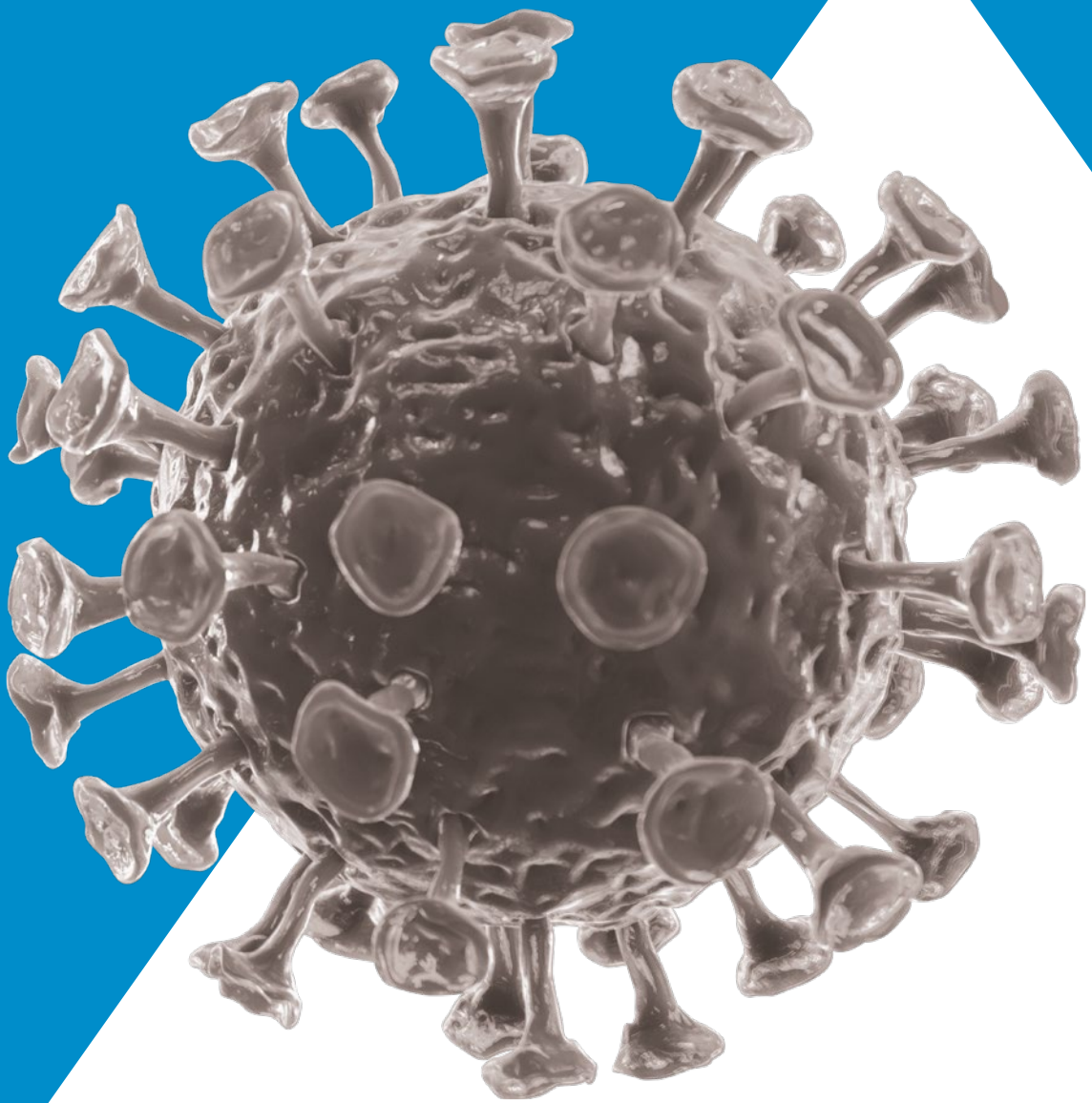
COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL



World Health Organization

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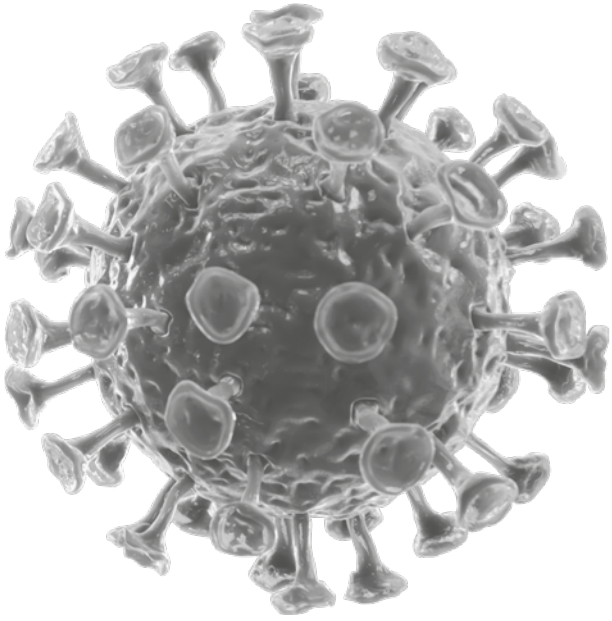

World Health Organization

Covid-19 vaccines: safety surveillance manual

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Abbreviations and acronyms

AACVS	African Advisory Committee on Vaccine Safety
ACE	Angiotensin-converting enzyme
ACT	Access to COVID-19 tools
ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
AVSS	Active vaccine safety surveillance
CEM	Cohort event monitoring
CEPI	Coalition for Epidemic Preparedness Innovations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
DCVMN	Developing Countries Vaccine Manufactures Network
DL	Data linkage
DNA	Deoxyribonucleic acid
EH	e-Health
EPI	Expanded programme on immunization
FIND	Foundation for Innovative New Diagnostics
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
GMP	Good manufacturing practices
GVAP	Global vaccine action plan
HCW	Health care worker
ICD	International classification of diseases
ICSR	Individual case safety report
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
ISoP	International Society of Pharmacovigilance
ISRR	Immunization stress-related response
MedDRA	Medical dictionary for regulatory activities
MH	m-Health
MoH	Ministry of Health
mRNA	Messenger RNA

NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
PASS	Post-authorization safety studies
PBRER	Periodic benefit-risk evaluation report
PHEIC	Public health emergency of international concern
PIDM	Programme for International Drug Monitoring
PSUR	Periodic safety update report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
RITAG	Regional Immunization Technical Advisory Groups
RMP	Risk management plan
RNA	Ribonucleic acid
SAGE	Strategic Advisory Group of Experts (for immunization)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SKG	Significant knowledge gap
SIA	Supplementary immunization activities
SS	Sentinel surveillance
TGA	Therapeutic Goods Administration (Australian Government Department of Health)
UMC	Uppsala Monitoring Centre (WHO Collaborating Centre for International Drug Monitoring)
VAED	Vaccine-associated enhanced disease
VLP	Virus-like particles
VPD	Vaccine preventable disease
WHO	World Health Organization

Glossary

Active safety surveillance	Active (or proactive) safety surveillance is an active system for the detection of adverse events. This is achieved by active follow-up after vaccination. Events can be detected by asking patients directly or by screening patient records. It is best done prospectively.
Adjuvant	A pharmacological or immunological agent added to a vaccine to improve its immune response.
Adverse event following immunization (AEFI): general definition	Any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
— AEFI by cause: coincidental events	— An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
— AEFI by cause: immunization anxiety-related reaction	— An AEFI arising from anxiety about the immunization (see immunization stress related responses).
— AEFI by cause: immunization error-related reaction	— An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, that, therefore, is preventable.
— AEFI by cause: vaccine product-related reaction	— An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
— AEFI by cause: vaccine-quality defect-related reaction	— An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Adverse event of special interest (AESI)	A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Causal association	A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally-associated events are also temporally associated (i.e. they occur after vaccine administration), but events that are temporally associated may not necessarily be causally associated.

Causality assessment	In the context of vaccine AEFI surveillance, a systematic review of data about the AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/ provider, health facility, and/or a vial of vaccine or a batch of vaccines.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/severe febrile illness.
Immunity	The ability of the human body to tolerate the presence of material 'indigenous' to the human 'body' (self) and to eliminate 'foreign' (non-self) material. This discriminatory ability provides protection from infectious diseases since most microbes are identified as foreign material by the immune system.
Immunization	Immunization is the process whereby a person is made immune or resistant to an infection, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection.
Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse event surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Immunization safety surveillance	A system for ensuring immunization safety through early detection, reporting, investigating, and quickly responding to AEFIs.
Immunization stress related responses (ISRR)	Stress response to immunization that may manifest just prior to, during, or after immunization.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g. transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Mass vaccination campaign	Mass vaccination campaigns involve administration of vaccine doses to a large population over a short period of time.
Non-serious AEFI	An event that is not 'serious' and does not pose a potential risk to the health of the recipient. Non-serious AEFIs should also be carefully monitored because they may signal a potentially larger problem with the vaccine or vaccination or have an impact on the vaccination acceptability; in general.

Risk management plan (RMP)	The risk management plan is a document established by the vaccine manufacturer that contains the following elements: (a) identification or characterization of the safety profile of the medicinal product(s) concerned; (b) indication of how to characterize the safety profile of the medicinal product(s) concerned further; (c) documentation of measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) documentation of post-authorization obligations that have been imposed as a condition of the marketing authorization.
Safe injection practice	Practices that ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.
Serious AEFI	An event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Severe vaccine reaction	Based on its intensity vaccine reactions can be mild, moderate or severe. The event itself, however, may be of relatively minor medical significance. Severe events do not have regulatory implications unless they are also serious.
Signal (safety signal)	Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
Surveillance	The continual, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.
Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation.
SAGE Values Framework	Values Framework, developed by WHO's SAGE, offers guidance globally on the allocation of COVID-19 vaccines between countries, and guidance nationally on the prioritization of groups for vaccination within countries while COVID-19 vaccine supply is limited.
Vaccine	A biological preparation that elicits immunity to a particular disease. In addition to the antigen, it can contain multiple components, such as adjuvants, preservatives, stabilizers, each of which may have specific safety implications.
Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.

Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or vaccination.
Vaccination failure	Vaccination failure can be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of sero-conversion or sero-protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate, i.e. an indicated vaccine was not administered appropriately for any reason or (ii) because the vaccine did not produce its intended effect.
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.
VigiBase	WHO global database of individual case safety reports (ICSRs) including ADRs and AEFIs, maintained by Uppsala Monitoring Centre.
VigiFlow	A web-based individual case safety report (ICSR) management system (E2B compatible) for medicines and vaccines, developed and maintained by Uppsala Monitoring Centre.

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 (PHEIC). By 12 March 2020, due to its rapid global spread, the outbreak was declared a pandemic. The pandemic has already caused the loss of more than 1.5 million lives[1] and disrupted the lives of billions more.

One essential strategy to control this pandemic is the rapid development of safe and effective vaccines. Unprecedented efforts are being made to develop large numbers of vaccines simultaneously, in a short time. Global equitable access to vaccines, particularly for protecting health care workers and those most-at-risk is one of the key strategies to mitigate the public health and economic impact of the pandemic.

The Access to COVID-19 Tools (ACT) Accelerator was launched at the end of April 2020 as a global collaboration to accelerate the development, production, and equitable access to COVID-19 diagnostic tests, treatments, and vaccines. This collaboration has brought together governments, scientists, businesses, civil society, and philanthropists and global health organizations (the Bill & Melinda Gates Foundation, CEPI, FIND, Gavi, The Global Fund, Unitaid, Wellcome, WHO, and the World Bank). The COVAX Facility offers participating countries secure access to safe and effective COVID-19 vaccines through its actively managed portfolio of vaccine candidates across a broad range of technologies. Its goal is to ensure equitable access to vaccines to all economies and ensure that income is not a barrier to access. The initial aim is to have 2 billion doses of vaccine available by the end of 2021.

The 42nd Global Advisory Committee on Vaccine Safety (GACVS) on 27–28 May 2020 addressed pharmacovigilance preparedness for the launch of the future COVID-19 vaccines. One of their recommendations was that 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 before a vaccine is introduced. This will require local, national, regional and global collaboration. Countries should include preparedness plans for COVID-19 vaccine safety in their overall plans for vaccine introduction, building on WHO guidance. This COVID-19 vaccine safety surveillance manual was developed following recommendations and guidance of the GACVS members, as well as experts from around the world. The manual incorporates current and available information that is critical for all stakeholders before, during and after the introduction of COVID-19 vaccines.

1 As of 8 December 2020, Source: https://covid19.who.int. accessed 8 December 2020.

2. Lessons learnt from novel vaccine introduction during pandemic and epidemic emergencies

Key lessons learnt from past situations where 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.[2,3] When adverse events were reported, some systems were unable to provide timely information about the potential association of events with H1N1 vaccination leading to lack of confidence in H1N1 vaccination which was challenging for vaccine uptake and communication.[4,5]

The 2014-2016 Ebola epidemic that affected three countries in West Africa led to accelerated development of vaccines and therapeutics. The African Vaccine Regulatory Forum, 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, the joint monitoring of trials and the joint authorization and deployment of vaccines.[6,7] Such models can be used to guide pharmacovigilance reliance for the deployment of COVID-19 vaccines, particularly in low- and middle-income countries (LMICs) with limited resources.

Pregnant women seem to be disproportionately affected during pandemics and emerging pathogen outbreaks, and were among the highest risk groups in the 2009 influenza pandemic and the 2014-2016 Ebola epidemic.[8,9] The Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) working Group, a multidisciplinary, international team of 17 experts, in consultation with external experts and stakeholders, have published a roadmap

2 World Health Organization. Main operational lessons learnt from the WHO pandemic influenza A(H1N1) vaccine deployment initiative. Available from: https://apps.who.int/iris/handle/10665/44711. Accessed 26 October 2020.

3 European Medicines Agency. Pandemic report and lessons learned: outcome of the European Medicines Agency's activities during the 2009 (H1N1) flu pandemic. Available from: https://www.ema.europa.eu/documents/report/pandemic-report-lessons-learned-outcome-european-medicines-agencys-activities-during-2009-h1n1-flu_en.pdf. Accessed 26 October 2020.

