 vaccines, particularly in low- and middle-income countries with limited resources.

Past experiences have shown that public concerns about the safety of novel vaccines, real or due to 'fake news' or rumours, can arise and, therefore, there is a need for immunization programme managers to be ready to address these issues through appropriate vaccine safety surveillance and communication strategies.

3. Aims and objectives of this manual

In this manual we aim to provide guidance and recommendations to ensure that countries have preparedness plans for monitoring the safety of COVID-19 vaccines and communication strategies about COVID-19 vaccine safety before the vaccines are deployed. This guidance is for governments, global, regional and national staff from immunization programmes, regulatory authorities, ministries of health, partners and pharmacovigilance centres as well as vaccine manufacturers.

The objectives of this manual are to:

- provide an overview of COVID-19 vaccines likely to be available and their characteristics;
- identify the safety implications for the potential priority populations and immunization strategies;
- identify all stakeholders, including vaccine manufacturers, and provide guidance on how they can collaborate to ensure transparent collection, analyses and sharing of COVID-19 vaccine safety data;
- define the elements of COVID-19 vaccine pharmacovigilance preparedness and identify current capacities and gaps in countries;
- provide guidance for enhancing and harmonizing vaccine safety surveillance systems, to guide processes for collecting, analysing and sharing safety data and information, including data management systems;
- support evidence-based programmatic decisions related to COVID-19 vaccines; and
- provide guidance to support vaccine safety communication during COVID-19 pandemic.

4. Organization of the manual

For ease of use, the manual has been divided into nine modules that can be consulted individually or as a single document. Given the rapidly evolving landscape, the modules will be updated as frequently as needed. For this reason, only an online electronic version will be made available, with links to appropriate reference documents and regular updates to incorporate new information and evidence as the COVID-19 vaccines are deployed. Each module will be linked to a slide deck in an editable format that can be adapted and used for training purposes.

5. COVID-19 vaccines: description and general safety considerations for implementation

The candidate COVID-19 vaccines are being developed using five main vaccine platforms:

- inactivated viral vaccines
- live attenuated viral vaccines
- viral vector-based vaccines
- protein-based vaccines
- nucleic acid vaccines (mRNA and DNA)

Once safe and effective vaccines have been identified, the next enormous challenge will be reaching and safely vaccinating the world's 7.4 billion people. These novel vaccines have never been used in humans therefore safety data in dossiers submitted to national regulatory authorities should be carefully assessed before a vaccine is authorized. Initially, at least, COVID-19 vaccines are likely to be delivered in mass immunization campaigns, therefore it is essential that efficient vaccine safety surveillance systems are in place and implemented before the deployment of the vaccines.

These surveillance systems should be capable of identifying both known adverse events following immunization (AEFIs) reported in COVID-19 vaccine clinical trials, and potential rare adverse events in all age groups, particularly adults. Different immunization strategies will be used for urban and rural areas and for specific target populations, therefore AEFI detection, investigation and response strategies should be adapted to take these differences into account. Preparedness and staff training to strengthen local capacity to enable them to follow national guidelines or protocols for AEFI surveillance should be planned and implemented.

6. Stakeholders for safety surveillance of COVID-19 vaccines

Different COVID-19 vaccines will be produced and used in various settings and administered to large numbers of people in a short period. International collaboration will be essential to ensure that safety data are shared and pooled to be able to verify continued vaccine safety and effectiveness. COVID-19 vaccine safety surveillance will require broad and timely collaboration between national, regional and global stakeholders, therefore it is essential to identify these stakeholders and their responsibilities. These stakeholders will continue their regular pharmacovigilance activities and many will have additional activities, particularly during COVID-19 vaccine introduction. It will, therefore, be important for them to share data and information and to collaborate to ensure the efficient handling of COVID-19 vaccine safety surveillance.

7. Establishing COVID-19 vaccine surveillance systems

The role of vaccine safety surveillance during COVID-19 vaccine introduction is to facilitate the early detection, investigation and analysis of AEFIs and adverse events of special interest (AESIs) to ensure an appropriate and rapid response. The type and scope of vaccine safety surveillance activities that countries can undertake will depend on their available resources and the maturity of their existing surveillance systems. Nevertheless, they should aim to strengthen their activities before and during COVID-19 vaccine introduction.

Countries should prioritise and strengthen existing passive AEFI (spontaneous) reporting by adapting their established AEFI surveillance systems to address the specific challenges associated with COVID-19 pandemic, particularly to accommodate the large numbers of AEFI/AESI reports expected because of the numbers of people who will be vaccinated. There should be coordination between stakeholders to enable information sharing, including for any deaths reported for individuals with a history of COVID-19 vaccination. When possible, following up specific vaccinated cohorts for at least one year will enable potential longer-term vaccine-type specific AESIs to be detected, including vaccine-associated enhanced diseases (VAEDs). With the expected high media and public attention on COVID-19 vaccines, communication about any adverse events and response to public concerns should be rapid to maintain public confidence in the COVID-19 vaccination.