4 Sturkenboom MC. The narcolepsy-pandemic influenza story: can the truth ever be unravelled? Vaccine. 2015;33(Suppl 2):B6-B13. doi: 10.1016/j.vaccine.2015.03.026.

5 Ropero-Álvarez AM, Whittembury A, Bravo-Alcántara P, Kurtis HJ, Danovaro-Holliday MC, Velandia-González M. Events supposedly attributable to vaccination or immunization during pandemic influenza A (H1N1) vaccination campaigns in Latin America and the Caribbean. Vaccine. 2015 Jan 1;33(1):187-92. doi: 10.1016/j.vaccine.2014.10.070.

6 Akanmori B, Bellah A, Ward M, Rägo L. The African Vaccine Regulatory Forum (AVAREF): A platform for collaboration in a public health emergency. WHO Drug Information 2015;29(2):127-132.

7 Kieny MP, Rägo L. Regulatory policy for research and development of vaccines for public health emergencies, Expert Rev Vaccines 2016;15(9):1075-1077. doi: 10.1080/14760584.2016.1188695.

8 Creanga AA, Johnson TF, Graitcer SB, Hartman LK, Al-Samarrai T, Schwarz AG, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstet Gynecol. 2010;115(4):717–26. doi: 10.1097/AOG.0b013e3181d57947.

9 Menéndez C, Lucas A, Munguambe K, Langer A. Ebola crisis: the unequal impact on women and children's health. Lancet Glob Health. 2015;3(3):e130. doi: 10.1016/S2214-109X(15)70009-4.

to guide the inclusion of the interests of pregnant women in the development and deployment of vaccines against emerging pathogens.[10]

The introduction of the first licensed dengue vaccine, while not in the context of an international public health emergency, illustrated a number of lessons for the pharmacovigilance of novel vaccines, particularly the vaccine-associated enhanced disease (VAED) that was observed. It is essential to prepare to manage VAED, which could be potentially induced by some of the COVID-19 vaccine candidates being developed.[11,12]

A common theme in these examples is the public concerns about the safety of the novel vaccines and rumours or adverse events that can arise during current and future pandemics. Hence there is a need for programme managers to be ready to address these issues through appropriate vaccine safety surveillance and communication strategies.

3. Objectives of this manual

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;[13]
- provide guidance on how the stakeholders can collaborate to ensure transparent collection, analyses and sharing of COVID-19 vaccine safety data;
- define the elements of COVID-19 vaccine pharmacovigilance preparedness;
- 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.

10 The PREVENT Working Group. Pregnant women & vaccines against emerging epidemic threats: ethics guidance on preparedness, research & response. 2018. Available from: http://vax.pregnancyethics.org/prevent-guidance. Accessed 17 November 2020.

11 Flasche S, Wilder-Smith A, Hombach J, Smith PG. Estimating the proportion of vaccine-induced hospitalized dengue cases among Dengvaxia vaccinees in the Philippines. Wellcome Open Res. 2019 Oct 31;4:165. doi: 10.12688/wellcomeopenres.15507.1.

12 Dayrit MM, Mendoza RU, Valenzuela SA. The importance of effective risk communication and transparency: lessons from the dengue vaccine controversy in the Philippines. J Public Health Policy. 2020 Sep;41(3):252-267. doi: 10.1057/s41271-020-00232-3.

13 For the purpose of this document, manufacturer also means marketing authorization holder.

4. Intended audience

This manual provides relevant guidance prior to, during and after COVID-19 vaccine introduction for governments, global, regional and national staff from immunization programmes, regulatory authorities, ministries of health, partners and pharmacovigilance centres as well as vaccine manufacturers.

5. Organization of the manual

This manual has been developed on the principles described in the Global vaccine safety blueprint[14], the WHO's Global manual on surveillance of adverse events following immunization[15] and the CIOMS guide to active vaccine safety surveillance.[16]

For ease of use the manual has been divided into an executive summary and nine modules (see below) which can be consulted individually. The modules contain hyperlinks to relevant sections of other modules.

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 that can be used for training purposes.

6. Scope of the manual

The modules included in this manual are:

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

This module provides a brief description about the different COVID-19 vaccines that are being developed, their platforms, technologies, development and licensing status, and their unique safety features and potential risks. It also highlights the safety implications for implementing immunization programmes for priority target populations.

14 World Health Organization. Global vaccine safety blueprint 2.0 (GVSB2.0). Available from: https://www.who.int/vaccine_safety/gvs_blueprint-consultation/en/. Accessed 26 October 2020.

15 World Health Organization. Global manual on surveillance of adverse events following immunization. Available from: https://www.who.int/vaccine_safety/publications/aefi_surveillance/en/. Accessed 26 October 2020.

16 CIOMS guide to active vaccine safety surveillance. Available from: https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/. Accessed 26 October 2020.

6.2 Stakeholders in COVID-19 vaccine safety surveillance

This module lists the various stakeholders, their roles and responsibilities in COVID-19 vaccine safety surveillance and pharmacovigilance, at the global, regional and national levels. It also provides guidance on how the stakeholders could collaborate to ensure the efficient handling of COVID-19 vaccine safety surveillance and pharmacovigilance.

6.3 Establishing surveillance systems in countries using COVID-19 vaccines

This module provides a list of the minimum requirements that should be in place to effectively monitor and manage COVID-19 vaccine safety issues and the resources required at global, regional and national levels in terms of tools, techniques, technologies and guidance. It defines what is meant by pharmacovigilance preparedness, and provides guidance for preparedness, planning and prioritization.

6.4 Monitoring and responding to adverse events following immunization (AEFIs)

This module outlines the minimal approaches that countries should have in place for detecting, handling and responding to adverse events following COVID-19 immunization (AEFIs) and also the additional approaches that countries with more resources can undertake. It describes the practical differences for establishing COVID-19 vaccine safety surveillance system based on the types of vaccine platforms, different population profiles, handling high number of AEFI reports and the need to anticipate new events not previously seen during vaccine clinical trials.

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

This module introduces the concept of adverse events of special interest (AESIs) which is a novel concept for many countries and regulatory agencies. It provides guidance on the selection and definition of these events. The need to prepare data on background rates of adverse events of special interest and to implement active surveillance for these events is discussed.

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

The module describes the different approaches and options available for collecting data using the tools available (some of which are still under development), the routing, timelines and the activities to be done at various levels when processing the data and generating information for action. It presents an overview of the approaches undertaken by countries and their efforts to share vaccine safety and pharmacovigilance data. Post-introduction safety trials will be essential to continue to increase 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. The various study designs that can be used for post-introduction evaluation are described. Guidance is provided to show how indicators to measure the functionality of data management systems and the quality of the pharmacovigilance could help programme managers at national, province and district levels.

6.7 Engaging with the pharmaceutical industry for COVID-19 vaccine safety surveillance

This module describes the essential role played by the pharmaceutical industry, in the development and introduction of vaccines, as well as in on-going pharmacovigilance activities to ensure efficacy, quality and safety throughout the vaccines' life cycle. The module provides guidance on transparent collaboration between the public and private sectors to ensure the safe and effective deployment of COVID-19 vaccines.

6.8 Regulatory reliance and work-sharing

This module provides definitions of regulatory reliance and work-sharing and presents some examples of how these approaches have been used. Guidance on how these approaches could be used for developing COVID-19 vaccine safety surveillance systems, particularly in resource-poor settings, is presented.

6.9 COVID-19 vaccine safety communication

This module provides recommendations for risk communication for COVID-19 vaccines from a programme perspective. It includes a description of factors that influence people's perceptions of vaccine safety. Case studies of past experiences with previous pandemics or vaccine safety issues are briefly presented to illustrate communication needs and solutions. A synthesis of evidence and recommendations for communication from risk communication is provided. Hypothetical scenarios where COVID-19 vaccine safety communication could be needed are presented with examples of how the recommendations in the module could be used to provide solutions. Finally, criteria on how responses to COVID-19 vaccine safety issues can be efficiently prioritized.

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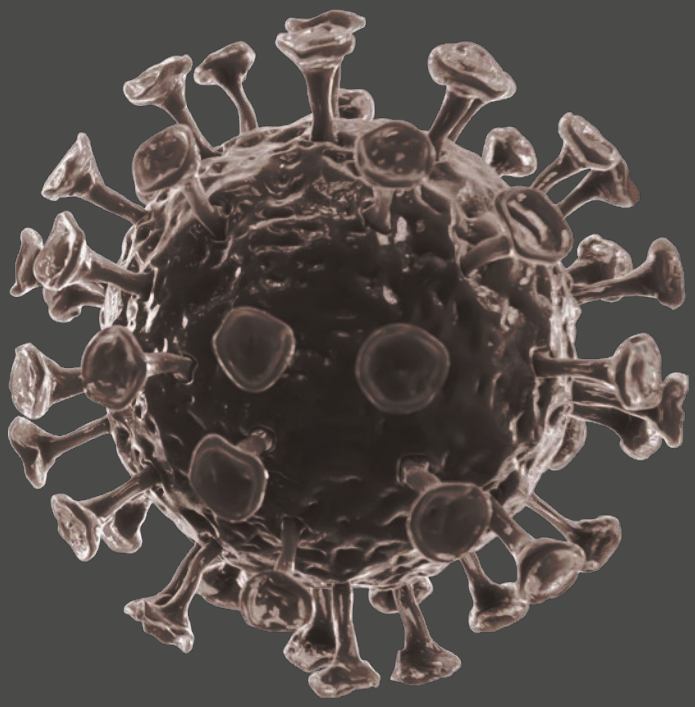
SAFETY SURVEILLANCE MANUAL

COVID-19 VACCINES: DESCRIPTION AND GENERAL SAFETY CONSIDERATIONS FOR IMPLEMENTATION



Contents

Key points

- 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
- When safe and effective vaccines have been identified and authorized by national regulatory authorities, the next challenge will be reaching and vaccinating the world's 7.4 billon people
- COVID-19 vaccines are novel vaccines that have never been used in humans on a large scale, therefore close safety monitoring post authorization should be carefully conducted to continue to assess the safety profile of each vaccine
- Adverse event following immunization (AEFI) surveillance systems should be capable of identifying both known AEFIs seen in clinical trials as well as new events, including potential rare serious adverse reactions in all age groups, particularly adults
- Clinics or settings that care for adults may not be familiar with AEFI reporting processes
- Adults, especially the elderly, have more comorbid conditions than children and, therefore, a higher incidence of coincidental AEFIs should be anticipated
- Different approaches for immunization strategies will be use in urban and rural areas and for different populations and, therefore, AEFI detection, investigation and response strategies should be adapted to take these differences into account
- Specific COVID-19 vaccine AEFI surveillance as outlined in this manual should be implemented before COVID-19 immunization programmes are implemented
- Preparedness and basic training of staff to follow national guidelines or protocols for AEFI surveillance and, therefore, strengthen local capacity, should be planned

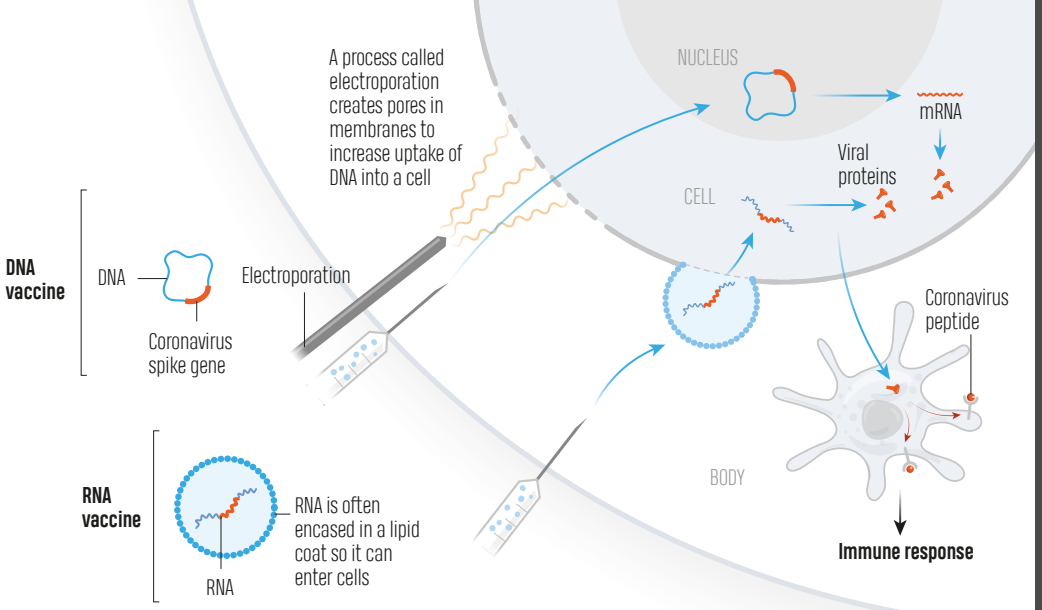
01 Introduction

With the early availability of the full sequence of the SARS-CoV-2 genome, developing a vaccine that could help countries to bring citizens' lives back to normal is the highest priority for the global community. It is critical that vaccines are both effective and safe and can be manufactured in sufficient quantities to ensure that they are available globally. As of 12 November 2020, 258 candidate vaccines are in different stages of development: 205 in preclinical studies; 43 in phase I/II clinical studies; and 11 in phase III studies. Information on candidate COVID-19 vaccines under development is regularly updated by the London School of Hygiene and Tropical Medicine and WHO.

In addition to some traditional approaches to designing vaccines, some relatively new platforms for SARS-CoV-2 vaccines are being tested.[1] **Fig 1** summarizes the four types of platform being explored.

1 Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020 May;19(5):305-306. doi: 10.1038/d41573-020-00073-5.

Fig 1: Landscape of platforms used for COVID-19 vaccines



VIRUS VACCINES

At least seven teams are developing vaccines using the virus itself, in a weakened or inactivated form. Many existing vaccines are made in this way, such as those against measles and polio, but they require extensive safety testing. Sinovac Biotech in Beijing has started to test an inactivated version of SARS-CoV-2 in humans.

Weakened virus
A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. Codagenix in Farmingdale, New York, is working with the Serum Institute of India, a vaccine manufacturer in Pune, to weaken SARS-CoV-2 by altering its genetic code so that viral proteins are produced less efficiently.

Inactivated virus
In these vaccines, the virus is rendered uninfectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus.

NUCLEIC-ACID VACCINES

At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus's spike protein.

RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.

VIRAL-VECTOR VACCINES

Around 25 groups say they are working on viral-vector vaccines. A virus such as measles or adenovirus is genetically engineered so that it can produce coronavirus proteins in the body. These viruses are weakened so they cannot cause disease. There are two types: those that can still replicate within cells and those that cannot because key genes have been disabled.

Replicating viral vector (such as weakened measles)
The newly approved Ebola vaccine is an example of a viral-vector vaccine that replicates within cells. Such vaccines tend to be safe and provoke a strong immune response. Nevertheless, existing immunity to the vector could blunt the vaccine's effectiveness.

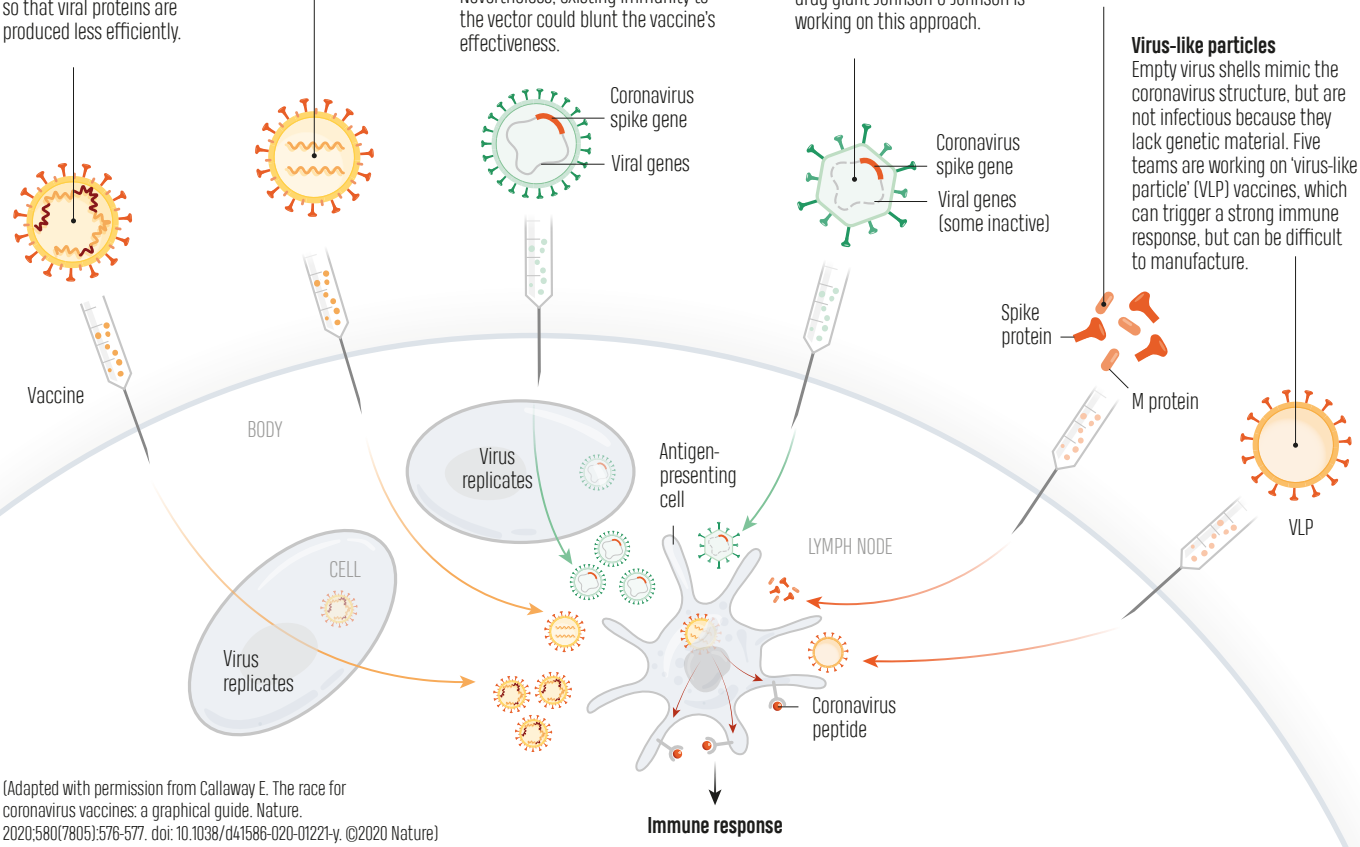
Non-replicating viral vector (such as adenovirus)
No licensed vaccines use this method, but they have a long history in gene therapy. Booster shots can be needed to induce long-lasting immunity. US-based drug giant Johnson & Johnson is working on this approach.

PROTEIN-BASED VACCINES

Many researchers want to inject coronavirus proteins directly into the body. Fragments of proteins or protein shells that mimic the coronavirus's outer coat can also be used.

Protein subunits
Twenty-eight teams are working on vaccines with viral protein subunits – most of them are focusing on the virus's spike protein or a key part of it called the receptor binding domain. Similar vaccines against the SARS virus protected monkeys against infection but have not been tested in people. To work, these vaccines might require adjuvants – immune-stimulating molecules delivered alongside the vaccine – as well as multiple doses.

Virus-like particles
Empty virus shells mimic the coronavirus structure, but are not infectious because they lack genetic material. Five teams are working on 'virus-like particle' (VLP) vaccines, which can trigger a strong immune response, but can be difficult to manufacture.



(Adapted with permission from Callaway E. The race for coronavirus vaccines: a graphical guide. Nature. 2020;580(7805):576-577. doi: 10.1038/d41586-020-01221-y. ©2020 Nature)

02 General safety considerations for viral vaccines

2.1 Inactivated viral vaccines

Some of the safety issues that may need to be considered for inactivated COVID-19 vaccines include incomplete inactivation of viral particles causing the vaccine to retain virulence and cause disease, and development of vaccine-associated enhanced disease (VAED) when vaccinated individuals encounter the pathogen after being vaccinated.[2,3] Although, VAED has not been reported for any of the COVID-19 vaccines, the theoretical risk is higher with inactivated vaccines because they contain proteins that are not involved in neutralization. Some of the vaccine additives used can also cause adverse events. Differences in risks between inactivated viral vaccines candidates could be due to differences in the adjuvants used. For example, some inactivated vaccines use a cytosine-phosphate-guanine (CpG) segment which is a bacterial DNA molecule that enhances immune response,[4] that could have specific risks related to the bacterial source.

2.2 Live-attenuated viral vaccines

As of 12 November 2020, there is one weakened or live-attenuated[5,6] COVID-19 candidate vaccines, generated by a genetic process called codon deoptimization, in clinical evaluation, and three vaccine candidates in the preclinical phase. Codon deoptimization involves replacement of commonly used codons with nonpreferred codons, which can dramatically decrease gene expression.[7] These candidate vaccines are based on attenuated versions of the wild type SARS-CoV-2 virus. One inherent problem of live-attenuated vaccines is that they can revert to the virulent strain but the risk is considerably minimized because usually more than one mutation is introduced.

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2 Sanders B, Koldijk M, Schuitemaker H. Inactivated viral vaccines. In: Vaccine analysis: strategies, principles, and control. Eds. Nunnally BK, Turula VE, Sitrin RD. Springer-Verlag Berlin Heidelberg. 2015: 45–80. doi: 10.1007/978-3-662-45024-6_2.

3 Kochhar S, Excler JL, Kim D, Robertson JS, Fast PE, Condit RC, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of inactivated viral vaccines. Vaccine. 2020 Sep 3;38(39):6184-6189. doi: 10.1016/j.vaccine.2020.07.028.

4 Weiner GJ, Liu HM, Wooldridge JE, Dahle CE, Krieg AM. Immunostimulatory oligodeoxynucleotides containing the CpG motif are effective as immune adjuvants in tumor antigen immunization. Proc Natl Acad Sci U S A. 1997;94(20):10833-7. doi: 10.1073/pnas.94.20.10833.

5 Minor PD. Live attenuated vaccines: Historical successes and current challenges. Virology. 2015;479-480:379-92. doi: 10.1016/j.virol.2015.03.032.

6 Gurwith M, Condit RC, Excler JL, Robertson JS, Kim D, Fast PE, et al. Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) standardized template for collection of key information for benefit-risk assessment of live-attenuated viral vaccines. Vaccine 2020 Nov 17;38(49):7702-7707. doi: 10.1016/j.vaccine.2020.09.042.

7 Zhou J, Liu WJ, Peng SW, Sun XY, Frazer I. Papillomavirus capsid protein expression level depends on the match between codon usage and tRNA availability. J Virol. 1999 Jun;73(6):4972-82. doi: 10.1128/JVI.73.6.4972-4982.1999.

2.3 Viral vector-based vaccines

Some COVID-19 vaccines are being developed using viral vectors, such as chimpanzee adenovirus, Sendai virus, modified vaccinia Ankara, parainfluenza and influenza viruses, measles, rabies, vesicular stomatitis virus. These vaccines are developed by introducing the genetic sequence coding for the antigen from the pathogen into a viral vector that has been previously rendered non-virulent by genetic techniques. In the past, vesicular stomatitis virus (VSV) and adenovirus have been used as vector for Ebola vaccines[8] and in clinical trials with vaccines for Middle East respiratory syndrome (MERS) coronavirus, showing that these vaccines are well tolerated.[9] Some viral-vector-based vaccines can replicate in the host cell (replicating viral-vector vaccines), such as the recently approved Ebola vaccine,[10] and some vectors do not replicate in the host cells (non-replicating viral vector vaccines), depending on the modifications introduced into the vector genome.

Understanding the potential risks related to such vaccines requires knowledge of their main components, the biology of the source virus, its wild-type behaviour and pathogenesis and the presence of pre-existing anti-vector immunity. Also, the behaviour of the genetically modified version (the vector) and the immunogenicity and pathogenesis of the specific vaccine should all be taken into consideration.[11]

A theoretical risk of mutagenesis due to DNA integration into the host genome exists,[12] as well as a very low potential risk of the return of the vector's original virulence. In addition, there is a risk of loss of the genetic material coding for the antigen during the manufacturing process which would result in vaccine failure.[13]

2.4 Protein-based vaccines

Viral antigenic proteins, produced using recombinant techniques, can be used to generate a response similar to that generated with the wild-type virus. These proteins may need to be combined with adjuvants to generate an acceptable immune response. The surface spike protein from the SARS-CoV-2 virus is the main target for this approach. Candidate vaccines

8 Li JX, Hou LH, Meng FY, Wu SP, Hu YM, Liang Q, et al. Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Glob Health. 2017 Mar;5(3):e324-e334. doi: 10.1016/S2214-109X(16)30367-9.

9 Folegatti PM, Bittaye M, Flaxman A, Lopez FR, Bellamy D, Kupke A, et al. Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial. Lancet Infect Dis. 2020;20(7):816–26. doi: 10.1016/S1473-3099(20)30160-2.

10 First vaccine to protect against Ebola. 2019.. Available from: https://www.ema.europa.eu/en/news/first-vaccine-protect-against-ebola. Accessed 17 November 2020.

11 Condit RC, Kim D, Robertson JS, Excler JL, Gurwith M, Monath TP, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of viral vector vaccines. Vaccine. 2020 Sep 6;S0264-410X(20)31030-6. doi: 10.1016/j.vaccine.2020.08.009.

12 European Medicines Agency. Guideline on quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines. London, UK: EMA; 2010. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-live-recombinant-viral-vectored-vaccines_en.pdf. Accessed 18 October 2020.

13 Bull JJ, Nuismer SL, Antia R. Recombinant vector vaccine evolution. PLoS Comput Biol. 2019;15(7):e1006857. doi: 10.1371/journal.pcbi.1006857.

have different molecular structures for the antigenic protein, use different adjuvants and are produced using different processes to enhance their efficacy. Some of these proteins may be assembled into a virus-like particles (VLP), which are empty viral shells that mimic the wild virus structure but are not infectious as they contain no genetic material.[11,14]

The type of safety assessment for these protein-based vaccines depends on the type of protein used (e.g. Protein S, M or N, dimeric, monomeric), the type of immune response (e.g. Th1/2), the production system and also the final composition of the vaccine (i.e. adjuvants, stabilizers). The use of different components could explain differences in safety profiles for these vaccines.

2.5 Nucleic acid vaccines

Adverse events following immunization (AEFI) could be associated with the nucleotide sequence of the antigenic gene, the surrounding sequences or promoters, the source of the plasmid and the nature of the microorganism and its origin.[15] The main theoretical risks are immune-mediated events, local and systemic reactions due to pro-inflammatory properties of the plasmids carrying the DNA sequence or the mRNA segment.[16]

2.5.1 mRNA vaccines

These vaccines are based on mRNA coding for an antigenic protein that is generated in vitro and encased with suitable material (e.g. lipid-based nanoparticle emulsion) that assures the delivery into the cell. The potential for integration into host cell DNA poses a theoretical risk; however, studies to date have shown that no retrovirus elements are available for their reverse transcription into DNA.[17,18] mRNA has been shown to stimulate innate immunity, therefore immune-mediated adverse events are also possible with this type of vaccine. Residual molecules, originating from raw materials, could induce unexpected immune responses.[18]

2.5.2 DNA vaccines

The nucleic-acid segment is integrated into a bacterial plasmid carrier that contains the encoding segment for the antigen, plus a promoter and other residual segments from the virus or bacteria of origin. Although the integration of the DNA into the host cell DNA

14 Syomin BV, Ilyin YV. Virus-like particles as an instrument of vaccine production. Mol Biol. 2019;53(3):323-334. doi: 10.1134/S0026893319030154.