8. Monitoring and responding to adverse events following immunization (AEFIs)

Surveillance systems need to be prepared before COVID-19 vaccination is implemented. They need to have sufficient funding and resources for identifying and responding to AEFIs and AESIs as well as other safety events that may cause public concern, including incidents involving substandard or counterfeit vaccines.

Since AEFIs are untoward medical events following immunization, they do not necessarily have a causal relationship with the usage of the vaccine. In the COVID-19 vaccination context, it will be difficult to clearly distinguishing genuine vaccine product-related events from coincidental events or concomitant medication-related adverse events (AEs). Immunization programmes should anticipate and prepare for increased AEFI reports, including clusters of AEFI, as the chance of immunization errors and immunization anxiety-related reactions occurring is much higher than during routine immunization.

AEFI detection takes place primarily through routine passive surveillance (spontaneous reporting) which involves vaccine recipients, parents of immunized infants and children, health care workers and staff in immunization or health care facilities detecting the AEFIs and reporting them to any health care worker. Because it is possible that more than one COVID-19 vaccine will be in use simultaneously in a country, it is important that AEFI reports include the brand name, the manufacturer, as well as the batch numbers, in addition to standard information. Where possible, it is recommended to use existing data collection tools for data collection, collation and processing for AEFIs, that can be adapted, if necessary.

All countries must establish an AEFI causality assessment committee and a process for causality assessment prior to the introduction of COVID-19 vaccines. The committee should be pluri-disciplinary, including adult and elderly specialities, since COVID-19 vaccines will be administered to individuals of all ages. There should be a designated committee communication spokesperson responsible for communication about the AEFIs assessed by the committee, particularly with the media and other stakeholders.

9. Monitoring and responding to adverse events of special interest (AESIs)

Conventional vaccine safety surveillance systems will need to be enhanced rapidly in the context of COVID-19 vaccine deployment to ensure that the safety of the public is not put at risk. Shortlisting pre-specified AESIs before COVID-19 vaccine introduction will enable countries and regions to:

- define and monitor potential adverse events,
- define protocols,
- ensure the availability of suitable tools for their detection, investigation and analysis,
- provide training for relevant staff,
- identify disease codes, using an international or national coding system (e.g. [ICD-11](#)), and
- estimate background rates for the listed events.

Countries should have efficient passive surveillance systems for detecting AEFIs before envisaging the implementation of active vaccine surveillance systems (AVSS). Different methods can be used to collect data on COVID-19 vaccine-related AESIs including cohort event monitoring (CEM), sentinel surveillance, data linkage, m-Health and e-Health, depending on available expertise, resources and funding and type of data available for AVSS.

AVSS can be used to detect delayed AESIs, serious AESIs, AESIs in specific populations, and AESIs occurring during mass COVID-19 vaccination programmes. They should be identified, irrespective of exposure to COVID-19 vaccine, based on a pre-specified list, which will be unique for each country or region, and the diagnosis of each AESI case identified should match an approved case definition.

Comparing the incidence of the AESI in COVID-19 vaccinated and unvaccinated individuals will enable to ascertain if there is a potential association between the AESI and the COVID-19 vaccine product and if there is need for further specific studies to confirm such an association. The causality assessment committee should be trained to review population-based scientific data arising from the specific types of studies in the active surveillance systems. When signals are detected the vaccination programme, national regulatory authorities, the vaccine manufacturers and WHO should be informed so that they can consult other countries and global experts to determine if the signal warrants further verification through specific studies.

Although no AESIs specific to pregnant women, foetuses or neonates have been reported, because these populations are not included in clinical trials, when COVID-19 vaccines are deployed it will be essential to follow pregnancy outcomes with, for example, a registry so that follow-up can be maintained for any adverse outcomes to the mother, foetus or new-born.

Keeping the community and all stakeholders at all stages updated on the status of investigation, causality assessment and the outcomes will be critical to maintain confidence in the vaccination programme, the health system and the health authorities.

10. Safety data management systems, methods of post-introduction evaluation and assessing performance in countries using COVID-19 vaccines

Processing AEFI and AESI data and monitoring the performance of the vaccine safety surveillance system is important to ensure that the systems are working and functioning efficiently. Data sharing at all levels is important to increase and merge knowledge that can be used rapidly to inform decisions about COVID-19 vaccine introduction and continuation strategies. When sharing data, it is important to consider data confidentiality, data security, autonomy, sovereignty and benefits for those providing and sharing data. Routine vaccination will continue during COVID-19 vaccine deployment, therefore, vaccine safety surveillance systems will collect data for all vaccines, not just COVID-19 vaccines. Individual case safety reports (ICSRs) for AEFIs should be sent to the WHO global database, VigiBase, which contains ICSR from all Member States of the WHO Programme for International Drug Monitoring. This database can be used to detect signals and safety concerns at national, regional and global levels.