15 Kim D, Robertson JS, Excler JL, 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 Jul 22;38(34):5556-5561. doi: 10.1016/j.vaccine.2020.06.017.

16 Myhr AI. DNA vaccines: Regulatory considerations and safety aspects. Curr Issues Mol Biol. 2017;22:79-88. doi: 10.21775/cimb.022.079.

17 Stenler S, Blomberg P, Smith CIE. Safety and efficacy of DNA vaccines: plasmids vs. minicircles. Hum Vaccin Immunother. 2014;10(5):1306-8. doi: 10.4161/hv.28077.

18 Liu MA. A comparison of plasmid DNA and mRNA as vaccine technologies. Vaccines (Basel). 2019;7(2):37. doi: 10.3390/vaccines7020037.

is a potential risk, none of the human or animal studies assessing these vaccines have reported integration.[19,20]

2.6 Characteristics and safety profile of COVID-19 vaccine candidates

The COVID-19 vaccine candidates are novel vaccines that have never been used in humans on a large scale. All currently available information has been provided by the vaccine manufacturers during clinical trials. Dossiers containing safety data that are submitted to national regulatory authorities should be carefully assessed before the vaccine is approved (authorized) for use in a country or region. The summary of product characteristics of vaccines authorized for use by the WHO prequalification process are accessible on the WHO platform for prequalified vaccines.

The number of individuals exposed to vaccines during clinical trials is limited and their profiles do not represent the broader spectrum of individuals who will be the actual vaccine recipients when the vaccine is commercialized. For example, safety information concerning vaccination and pregnancy is rarely available at the time of vaccine licensure. As with other newly licensed vaccines, it is unlikely that rare AEFIs, particularly those that are unique to specific populations, will be known when the COVID-19 vaccines are licensed. It is strongly recommended that high quality national or regional surveillance systems capable of identifying both known AEFIs seen in clinical trials and new adverse events, including potential rare adverse events are implemented to ensure that any safety issues are detected in a timely fashion.

Since 24 August 2020, the London School of Hygiene and Tropical Medicine has been maintaining a living review that summarises the available clinical trial data on different COVID-19 vaccine candidates. For this they perform a weekly search of medRxiv and PubMed to identify publications reporting outcome data from human clinical trials of COVID-19 vaccine candidates from which they extract immunogenicity and safety data. As of 4 December 2020, they have identified 116 clinical trials. Updated information can be consulted via the link above.

The Brighton Collaboration has developed Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) safety templates for each of the major COVID-19 vaccine platform technologies (nucleic acid, protein, viral vector, inactivated and live-attenuated viral vaccines). WHO's Global Advisory Committee on Vaccine Safety (GACVS) recommends vaccine developers to use these safety templates, which provides a structured approach for evaluating safety, to facilitate scientific exchange among key stakeholders.[21]

19 Ledwith BJ, Manam S, Troilo PJ, Barnum AB, Pauley CJ, Griffiths TG, et al. Plasmid DNA vaccines: investigation of integration into host cellular DNA following intramuscular injection in mice. Intervirology. 2000;43(4–6):258–72.

20 Sheets RL, Stein J, Manetz TS, Duffy C, Nason M, Andrews C, et al. Biodistribution of DNA plasmid vaccines against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile virus is similar, without integration, despite differing plasmid backbones or gene inserts. Toxicol Sci. 2006;91(2):610–9. doi: 10.1093/toxsci/kfj169.

21 Global Advisory Committee on Vaccine Safety (GACVS). Pharmacovigilance preparedness for launch of a COVID-19 vaccine. WER. 2020;95(28):330-33.

03 Safety implications for implementing immunization programmes

Many manufacturers are racing to develop safe and effective COVID-19 vaccines, based on diverse platforms. When suitable safe and effective vaccines are identified the next enormous challenge will be the task of reaching and vaccinating the world's 7.4 billon people. In addition to monitoring safety in those vaccinated, there are also significant safety considerations related to bulk production, licensing, shipping, cold chain capacity, distribution, storage, communication with stakeholders and vaccine administration in large heterogenous populations.

3.1 Prioritising populations for COVID-19 vaccination

When the initial COVID-19 vaccination programmes are initiated there will be limited supplies of the COVID-19 vaccines. Hence, a strategy to prioritize the allocation of available COVID-19 vaccines between countries and between populations will be needed. WHO's Strategic Advisory Group of Experts (SAGE), has developed guidance for the allocation of COVID-19 vaccines between countries, and for the prioritization of groups to be vaccinated within countries, while supply is limited.[22] In addition, a 'roadmap' that proposes public health strategies and target priority groups in different epidemiological settings and for different levels of vaccine availability has been developed by WHO's SAGE to support countries in their planning for prioritizing use of COVID-19 vaccines.[23]

Fig 2 shows that the potential priority target groups include adults such as frontline workers in health care settings, other individuals who are likely to be exposed and spread virus, adults over 65 years old and adults under 65 years old who have underlying conditions that are at a higher risk of mortality. Pregnant women warrant specific consideration, as they were disadvantaged with respect to the development and deployment of vaccines in previous pandemics. Evidence is emerging that pregnant women are at elevated risk of serious COVID-19 disease, which is further increased if they have pre-existing comorbidities. There may also be an elevated risk of adverse pregnancy and birth outcomes. Also several groups prioritized in the roadmap, including health care workers and teachers, are in age groups likely to include significant numbers of women who are pregnant, even if they are unaware of the pregnancy status when they are vaccinated.

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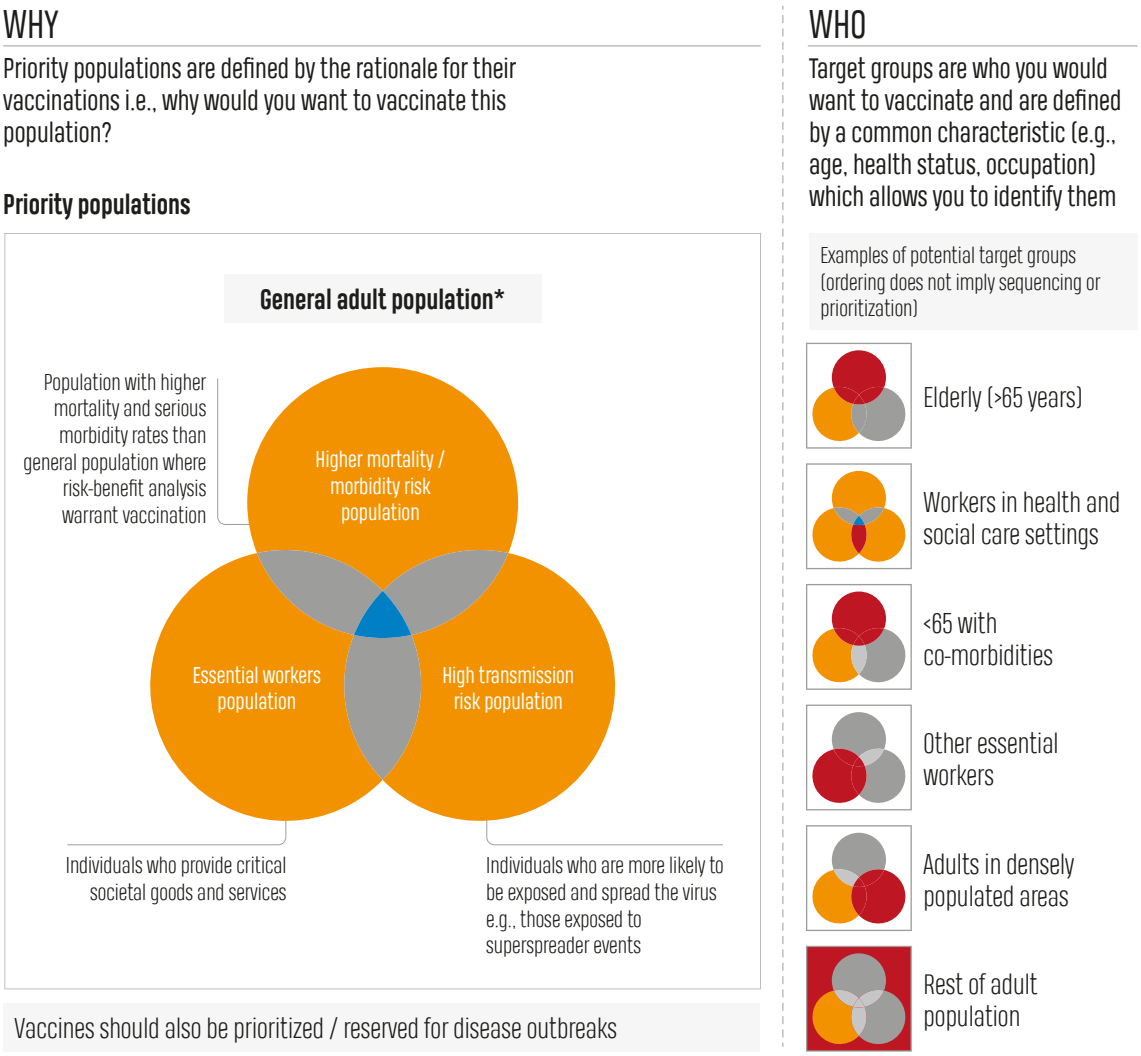
22 WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination, 14 September 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/334299/WHO-2019-nCoV-SAGE_Framework-Allocation_and_prioritization-2020.1-eng.pdf?ua=1&ua=1. Accessed 19 October 2020

23 Strategic Advisory Group of Experts on Immunization (SAGE). COVID-19 materials. Available from: https://www.who.int/immunization/sage/covid-19_documents/en/. Accessed 30 October 2020.

Fig 2: Potential priority populations for COVID-19 vaccination



** Non-adult populations require further consideration*

3.2 Potential safety implications related to prioritization

3.2.1 Safety implications in priority target populations

Clinics or settings that care for adults may not be familiar with AEFI reporting processes as vaccines are more generally administered to children. Adults, especially the elderly, have more comorbid conditions than children and, therefore, a higher incidence of coincidental AEFIs should be anticipated. Therefore, AEFI surveillance systems should ensure that they can capture AEFIs in all age groups, particularly adults.

COVID-19 vaccine interactions with medications, other vaccines and other products used by potential vaccine recipients are currently unknown. This may be a concern, particularly for older individuals who often take medications for underlying conditions.

Health care workers (HCWs) will be among the priority target groups when vaccines become available and this population includes many women, some of whom will be in the reproductive

age group. These women may be unaware of their pregnancy status when they receive the vaccine. Surveillance systems will need to consider specific processes to monitor the safety of COVID-19 vaccines administered inadvertently or not to pregnant and lactating women.

3.2.2 Safety implications for immunization programmes

Immunization programmes must ensure training of HCWs to avoid immunization error-related reactions and ensure administration of COVID-19 vaccines as recommended in the product information leaflet. Immunization strategies in urban and rural areas and in special populations will use different approaches, and therefore AEFI detection, investigation and response strategies should be adapted to take these differences into account.

Some vaccines schedules may require two or more doses per person at specified time intervals. As there is currently no information on the interchangeability of the vaccines, subsequent doses of the same vaccine should be delivered to the vaccine recipients at the correct interval. In addition, immunization programmes need to ensure **accurate recording of the brand name and batch number of the COVID-19 vaccine** given to each individual. This will require accurate tracking of which specific COVID-19 vaccine was received by each vaccinee. Ideally this be done via two-dimensional (2-D) barcodes. This means COVID-19 vaccines will need to be shipped with 2-D barcodes that can be scanned and linked digitally to immunization information systems (with paper backup for digital divided locations). Since few low- and middle-income country settings are currently doing this for routine vaccines, national regulatory agencies, vaccine manufacturers,[24] and expanded programmes on immunization or national immunization programmes (EPIs/NIPs) will need to work together to pioneer these processes for COVID-19 vaccines.

3.2.3 Safety implication for vaccine pharmacovigilance

All COVID-19 vaccines used in countries should be authorized for use by the national regulatory authorities. Countries with inadequate regulatory capacity may use COVID-19 vaccines prequalified by WHO or on their emergency use listing.

National regulatory authorities should review the risk management plan (RMP) submitted by vaccine manufacturers at the time of licensure and country surveillance systems should be prepared for detecting AEFIs. Surveillance for the list of events selected by countries/regions as adverse events of special interest (AESIs) should be conducted in accordance with standard guidelines.

National AEFI committees for AEFI review and causality assessment should be established or strengthened to ensure capacity to evaluate AEFIs in adults and individuals with underlying medical conditions.

Larger volumes of AEFI reports than usual should be anticipated, as vaccines will be given to a larger proportion of the population than those included in routine immunization programmes, many of whom may have one or more co-morbidities. Also, the level of awareness of the public

24 For the purpose of this document, manufacturer also means marketing authorization holder

and HCWs may be increased by the media attention and this could result in higher levels of reporting of adverse events, including many known and non-serious AEs.

Data collation on AEFIs and transmission to the WHO global pharmacovigilance database, VigiBase[25], using standard procedures, should be done to ensure timely global signal detection.

3.3 Immunization strategies during COVID-19 vaccine introduction

During the global initial introduction of COVID-19 vaccines, various immunization strategies will be used for different target population groups in a wide range of settings. Some general considerations for the implementation of safe immunization strategies should be taken into account by national immunization programmes.

3.3.1 Safety considerations for COVID-19 vaccine administration in mass immunization campaigns

WHO has published guidance document for the assessment of vaccine safety in the setting of mass immunization campaigns[26] and also a Guidance on Developing a National Deployment and Vaccination Planning for COVID-19 vaccines. When COVID-19 vaccines will be used, the following additional key safety aspects for mass vaccination immunization campaigns need to be considered:

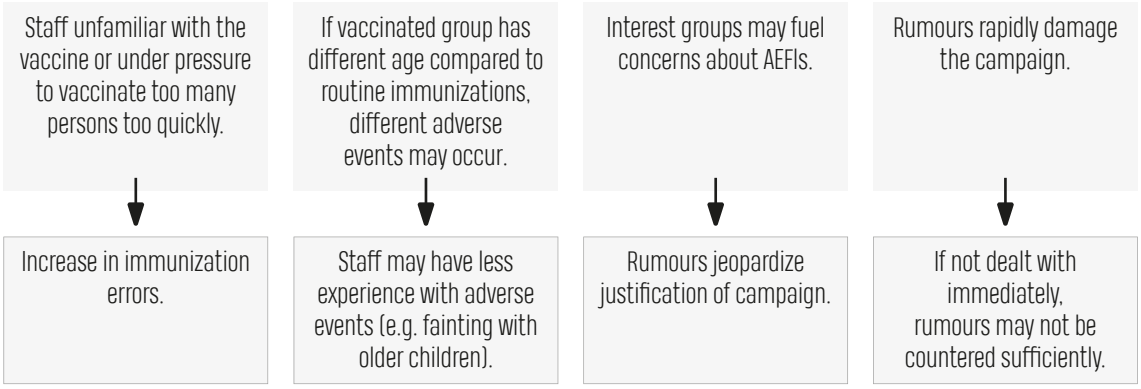
- training for the use of the vaccines and infection prevention and control measures;
- personal protective equipment requirements for HCWs;
- size and characteristics of the target population;
- immunization goal for priority target population;
- period of time for deployment and vaccination;
- standard operating procedures (SOPs) and training for the management of possible AEFIs;
- SOP for safe waste disposal;[27]
- additional human and financial resources needed;
- joint health information system for reporting vaccination coverage and AEFI reporting; and
- rapid response teams for responding to safety concerns, conducting AEFI investigations and crisis management.

The common safety challenges during mass immunization campaigns and consequences if they are not addressed are summarized in **Fig 3**. To prevent immunization error-related reactions in mass immunization campaigns, specific training of HCWs is needed and processes

25 VigiBase. https://www.who-umc.org/vigibase/vigibase/. Accessed 19 October 2020.
26 World Health Organization (2002). Safety of mass immunization campaigns. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/67726. Accessed 16 October 2020.
27 World Health Organization (2004). Management of wastes from immunisation campaign activities, Practical guidelines for planners and managers. Available at: https://www.who.int/water_sanitation_health/publications/hcwm/en/. Accessed 12 November 2020.

for safe vaccine administration and waste disposal should be implemented. Before vaccinating, HCWs should verify the product information on vaccine and diluent vial labels, check for vaccine contraindications, as indicated in the product information leaflet. A clear communications strategy prior to vaccine introduction is also critical to ensure the right safety messages are communicated prior to, during and after mass immunization campaigns in order to maintain public trust in the immunization programme if any serious AEFIs occur.

Fig 3: Common safety challenges in mass immunization campaigns



In addition, appropriate measures to prevent Immunization stress-related response (ISRR) during mass immunization programmes should be taken, e.g. separate areas for waiting, vaccination, and if necessary, for observation after vaccination.

3.3.2 Safety considerations for all immunization programmes

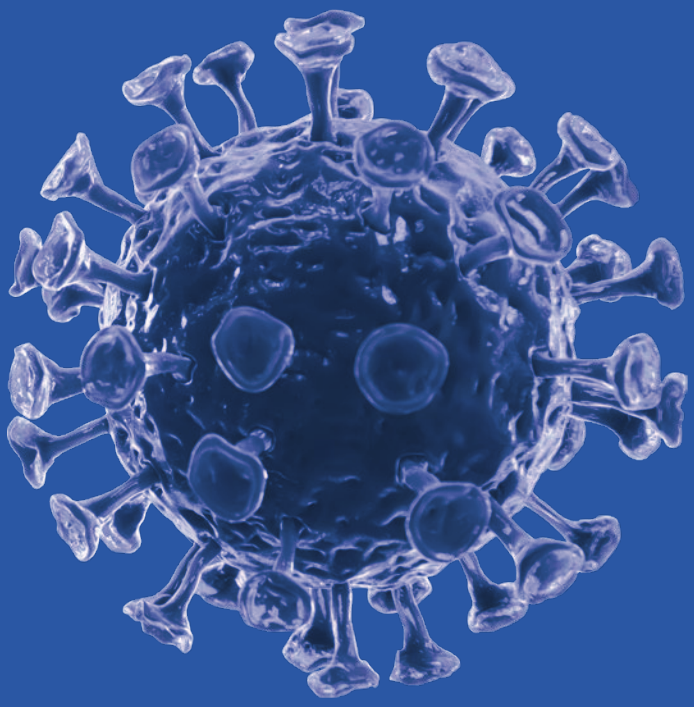
The global manual on surveillance of adverse events following immunization provides generic guidance for vaccine safety surveillance for countries, which can be adapted to the local context in Member States and WHO regions.[28] Specific COVID-19 vaccine AEFI surveillance as outlined in this manual should be implemented where COVID-19 immunization programmes are set-up. They should also be implemented regardless of the specific immunization programmes and strategies used, which could include routine immunization strategies and practices, house to house programmes and outreach strategies for hard-to-reach areas, catch-up vaccination programmes, institution-based immunization (e.g., workplaces and care homes) and mobile strategies (e.g., in the event of humanitarian emergencies) in all settings, including the private sector. This will require preparedness and basic training of staff to strengthen the local capacity to follow national guidelines or protocols for AEFI surveillance (detection, reporting, investigation, causality assessment and coordinated response).

28 World Health Organization. (2014). Global manual on surveillance of adverse events following immunization. Available from: https://www.who.int/vaccine_safety/publications/aefi_surveillance/en/. Accessed 19 October 2020

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

STAKEHOLDERS IN COVID-19 VACCINE SAFETY SURVEILLANCE



Contents

Key points

- Vaccine safety monitoring requires broad and timely collaboration between national, regional and global stakeholders.
- International collaboration will be essential to verify the safety and effectiveness of the many COVID-19 vaccines that will be produced and used in many different countries and administered to large numbers of people in a short period of time.
- Mapping national, regional and global stakeholders and their responsibilities is key for ensuring appropriate vaccine safety monitoring of the COVID-19 vaccines when they are deployed.
- Stakeholders will continue their regular pharmacovigilance activities and many will have additional activities, particularly during COVID-19 vaccine introduction.

01 Introduction

Vaccine safety monitoring, including effective reporting of adverse events following immunization (AEFIs), investigation and assessment of reported cases and taking necessary actions, requires broad and timely collaboration between national, regional and global stakeholders. These stakeholders include:

- vaccine developers, and manufacturers;[1]
- regulatory authorities who initially approve vaccine clinical trial protocols, assess their results and, if shown to be safe and efficacious, grant marketing authorizations, and withdraw marketing authorization if the vaccine is found to be unsafe;
- policy makers who recommend the use of vaccines, and specify the relevant vaccine target groups;
- vaccine providers who deliver vaccines and report possible AEFIs;
- the public health institutes that investigate and assess adverse events; and
- beneficiaries.

International collaboration will be essential to verify the safety and effectiveness of the many COVID-19 vaccines that will be produced and used in many different countries and administered to large numbers of people in a short period of time. Therefore, mapping national, regional and global stakeholders and their responsibilities is key for ensuring appropriate vaccine safety monitoring of these newly developed vaccines.

1 For the purpose of this document, manufacturer also means marketing authorization holder.

02 Identification of stakeholders and their roles

At the core of this collaboration are the immunization service providers who can be public or private, or both, depending on the organization of the country's health care system. It is possible that the role of country's immunization service providers will be extended to offer COVID-19 vaccines to selected target population groups during COVID-19 vaccination campaigns.

Here we list the main national, regional and global stakeholders and describe their routine roles in vaccination and their roles in safety monitoring and assessment for COVID-19 vaccines. The list of stakeholders is not exhaustive; there are many other stakeholders who provide regional or country-specific pharmacovigilance.

In addition to the stakeholders listed here, if pregnant or lactating women are included as a target group for COVID-19 vaccination, collaboration with the relevant maternal and neonatal-child health programmes should be considered.

03 National stakeholders

In some countries, these stakeholders are present in autonomous regions.

3.1 Ministries of Health

The routine roles of Ministries of Health (MoHs) are to:

- increase support for national immunization programmes and ensure financial sustainability;
- develop and introduce laws, regulations, and policies that support immunization programmes;
- ensure a secure high-quality supply base of vaccines;
- develop region- and country-specific plans, in collaboration with other regional and national stakeholders, when necessary;
- prioritize and assume full ownership of national immunization programmes; and
- create equity-driven programmes that reach all members of the community.

In the context of COVID-19 vaccine safety monitoring, MoHs are expected to:

- ensure availability of funding for national stakeholders to conduct key activities to strengthen safety monitoring for COVID-19 vaccines;
- establish a national coordination task force or working group consisting of multi-disciplinary and multi-agency representatives to ensure inter-stakeholder coordination and cooperation;
- generate vaccine demand and ensure acceptability;
- establish efficient communication mechanisms about COVID-19 vaccines between regulatory authorities, immunization programmes, Ministry of Education and other authorities, so that the population is informed about vaccine safety issues and can report any concerns; and
- be prepared to respond to rumours and media and community concerns.

3.2 National regulatory authorities

The national regulatory authorities (NRA) are responsible for ensuring that any pharmaceutical product, including vaccines, used within the country is (i) of good quality, (ii) effective, and (iii) safe for the purpose or purposes for which it is proposed.

The core functions of the NRA are:

- marketing authorization activities;
- pharmacovigilance, including surveillance of AEFIs;
- NRA batch release, with a system for batch release of vaccines;

- laboratory access, with use of laboratories when needed;
- market surveillance and control;
- regulatory inspection, with regular inspection of vaccine manufacturers for good manufacturing practices (GMP) compliance; and
- regulatory oversight of clinical trials, with evaluation of clinical performance through authorized clinical trials.

It should be noted that not all NRAs engage in all the listed activities and, instead, may adopt the principles of regulatory reliance and work sharing.

In the context of COVID-19 vaccine safety monitoring, NRAs are expected to:

- oversee preparations for emergency use listing (EUL);
- verify submission and review of risk management plans prior to marketing authorization and making risk-based recommendations for post- authorization safety surveillance;
- oversee communication and information sharing with immunization programmes, pharmacovigilance centres and other key institutions on COVID-19 vaccines safety updates to enhance the NRA's ability to make evidence-based decisions to protect public health;
- have authority to mandate COVID-19 vaccine safety studies by the vaccine manufacturers and importers of vaccines, as required;
- have the independent authority to investigate potential safety signals and assure the continued post-authorization safety of COVID-19 vaccines;
- oversee the monitoring of COVID-19 vaccine safety by reviewing the periodic safety update reports (PSURs) / periodic benefit-risk evaluation reports (PBRERs);
- share safety information generated with national, regional, international decision-makers and vaccine manufacturers.

3.3 Expanded programmes on immunization and national immunization programmes

Their routine roles of expanded programmes on immunization (EPIs) and national immunization programmes (NIPs) are to:

- protect the population against vaccine-preventable diseases (principal role);
- respond with timely information, when public concerns about safety and efficacy of vaccines are raised to sustain public trust in vaccines and vaccination;
- be responsible for safe storage, handling, including maintenance of the cold chain i.e., (continuous refrigeration), delivery and administration of vaccines released by the NRA;
- ensure that health care workers respond to adverse events and report them;
- ensure that sufficient training and capacity is provided so that AEFIs are minimized;
- provide feedback to all levels on the findings of the AEFI investigations and causality assessments;
- provide guidance on monitoring, supervision and training to all stakeholders;

- if there are no pharmacovigilance centres in the country:
  - oversee monitoring, information collection, assessment of serious AEFIs;
  - ensure that causality assessments for AEFIs are conducted as per guidelines; and
  - search for and analyse safety signals.
- provide expert support for field investigations; and
- recommend decisions for vaccination policies.

The roles of the EPIs and NIPs for COVID-19 vaccine safety monitoring, in collaboration with NRAs, are expected to include:

- when recommended, conducting specific active surveillance studies for COVID-19 vaccines, similar to those for other new vaccines i.e., typhoid conjugate, malaria, Ebola, and dengue vaccines, with active surveillance and sentinel sites to identifying signals and establish causality;
- regularly reviewing reports submitted to passive safety surveillance systems to identify rates and unexpected patterns, with special attention to serious outcomes, such as death, disabilities, life-threatening events, and programmatic errors;
- identifying and quantifying public concerns surrounding vaccines through cross-sectional surveys and monitoring of social media;
- developing a national framework to process vaccine safety signals and determine which should be prioritized for more rigorous evaluation and risk assessment;
- measuring and characterizing background rates of medical outcomes that may be temporally associated with COVID-19 vaccines;
- measuring and characterizing other AEFIs identified in active surveillance and sentinel systems; and
- coordinating existing active and sentinel surveillance nationally, regionally and globally to ensure harmonization, avoid duplication, increase power to detect rare events and take advantage of variability in vaccination practices and target population.

3.4 National pharmacovigilance centres

The routine roles for national pharmacovigilance centres, when they exist, include:

- collecting and analysing case reports for AEFIs;
- supporting AEFI committees in performing causality assessment for AEFIs;
- detecting and analysing vaccine safety signals;
- alerting prescribers, vaccine manufacturers and the public if new risks for adverse reactions are observed;
- review risk management plans and oversee implementation for pharmacovigilance centres that are within regulatory agencies; and
- overseeing vaccine safety and risk communication.

The roles of the national pharmacovigilance centres for COVID-19 vaccine safety monitoring are expected to include:

- ensuring timely submission of COVID-19 AEFIs and adverse events of special interest (AESIs) data from EPIs, NIPs and pharmacovigilance centres across the country for data compilation, analysis and signal detection; and
- sharing information with key national stakeholders on COVID-19 vaccine safety and with the global community by uploading the information on the WHO global pharmacovigilance database, Vigibase, maintained at Uppsala Monitoring Centre (UMC) in Sweden under the WHO International Drug Monitoring Programme.