Safety data will also be available as aggregated data from various local databases and from ad hoc research. Data will have to be stored using agreed international standards, or data transformation will have to be performed to ensure compatibility for successful data sharing.

Post-introduction safety trials will be essential to continue to increase our knowledge about COVID-19 vaccine safety and efficacy, particularly in populations absent or underrepresented in pre-authorization clinical vaccine trials, such as children, the elderly and pregnant women. Various study designs can be used for post-introduction evaluation and as each has their own strengths and weaknesses, using different methods should be considered. In addition, the impact of changes in health care use and provision during the COVID-19 on reporting of adverse events of special interest should be assessed.

It is important for countries to plan to assess the performance of safety data, reporting and management.

11. Engaging with the pharmaceutical industry on COVID-19 vaccine safety

The pharmaceutical industry plays a critical role in the accelerated development of vaccines and therapeutics and in ensuring the safety of COVID-19 vaccines through safety surveillance activities described in risk management plans (RMPs) for authorized vaccines and through periodic safety update reports. Vaccine manufacturers are encouraged to adopt existing formats for COVID-19 vaccine RMPs, and these should contain essential elements, such as a safety specification section, pharmacovigilance activities, risk minimization activities, and evaluation of the effectiveness of the risk minimization measures.

Countries are encouraged to rely on RMPs assessed by the WHO prequalification programme or the reference regulatory agency. Effective data flow should be established between the national immunization programmes, national regulatory agencies (NRAs), the vaccine manufacturers, WHO prequalification team and Vigibase, the WHO global database of individual case safety reports, while respecting data security and patient privacy. Training to enhance pharmacovigilance competencies should be coordinated and existing training materials and programmes should be leveraged as much as possible.

12. Regulatory reliance and work-sharing

Regulatory reliance is the act whereby a NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institute, or any other authoritative information in reaching its own decision. Levels of regulatory reliance between NRAs can range from independent decisions by NRAs (no reliance) to mutual recognition (full reliance). Work-sharing is a process by which NRAs of two or more jurisdictions share activities to accomplish specific regulatory tasks. These both are particularly important for countries with limited regulatory capacity.

In the context of the current COVID-19 pandemic, regulatory reliance should be considered whenever possible. This will improve regulatory efficiency, thereby facilitate timely access to COVID-19 vaccines, as well as effective monitoring of COVID-19 vaccine safety issues and implementation of risk minimization measures. Work-sharing at the regional level will be an important mechanism for effective regulatory oversight. Activities that could be shared include review of risk management plans, use of common templates for post-authorization safety studies (PASSs), joint review of post-authorization safety data and pharmacovigilance inspections.

13. COVID-19 vaccine safety communication

Effective communication strategies about COVID-19 vaccine safety will play a key role in building and maintaining the public's confidence in vaccination. To be effective, the strategies should be planned and necessary resources allocated. Where possible, the communication strategy should be implemented prior to the deployment of COVID-19 vaccines to improve efficiency. Vaccine safety perceptions are complex, involving diverse factors, such as individual knowledge, attitudes and beliefs, social networks, messages about vaccine safety, the communication environment, cultural and religious influences, organization of health services and expectations created by political leaders. The goal of vaccine safety communication should be to empower individuals to make evidence-informed choices about COVID-19 vaccination and to encourage trust in health authorities and those delivering the vaccines, as well as facilitate access to timely, accurate and credible information about COVID-19 vaccination safety. Timely response and regular updates are key to avoid the development of information voids that might be filled by inaccurate information.

The communications team should be integrated into vaccine safety planning and decision-making activities to facilitate appropriate and proactive communication activities. It is important to identify and monitor for potential threats as an integral part of the communication strategy because a poorly managed incident concerning a COVID-19 vaccine safety issue will attract negative public attention. It will also be important to identify target audiences and tailor messages to them, while ensuring that the information remains the same to effectively communicate.

Partnerships should be established with other vaccine safety stakeholders to ensure coordinated information sharing and dissemination. Establishing relationships with journalists and engaging with them regularly is important. For instance, briefing them regularly, and supporting their information needs around vaccine safety issues and concepts, may help to reduce sensationalist reporting.

Social media should be used to communicate regularly to the public and give real-time updates about COVID-19 vaccine safety. Negative claims about COVID-19 vaccine safety are inevitable. Available resources, opportunity costs and the potential impact of the claim should be taken into consideration in the decision about the scale of response.

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