3.5 AEFI review committees

The main routine responsibilities of AEFI review committees are to:

- provide guidance for AEFI investigations so that the cause can be determined correctly;
- assess potential causal links between AEFIs and vaccines, using standard procedures;[2]
- monitor reported AEFI data for potential signals of previously unrecognized vaccine-related adverse events and support further investigations to establish if causality exists;
- make the necessary recommendations to rectify problems, communicate with national stakeholders and other national and international experts, when required.

The terms of reference for the AEFI review committees for COVID-19 vaccine safety monitoring are expected to include:

- assessing potential causal links between AEFIs and AESIs and COVID-19 vaccines;
- monitoring AEFI data for identification of potential signals of previously unidentified COVID-19 vaccine related adverse events;
- reviewing all serious AEFIs presented for expert opinion and arranging further investigation to establish causality, if required;
- communicating with other national and international experts, when required, to establish causality and resolve vaccine quality issues;
- advising NRAs, EPIs and NIPs on COVID-19 vaccines AEFI- and AESI-related issues when requested; and
- advising the Ministry of Health (MoH) on COVID-19 vaccines and Immunization safety-related matters when requested.

The committee should be independent of the NRAs, NIPs/EPIs, MoHs and vaccine manufacturers, and the members should have no conflicts of interest.

2 World Health Organization. Causality assessment of an adverse event following immunization (AEFI) User manual for the revised WHO AEFI causality assessment classification (Second edition). Available from: https://www.who.int/vaccine_safety/publications/gvs_aefi/en/. Accessed 30 October 2020.

3.6 National immunization technical advisory groups

The main routine roles of national immunization technical advisory groups (NITAGs) are to:

- guide national governments and policymakers for the development and implementation of evidence-based, locally-relevant immunization policies and strategies that reflect national priorities;
- support NIPs, EPIs and NRAs and empower them to address issues associated with vaccine quality and safety and the introduction of new vaccines and immunization technologies; and
- help governments, NIPs and EPIs to address public concerns.

The roles of NITAGs (or of a COVID-19 working group within the NITAG) for COVID-19 vaccine safety monitoring are expected to include:

- providing the latest information on different COVID-19 vaccine platforms, risk/benefit analyses, COVID-19 vaccine EUL status, etc.; and
- reviewing the available evidence to be considered for recommendations for COVID-19 vaccine introduction, including the identification of priority target groups for COVID-19 introduction.

3.7 Vaccine manufacturers

The routine roles of the vaccine manufacturers are to:

- continue to develop, produce and supply innovative and high-quality vaccines that meet countries' needs in compliance with international GMP standards;
- support research and vaccine specific training needs for immunization;
- establish risk minimization plans for new vaccines;
- participate in open dialogue with countries and the public sector to ensure sustainable access to current and new vaccines; and
- to continue to innovate manufacturing processes and pricing structures.

The roles of vaccine manufacturers for COVID-19 vaccine safety monitoring are expected to include:

- sharing risk management plans and information on detected signals for COVID-19 vaccines with NRAs;
- conducting phase IV studies on COVID-19 vaccines and submitting periodic safety update reports (PSURs) on a regular basis to help policy decisions; the frequency of PSUR submissions may be increased to bi-monthly/monthly to guide quick corrective actions and decisions;
- responding to national requests to share additional and updated product information and clinical trial data;
- responding to national requests to implement innovative risk minimization measures, for example, peel-off labels on vaccine vials; and

- keeping countries updated on all safety and efficacy findings in other countries, particularly from phase IV studies.

3.8 Academia

The main routine roles of academia are to:

- promote innovation to accelerate the development of new and improved vaccines;
- pursue a multidisciplinary research agenda that focuses on transformational impact and is based on the needs of end users;
- provide pharmacovigilance training through its curriculum;
- embrace new ways of working that speed up and improve dialogue with other researchers, regulators and manufacturers; and
- align actions and increase effectiveness in responding to local and global immunization challenges.

The roles of academia for COVID-19 vaccine safety monitoring are expected to include advising and facilitating research activities concerning COVID-19 vaccines, including sentinel-site based and specific studies related to AESIs.

3.9 Health care workers

The routine roles of health care workers are to:

- provide vaccine and vaccination information and then providing high-quality immunization services;
- identify areas where immunization services could be improved and innovations implemented;
- serve as proactive, credible advocates to promote the value of vaccines and vaccination and recruit other advocates;
- use existing and emerging technologies to improve information delivery and capture, using beneficiaries[3], if possible;
- dialogue with communities and the media and use effective communications techniques to convey messages about vaccines; and
- address clinical case management for adverse events.

The roles for health care workers for COVID-19 vaccine safety monitoring are expected to include:

- ensuring staff training on detection, management and reporting of COVID-19 vaccine AEFIs identified through active and passive surveillance;

3 Beneficiaries could be encouraged to report potential adverse events using mobile apps and other software, although this could raise problems of confidentiality of information; during the preparedness stage, this issue should be analysed.

- providing supervision to ensure both serious and non-serious AEFIs are captured and that serious AEFIs are adequately investigated; and
- developing a communication protocol, including the use of a trusted spokesperson, to promptly inform the public about any investigation or rumours.

3.10 Beneficiaries

The roles of beneficiaries are the same in the context of COVID-19 vaccine safety monitoring as for routine vaccine safety monitoring, and include to:

- understand the risk and benefits of vaccines and immunization, viewing this as part of being a responsible citizen;
- play an active role in identifying what they feel is important to help define certain adverse effects, if possible;
- differentiate between genuine and false information and ensure that correct information is communicated, and prevent the circulation of false information;
- demand the right to safe and effective immunization programmes from their leaders and government and hold leaders and government accountable for providing them;
- participate in public-health discussions;
- be involved in key decisions about immunization processes;
- participate and contribute to the immunization delivery process; and
- convey the needs and perspectives of their communities to policymakers.

3.11 Media

The routine roles of the media are to:

- understand the benefits of, and concerns about, immunization in order to accurately report on and effectively promote immunization programmes;
- engage in country, regional and global advocacy beyond the immunization community to ensure vaccines and immunization are understood to be a right for all; and
- use effective communications techniques to convey messages about vaccines and to address safety concerns.

The roles for media for COVID-19 vaccine safety monitoring are expected to include:

- keeping up to date with media releases, press information packages, briefing papers, web materials, talking points disseminated by MoHs on COVID-19 vaccines and vaccination;
- proactively identifying, filtering out and preventing the spread of misinformation;
- participating in media workshops and training sessions to learn about the rationale for COVID-19 vaccine introduction and understand the key messages; and
- ensuring the dissemination of clear, factual messages that have been confirmed by the relevant authorities to the public.

3.12 Non-governmental organizations and professional societies

Non-governmental organizations and professional societies do get involved in the promotion and implementation of routine immunization programmes at both the country and global levels, follow national guidelines and regulations for the design and delivery of immunization programmes that fulfil the duty of accountability to national authorities, contribute to improved evaluation and monitoring systems within countries.

Non-governmental organizations and professional societies should participate in the development and testing of innovative approaches for the delivery of COVID-19 immunization services that reach the most vulnerable people.

04 Regional stakeholders

4.1 Regional regulatory networks

Regional regulatory networks such as the African Vaccine Regulatory Forum (AVAREF), the South-East Asia Regulatory Network (SEARN), the European Medicines Agency (EMA) play an essential role in routine pharmacovigilance. For example, EMA's large Eudravigilance database is a system for managing and analyzing information on suspected adverse reactions to medicines, including vaccines, that have been authorized or are being studied in clinical trials in the European Economic Area and also those authorized for use outside the European Union, the Article 58 authorized vaccines. These latter include vaccines for protection against a WHO public health priority disease, such as COVID-19. These networks play a key role in implementing regulatory reliance for pharmacovigilance of COVID-19 vaccines as described in the module on regulatory reliance.

4.2 Regional technical advisory committees on vaccine safety

The roles of regional advisory committees on vaccine safety vary between regions. All WHO regions have established Regional Immunization Technical Advisory Groups (RITAGs) that play different roles to those played by the NITAGs as they provide recommendations on regional

immunization priorities and strategies in the light of regional epidemiological and social issues to the WHO regional directors as well as the countries in their respective regions.

The roles for RITAGS for COVID-19 vaccine safety monitoring are expected to include rapid, real-time exchange of information and joint assessment of routine safety data, should there be a safety signal.

05 Global stakeholders

5.1 International Coalition of Medicines Regulatory Authorities

The International Coalition of Medicines Regulatory Authorities (ICMRA) is a voluntary, executive-level entity of worldwide medicines regulatory authorities set up to provide strategic coordination, advocacy and leadership. ICMRA acts as a forum to support international cooperation among medicines regulatory authorities. The coalition aims to identify ways to better use existing initiatives and resources, develop strategies to address current and emerging challenges in global human medicine regulation, such as the growing complexity of globalized supply chains and provide direction for common activities and areas of work.

ICMRA aims to expedite and streamline the development of COVID-19 vaccines and treatments. In April 2020, ICMRA members pledged to strengthen global collaborative efforts to align the facilitation of rapid development, approval and global roll-out of safe and effective medicines and vaccines to prevent and treat COVID-19. Collective statements and efforts including describing the key characteristics of clinical trials that are most likely to generate the conclusive evidence needed to enable the accelerated approval of potential treatments and vaccines against COVID-19.

5.2 The Council for International Organizations of Medical Sciences

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. Its mission is to advance public health through guidance on health research and policy including ethics, medical product development and safety. CIOMS has an official relationship with WHO

and is an associate partner of UNESCO. The CIOMS pharmacovigilance guidelines have been used as the basis for International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines (see **Section 5.3**). The longest running of the CIOMS Working Groups, since 2002, is dedicated to standardized MedDRA queries (SMQs). This implementation working group has produced the 'Red Books' on the Development and Rational Use of Standardised MedDRA Queries (SMQs), updated in 2016. The CIOMS Guide to Active Vaccine Safety Surveillance, published in 2017 will be used for guidance for COVID-19 vaccine safety monitoring. The 2012 report of the CIOMS WHO working group on the Definitions and Applications of Terms for Vaccine Pharmacovigilance is used as the reference document for AEFI surveillance and causality assessment.

5.3 International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and pharmaceutical industries to discuss scientific and technical aspects of pharmaceuticals and to develop ICH guidelines. Since its inception in 1990, ICH has gradually evolved, to respond to increasingly global developments in the pharmaceutical sector and the ICH guidelines are used by a growing number of regulatory authorities. ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective and high-quality medicines are developed, registered and maintained in the most resource efficient manner whilst meeting high standards. Since its announcement of organizational changes in October 2015, ICH has grown as an organization and now includes 17 Members and 32 Observers.

The COVID-19 pandemic has prompted an urgent need for a harmonized, standardized approach for coding and reporting COVID-19 infections as a global health issue. ICH has defined E2B[4] as the international standard for transmitting adverse event reports that includes message standards required for effective transmission of individual case safety reports (ICSR). The ICH M1 Points to Consider Working Group and the medical dictionary for regulatory activities (MedDRA) maintenance and support services organization (MSSO), with the approval of the MedDRA Management Committee, are issuing notifications for MedDRA users regarding existing and new terms for COVID-19 concepts. These notifications are available on the MedDRA website. The latest version 23.1 notifies the addition of new terms to MedDRA.

5.4 WHO prequalification

The WHO prequalification (PQ) team has a major role in assuring the quality of all vaccines that could be purchased by UN agencies. It provides Member States and procurement agencies, such as Gavi, the Vaccine Alliance, the Global Fund and UN organizations like UNICEF,

4 E2B(R3) individual case safety report (ICSR) specification and related files. Available from: https://ich.org/page/e2br3-individual-case-safety-report-icsr-specification-and-related-files. Accessed 23 November 2020.

with the information required to purchase vaccines matching the specific needs of their programme. The WHO prequalification process for vaccines is a comprehensive assessment that takes place through a standardized procedure aimed at determining whether the product meets requirements for quality, safety and efficacy in immunization programmes. The full prequalification assessment process includes the following components:

- review of the quality, safety and efficacy data,
- review of production process and quality control procedures,
- laboratory testing,[5] and
- WHO site audit of the manufacturing facilities with the responsible NRA.

Once a vaccine is prequalified and introduced to the market, the WHO PQ team ensures it continues to meet standards by, for example, investigating complaints from the field and reports of AEFIs.

The WHO PQ team is playing this major role for the prequalification of new COVID-19 vaccines and for possible EUL of COVID-19 vaccines.

5.5 WHO Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GACVS) provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short- or long-term national immunization programmes. This includes providing advice on urgent matters, such as COVID-19 vaccine safety monitoring, as needed.

Issues to be considered by the Committee are jointly decided by the WHO Secretariat and the Committee. More specifically, the role of the GACVS is expected to include:

- rigorous review of the latest knowledge, in all fields ranging from basic sciences to epidemiology, concerning all aspects of vaccine safety of global or regional interest, in close collaboration with all parties involved, including experts from national governments, academia, and industry;
- assessment of causality between COVID-19 vaccines and/or their components and adverse events attributed to them;
- creation of ad hoc task forces, when necessary, with a mandate to commission, monitor and evaluate appropriate methodological and empirical research on any suspected association between specific vaccines/vaccine components and adverse event(s); and
- providing scientific recommendations that are intended to assist WHO, the WHO's Strategic Advisory Group of Experts (SAGE) for vaccines and immunization, national governments

5 Quality testing of vaccines is organized by the Laboratory Networks & Services (LNS) team. The WHO LNS team leads the WHO National Control Network for Biologicals who bring together national control laboratories and NRAs of vaccine-producing and vaccine-recipient countries, manufacturer's associations as well as other stakeholders. The Network facilitates access to and availability of prequalified vaccines through reliance on batch release of respective network recipient countries.

and international organizations in formulating policies regarding vaccine safety issues, with particular attention to those problems that affect developing countries.

5.6 WHO Strategic Advisory Group of Experts

SAGE serves as the principal advisory group to WHO for the development of policy related to vaccines and immunization. SAGE is charged with advising WHO on overall global policies and strategies, ranging from vaccine and technology research and development, to delivery of immunization and linkages between immunization and other health interventions. The mandate of SAGE is to provide strategic advice rather than technical input, and it is not restricted to childhood vaccines and immunization but extends to the control of all vaccine-preventable diseases. SAGE advises the WHO Director-General specifically on:

- adequacy of progress towards the achievement of the goals of the Global Immunization Vision and Strategy (GIVS)[6];
- major issues and challenges to be addressed with respect to achieving the goals of GIVS;
- immunization programme response to current public health priorities;
- major general policies, goals and targets, including those related to vaccine research and development;
- adequacy of WHO's strategic plan and priority activities to achieve the GIVS goals consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
- cross-departmental activities and initiatives related to vaccine and immunization technologies and strategies and linkages with other health interventions; and
- engagement of WHO in partnerships that will enhance achievement of global immunization goals.

In the context of COVID-19 vaccine safety monitoring, a WHO SAGE working group has been formed to:

- provide continuous review of the available evidence on the progress of candidate vaccines against COVID-19, and provide regular updates to SAGE;
- provide guidance for the development of prediction models to determine the optimal age groups and target populations for vaccine introduction and guide vaccine introduction for optimal impact, and contribute to updates of target population profiles of COVID-19 vaccines for outbreak and endemic use;
- provide policy advice to SAGE on the accelerated use of COVID-19 vaccines (pre-licensure and post-licensure) to mitigate the public health impact of COVID-19, to possibly curtail the ongoing pandemic, as well as to prevent or reduce the risk of spread of disease in the future; this will include recommendations for early allocation of vaccines when vaccine supplies are still limited; and

6 World Health Organization. Global Immunization Vision and Strategy. Available from: https://www.who.int/immunization/givs/en/. Accessed 8 December 2020.

- provide guidance to ensure equitable access to vaccination, and guidance on the safety of vaccines when safety data from wider population use become available, in close collaboration with GACVS.

The following COVID-19 documents have been endorsed by WHO SAGE:

- WHO SAGE Values framework for the allocation and prioritization of COVID-19 vaccination; and
- Roadmap for prioritizing population groups for vaccines against COVID-19.

5.7 WHO Immunization, Vaccines and Biologicals Department

The Immunization, Vaccines and Biologicals (IVB) Department is responsible for targeting vaccine-preventable diseases, vaccines, immunization policy and research. IVB is involved in addressing immunization challenges in the context of accelerating urbanization, migration and displacement, conflict and political instability, unaffordability of newer vaccines in middle-income countries, unexpected vaccine supply shortages both locally and globally, and rising vaccine hesitancy. Strategies for the continued vaccine preventable infectious disease outbreaks, and disease elimination goals that have not yet been achieved are being developed and pursued.

In the context of COVID-19 vaccine safety monitoring, guidance on national deployment and vaccination plans for COVID-19 vaccines and checklists for immunization programmes preparing for COVID-19 vaccination programmes are being prepared but are not yet available.

5.8 UNICEF

UNICEF and its partners support immunization programmes in over 100 countries. Their activities include logistics, monitoring and advocacy for immunization and acting on infodemics, and documenting vaccine coverage through the WHO/UNICEF Joint Reporting Form.

In the context of COVID-19 vaccine safety monitoring, UNICEF will provide support to the immunization programmes in countries for vaccination activities and distribution of COVID-19 vaccines.

5.9 Uppsala Monitoring Centre

The Uppsala Monitoring Centre (UMC) is a WHO Collaborating Centre, located in Uppsala, Sweden that provides training, guidance and support to countries in the WHO Programme for International Drug Monitoring. They manage VigiBase, WHO's database of individual case safety reports (ICSRs) and the world's largest repository of adverse effects from medicines, including vaccines. Member countries submit reports of suspected adverse drug reactions to the database VigiBase. In 2019 VigiBase contained more than 20 million reports. It is used to analyse global patterns of suspected harm caused by medicines and vaccines and can also be

used to analyse data at national and regional levels. They have also developed and maintain VigiFlow, a web-based ICSR management system for medicines and vaccines, that is E2B compatible. VigiFlow is available to member countries of WHO Programme for International Drug Monitoring (PIDM) and is currently used by more than 90 countries. UMC also provides VigiBase aggregated safety data for the public via VigiAccess™. In the context of COVID-19 vaccine safety monitoring, UMC will be involved in safety signal detection.

5.10 Brighton Collaboration

The Brighton Collaboration develops case definitions for adverse events and guidelines for investigations and assessment of adverse events in formal pharmacoepidemiological studies. In the context of COVID-19 vaccine safety monitoring, a list of possible AESIs have been developed under contract with CEPI (See **Section 5.13**). Case definitions to be used for investigating possible AESIs including background rates are under development. Study protocols are being developed for background incidence studies and association studies initiated for confirmatory studies should a safety signal arise.

Additionally, The Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) template has been developed. This was originally a standardized template to describe the key considerations for the benefit-risk assessment of viral vector vaccines, which has now been broadened to include templates for each of the other major COVID-19 vaccine platform technologies.

5.11 COVID-19 Vaccines Global Access Facility

GAVI co-leading the COVID-19 Vaccines Global Access (COVAX) facility the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator. Gavi's impact draws on the strengths of its core partners, the World Health Organization, UNICEF, the World Bank and the Bill & Melinda Gates Foundation. This is a global risk-sharing mechanism for pooled procurement and equitable access to COVID-19 vaccines when they become available. COVAX aims to end the acute phase of the pandemic by the end of 2021.

5.12 Vaccine Safety Net

The Vaccine Safety Net (VSN)[7] established by WHO, is a network of a diverse digital information resources (websites), VSN members, located in countries around the world and providing scientifically based information on vaccine safety in various languages. The mission of the VSN is to help internet users find reliable vaccine safety information tailored to their needs. A key player in the project is the GACVS (see **Section 5.5**), who developed three categories of criteria for good information practices - regarding credibility, content and accessibility/design to which sites providing information on vaccine safety should comply. VSN evaluates websites

7 World Health Organization. Vaccine Safety Net. Available from: https://www.vaccinesafetynet.org/. Accessed 8 December 2020.

for their adherence to these criteria. This will be an invaluable resource for information on COVID-19 vaccines and vaccination for all stakeholders.

5.13 The Coalition for Epidemic Preparedness Innovations

The Coalition for Epidemic Preparedness Innovations (CEPI) is a global partnership launched in 2017 to develop new vaccines for emerging infectious diseases and bring them through to phase I and II vaccine trials. In the context of COVID-19 vaccine safety monitoring, CEPI has signed contracts with 10 vaccine developers and have established partnerships with 5 clinical sample testing laboratories to create a centralised global network for reliable assessment and comparison of the immune responses generated by COVID-19 vaccine candidates. This approach will ensure uniformity in assessment and informed identification of the most promising vaccine candidates. Through this specific network, up to the limit of programme funding, eligible COVID-19 vaccine developers (both CEPI-funded and non-CEPI funded developers) can use the laboratories, without per-sample charges, to analyse the immune response elicited by their COVID-19 vaccine candidates in preclinical, phase I and phase IIa vaccine trials. CEPI has partnered with the Brighton Collaboration in funding the Safety Platform for Emergency vACcines (SPEAC) project in 2019 through the Task Force for Global Health. SPEAC aims to create capacity and solutions for harmonized safety assessment of CEPI vaccines.

5.14 International Federation of Pharmaceutical Manufacturers and Associations

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) represents the research-based pharmaceutical companies and associations across the globe. In the context of COVID-19 vaccine safety monitoring, IFPMA members, which include the leading innovative biopharmaceutical companies in the vaccine field, are aiming to develop safe and effective COVID-19 vaccines.

5.15 Developing Countries Vaccine Manufactures Network

The members of the Developing Countries Vaccine Manufactures Network (DCVMN) are vaccine manufacturers from developing countries that aim to provide a consistent and sustainable supply of quality vaccines at an affordable price that are accessible to developing countries. In 2020, DCVMN was an alliance between 41 public and private vaccine manufacturing companies from 14 countries and territories engaged in the supply of vaccines for local and international use.

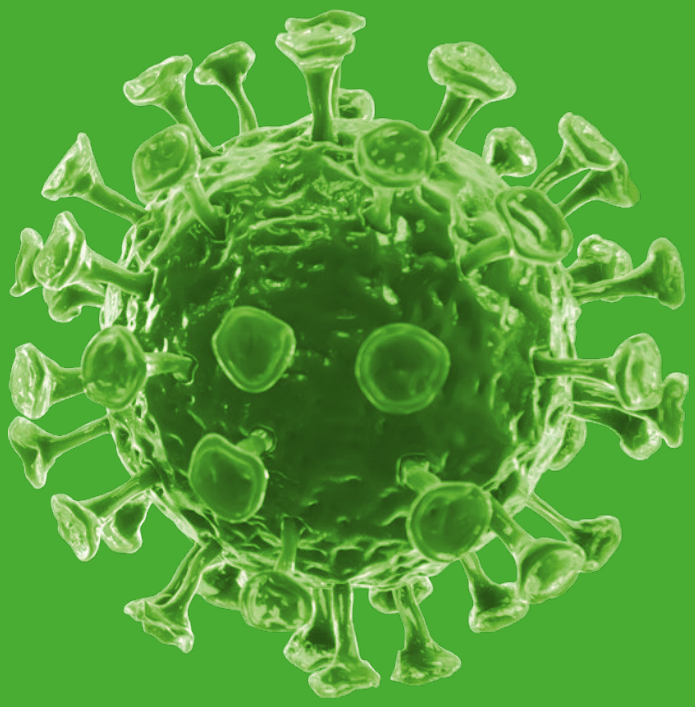
To provide DCVMN members and the Executive Committee with all the information required to make high-level policy decisions, they have set up a COVID-19 committee whose objective is to assess the evolving situation of the pandemic and to:

- evaluate prime COVID-19 vaccine candidates;
- evaluate technical information (research roadmaps, animal models, clinical trial protocols, formulation (e.g. adjuvant effects) etc.);
- evaluate solutions provided by organizations such as, but not limited to, WHO, CEPI, Gavi, PAHO, UNICEF (e.g., COVID-19 AMC, ACT-accelerator, COVAX Facility);
- develop and support solid bases for statements to support DCVMN dialogue with global stakeholders and in public meetings; and
- assess and share technologies important for COVID-19 vaccine development, through surveys and reports.

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

ESTABLISHING SURVEILLANCE SYSTEMS IN COUNTRIES USING COVID-19 VACCINES



Contents

Key points

- The role of vaccine safety surveillance during COVID-19 vaccine introduction is to facilitate the early detection, investigation and analysis of adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) to ensure an appropriate and rapid response
- The type and scope of vaccine safety monitoring activities that countries can undertake will depend on the resources available and the maturity of their pharmacovigilance surveillance systems but they should aim to strengthen their activities before and during COVID-19 vaccine introduction
- Countries will need to adapt their established AEFI surveillance systems to address the specific challenges associated with COVID-19 pandemic
- Following up of specific vaccinated cohorts for at least one year will enable potential vaccine-type specific AESIs to be detected, including potential vaccine-associated enhanced disease (VAED) in vaccinated individuals who develop COVID-19 disease
- Surveillance systems will need to accommodate large numbers of AEFI/AESI reports expected because of the numbers of people who will be vaccinated
- Coordination between all stakeholders handling deaths should be established for reporting deaths in persons with a history of COVID-19 vaccination and specific protocols for investigating these deaths should be defined
- Communication about any adverse events and response to public concerns should be rapid in order to maintain public confidence, in the setting of high media and public attention on COVID-19 vaccines

01 Introduction

The role of vaccine safety surveillance during COVID-19 vaccine introduction is to facilitate the early detection, investigation and analysis of adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) to ensure an appropriate and rapid response. This will decrease the negative impact of these events on the health of individuals and the immunization programmes and maintain the confidence of health care workers (HCWs) and the general population. To achieve this, the global goals of COVID-19 vaccine safety surveillance are to:

- detect serious AEFIs/AESIs rapidly in order to provide timely data that can be shared with relevant stakeholders for action;
- generate data to characterize the safety profile of the COVID-19 vaccines in use;
- help to monitor the acceptable benefit-risk ratio throughout the COVID-19 vaccine life-cycle;
- identify, investigate, assess and validate safety signals and recommend appropriate public health or other interventions; and
- maintain public and stakeholder confidence in vaccines and immunization by ensuring high quality safety surveillance.

The type and scope of vaccine safety monitoring activities that countries choose to adopt to achieve these goals will depend on the resources available and the maturity of their pharmacovigilance surveillance systems. However, all countries should aim to strengthen their ability to detect, investigate, assess, report and respond to serious AEFIs before and during COVID-19 vaccine introduction. The key objectives are to:

- strengthen routine passive surveillance reporting systems to enable them to cope with the expected increase in frequency or severity of AEFI (mild, moderate, and severe);
- detect and investigate safety signals or clustering of serious events, immunization errors, community concerns etc.;
- perform systematic causality assessments for AESIs;
- prepare comprehensive plans to respond rapidly to any COVID-19 vaccine-related events; and
- be able to respond to any concerns expressed by HCWs and maintain community confidence.

Countries that have mature pharmacovigilance systems or have to face particular situations, such as, the introduction of a novel vaccine platform requiring enhanced safety monitoring may consider the following additional safety monitoring objectives:

- implement active surveillance systems for AESIs;
- conduct research on identified or newly observed vaccine safety concerns in large populations or target groups, for example, comparison between vaccinated and unvaccinated cohorts

to identify immunological markers of risk for severe COVID-19 disease and types of adverse events among vaccinated;

- improve the use of local and national safety data to generate information to inform effective communication strategies about the safety of the COVID-19 vaccines being used, targeting the public, the community, media, national regulatory authorities (NRAs), vaccine manufacturers[1], WHO and other stakeholders; and
- contribute to continuous updating of the safety profile of COVID-19 vaccines being deployed.

02

Key considerations for adaptation of vaccine safety surveillance systems

To prepare for COVID-19 vaccine introduction, countries will need to adapt their established AEFI surveillance systems to address several key challenges specific to the COVID-19 pandemic. A generic checklist for preparedness for vaccine safety during pandemics is shown in **Appendix 6.1**. This could also be used to verify the country preparedness for COVID-19 vaccines. Due to the variety of vaccine platforms being developed, it is likely that more than one vaccine type will be used simultaneously or sequentially in the same setting. Hence, the surveillance systems must be able to collect full information about all vaccines (including brand names and batch numbers for COVID-19 and other vaccines) and any medications that the person with an AEFI received. Following up specific vaccinated cohorts for at least one year will enable potential vaccine-type specific AESIs to be included, including potential vaccine-associated enhanced disease (VAED) in vaccinated individuals, who develop COVID-19 disease.

It is likely that COVID-19 immunization programmes will focus on adult populations initially. Hence, it will be important to ensure that the surveillance systems are capable of capturing AEFIs in adults, as is necessary for seasonal influenza and pneumococcal polysaccharide vaccination used in adults and for other novel vaccines that have been introduced, e.g., Ebola, meningococcal A and pandemic influenza vaccines.[2,3] Clinics, hospitals and other settings that care for adults may not be familiar with AEFI reporting processes. There may be higher rates of coincidental AEFIs since adults have higher rates of comorbidities than children.

1 For the purpose of this document, manufacturer also means marketing authorization holder.

2 World Health Organization. Guidance for establishing AEFI surveillance systems in countries planning to use Ebola vaccines. Available from: https://www.who.int/csr/resources/publications/ebola/GEVIT_guidance_companion-tool_AEFI.pdf?ua=1. Accessed 29 October 2020.

3 Ateudjieu J, Stoll B, Bisseck AC, Tembei AM, Genton B. Safety profile of the meningococcal conjugate vaccine (Menafrivac™) in clinical trials and vaccination campaigns: a review of published studies. Hum Vaccin Immunother. 2020;16(6):1245-1259. doi: 10.1080/21645515.2019.1652041.

In addition, expert AEFI committee for AEFI/AESI review and causality assessment may not exist everywhere, and when they do, they may have limited experience in the evaluation of AEFI/AESI in adults and people with complex medical conditions.

Surveillance systems will need to be able to accommodate the large numbers of AEFI/AESI reports expected because a large proportion of the population will be vaccinated. AEFI reporting from health facilities or districts may need to be more frequent than routine reporting, to ensure that any safety signals can be detected rapidly and responded to in an appropriate and timely manner.

Finally, as for any new vaccine, the safety data from clinical trials that will be available at the time of the COVID-19 vaccine introduction will be limited and insufficient to detect rare adverse events. There will also be limited safety data for certain populations and for adverse events with a latency longer than the trial follow-up period. There will be a need to communicate rapidly about any adverse events and to respond to public concerns in order to maintain public confidence, in the setting of high media and public attention on COVID-19 vaccines. To prevent alarm or uncertainty in public opinion and in the media, it will be essential to develop an appropriate communication strategy on COVID-19 vaccine safety. Please refer to the communication module for further information.

It is highly likely that phase III clinical trials will still be ongoing when some vaccination programmes are implemented with COVID-19 vaccines that have been granted emergency use listing status. It will be important that rapid access to periodic safety update reports (PSURs) and other safety reports is coordinated between regulatory agencies and vaccine sponsors and vaccine manufacturers in each country. This shared information will be valuable for interpreting passive system safety data and for conducting causality assessments by AEFI committees.

Increases in immunization-error related reactions may occur due to lack of experience in the management of the new COVID-19 vaccines with special handling conditions, e.g., vaccine storage at -80°C or new administration devices or methods and the participation of HCWs who are not traditionally involved in vaccination in many countries. Medical devices surveillance units from NRAs, the National Immunization Programme (NIP), or the Expanded immunization Programme (EIP), or the Ministry of Health (MoH) should also be involved in planning the responses to suspected adverse events, depending on the specificities of the vaccine administration devices for the COVID-19 vaccines that will be implemented.

Table 1 summarizes the recommended safety surveillance activities for all countries introducing COVID-19 vaccine(s) regardless of AEFI surveillance capacity.

Table 1: Recommended AEFI surveillance activities for all countries introducing COVID-19 vaccination, regardless of their AEFI surveillance capacities

Objective	Recommended AEFI surveillance activities
Strengthen routine passive AEFI surveillance reporting systems for the management of increased frequency or severity of AEFI reports (mild, moderate and severe)	1. Conduct training on identification and reporting of AEFI for health care workers. 2. Update, print and distribute AEFI surveillance tools. 3. Use both vaccine tracking information and passive AEFI reporting information to perform vaccine-specific safety analyses. 4. Review and adapt processes for timely reporting, reviewing and data sharing nationally, regionally and globally, e.g. uploading data to global databases such as WHO's VigiBase. 5. Develop clear standard operating procedures (SOPs) for coordination between the NRA, NIP/EIP, and other institutions with responsibilities for AEFI surveillance. 6. Consider coordination of activities with Public Health Emergency Units. 7. Consider setting up AEFI committees at subnational as well as national level, particularly in large countries.
Investigate potential AEFIs causing concern, such as clusters, serious events, programmatic errors, community concerns	1. Prepare investigation teams and train them for AEFI investigation activities that are relevant to the population being vaccinated. 2. Update, print and distribute AEFI investigation tools to obtain information on specific outcomes. 3. Ensure the collection and storage of all relevant data to help make a causality assessment (AEFI reporting and investigation forms, clinical case record, laboratory reports, autopsy reports, etc.). 4. Provide feedback to reporting health care worker, including suggestions for the management of the AE at the local level.
Perform systematic causality assessment of AEFIs causing concern	1. Constitute a National AEFI committee to review and respond to AEFI safety signals and public concerns or contact the WHO Country or Regional Office or send an email to gvsi@who.int to ask for assistance. 2. Provide training on causality assessment processes using WHO causality assessment guidelines for members of the National AEFI committee. 3. Provide regular updates to the Committee members on COVID-19 vaccine development and safety data, including safety reports from ongoing phase III clinical trials or any events reported in clinical trials. 4. Foster and use the committee's expertise to identify AEFI cases in need of further investigation, such as AESIs. 5. Anticipate an increased number of AEFI reports that will need to be reviewed and consider including AEFI committees at subnational as well as national level, particularly in large countries.
Use AEFI and disease surveillance data to detect potential safety signals or clustering of events	1. Regularly review and report AEFI surveillance data, particularly those relevant to AESIs or other conditions identified during pre-licensure COVID-19 vaccine clinical trials. 2. Explore the use of disease surveillance data to complement AEFI surveillance systems for the detecting of AESIs, if indicated. 3. Consider use of early signal detection methods, especially for certain AESIs.

Objective	Recommended AEFI surveillance activities
Prepare comprehensive plans to respond rapidly to all COVID-19 vaccine-related events	1. Outline roles and responsibilities of key stakeholders (both public and private, including vaccine manufacturers) for the implementation of safety surveillance activities and response to vaccine-related events. 2. Keep stakeholders up to date with COVID-19 vaccine safety information. 3. Communicate with WHO regions and headquarters and share data on outcomes of AEFIs and AESIs in a rapid, timely and regular manner.
Address concerns of HCWs and maintain community confidence	1. Create and share a COVID-19 vaccine safety communication plan with relevant stakeholders. 2. Train and support personnel at all levels to address concerns that may arise before, during and after COVID-19 vaccine introduction. 3. Develop, print, and distribute messages concerning the safety COVID-19 vaccines.

03

Surveillance strategies to be adapted to COVID-19 vaccination strategies

The adaptations of AEFI surveillance systems needed will depend on the capacity and functionality of existing systems. All countries should strive to strengthen or enhance their routine passive surveillance capacities by, for example, streamlining processes such as data entry into national databases. Increasing functionality by introducing cohort event monitoring, sentinel sitebased active reporting, and use of electronic data systems at sentinel sites or at populational levels, if possible, should be considered. In addition, some countries may consider active surveillance or specific studies to assess the causal relationship between specific events and COVID-19 vaccination.

3.1 Application of surveillance concepts to COVID-19 vaccine-related AEFI and AESI

The primary purpose of passive AEFI surveillance is to identify and respond to events that are temporally associated with immunization. In contrast, AESI surveillance focuses on the specific events irrespective of vaccination, and then assessments are performed to determine if the event occurs more frequently in vaccinated individuals than in non-vaccinated individuals or following up vaccinated cohorts and assessing the health status.

As there are similarities between the terminology used for the surveillance of AEFIs and AESIs, it is important that HCWs are trained to understand the differences and the implications of the differences. Some key basic concepts are outlined below.

- **Routine passive surveillance (spontaneous reporting):** Cases are not actively sought; surveillance sites passively notify a network when they encounter AEFIs and reports are generated and sent by local staff.[4] In some countries, passive surveillance also includes spontaneous reporting by patients themselves.
- **Active surveillance:**[5] Active surveillance is a data collection system that seeks to ascertain as completely as possible the number of AEFIs in a given population through a continuous, organised process. This may involve designated staff visiting health care facilities, talking to HCWs and reviewing medical records to identify suspected cases of AESI. It can also be done remotely using electronic health databases. When cases are identified, their vaccination status is determined. Active surveillance can also be done through cohort event monitoring or sentinel surveillance.
- **Cohort event monitoring (CEM):** AEFIs are reported by HCWs who are trained to encourage reporting and follow-up of a cohort of those vaccinated through defined channels, e.g., phone call, email, home visit. The system is closely monitored by a central coordinating unit through identified reporting points. Cohort event monitoring could be useful for close monitoring of serious AEFIs and signals following the introduction of COVID-19 vaccines or after mass COVID-19 vaccination campaigns.
- **Sentinel surveillance:** This system is used when high-quality data are needed for a particular disease that cannot be obtained through a passive system. Selected reporting units, with a high probability of seeing patients with the disease, good laboratory facilities and experienced well-qualified staff, identify and report AEFIs. Unlike most passive surveillance systems that receive data from as many HCWs and health care facilities as possible, a sentinel system deliberately collects data from only a limited network of carefully selected reporting sites.

3.2 Routine passive surveillance for AEFIs following COVID-19 vaccine introduction

Routine passive surveillance, whether via electronic- or paper-based systems, is the fundamental, basic type of surveillance for all immunization strategies, i.e., routine, supplementary immunization activities, and mass immunization campaigns. It aims to:

- detect safety signals for further evaluation (sometimes from media reports and public concerns);
- identify rare AEFIs and immunization-error related adverse reactions;
- assess reporting of clusters; and
- generate hypotheses for AESI / AEFI.

4 World Health Organization. National passive surveillance: Available from: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/en/. Accessed 29 October 2020.

5 World Health Organization. Accelerated disease control: Available from: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/en/. Accessed 29 October 2020.

Date from this surveillance can be used to compare rates of AEFI reported in different populations (age, occupation, medical condition, etc.) and by the type of COVID-19 vaccine received.

However, routine passive reporting systems will not be sufficient to allow the rapid assessment and appropriate public health response that will be needed during COVID-19 vaccine introduction. Routine systems will need to be enhanced with active surveillance to improve detection of AEFIs (Table 2). Another approach to enhancing passive systems could involve raising stakeholders' awareness, including the National AEFI committee, about certain events reported as AEFIs that should trigger additional investigation and potential categorization of specific events.

3.3 Active surveillance for AESIs following COVID-19 vaccine introduction

One of the primary aims of active surveillance systems is to estimate the risk of a AESI in a population exposed to a vaccine. As this surveillance is focused on a well-defined population, it can be used to estimate event rates accurately.[6] The staff of active surveillance systems initiate and maintain regular contact with HCWs to identify individuals with the health condition(s) of interest. This information can also be obtained by regularly extracting data from health care databases. Some approaches used for active surveillance of AESIs are cohort event monitoring (CEM) and sentinel surveillance. These are described in detail in the module on AESIs.

Pregnancy registries are an important tool for determining pregnancy outcomes when vaccines are likely to be administered inadvertently or intentionally to women who are pregnant or to women of reproductive age who become pregnant post-immunization.

6 CIOMS Guide to Active Vaccine Safety Surveillance. Available from: https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/. Accessed 29 October 2020.

Table 2: Recommended activities for enhancing safety surveillance systems in countries, based on their current surveillance systems

Level of existing surveillance capacity	Relevant additional objectives	Recommended additional activities
Established passive surveillance – partially functioning	— improve the use of local and national safety data to generate information to communicate with the public, the community, media, NRAs, vaccine manufacturers, WHO and other stakeholders about the safety of COVID-19 vaccines being used; and — contribute to continuous updating of the safety profile of COVID-19 vaccines being used;	1. Assess the functionality of the existing AEFI surveillance system to identify key gaps and ability to expand capacity needed to take on additional safety activities. 2. Strengthen national AEFI committee capacity to review and respond to AEFI safety signals, public concerns or collaborate with WHO to provide this capacity. 3. Consider sentinel site surveillance for AESIs if the above can be achieved and activities can be supported. 4. Consider implementing active surveillance for AESIs, if relevant objectives are addressed.
Established passive surveillance – fully functioning	— improve the use of local and national safety data to generate information that can be used to communicate effectively with the public, the community, media, NRAs, vaccine manufacturers, WHO and other stakeholders about the safety of COVID-19 vaccines being used; — contribute to continuous updating of the safety profile of COVID-19 vaccines being used; and — consider active surveillance for AESIs.	1. Establish active AESI surveillance at selected sentinel sites. 2. Inform the National AEFI committee about potential concerns for COVID-19 vaccines. 3. Share information within the region. 4. Countries could act as resources for neighbouring countries with less capacity. 5. Review sources of epidemiological data at the national and subnational level that could provide information on background rates of selected AESIs, i.e. disease surveillance systems, national or subnational health surveys, specific epidemiological research projects. 6. If information from disease surveillance systems is not available, then consider potential secondary sources that could be used to estimate the background rates.

Level of existing surveillance capacity	Relevant additional objectives	Recommended additional activities
Established passive, active (e.g. database or other) surveillance systems Ability to detect and evaluate signals consistently	— implement active surveillance for AESIs; — conduct research on predefined or newly identified important vaccine safety concerns in large populations or particular target groups, e.g., VAED; — improve the use of local and national safety data to generate information which can be used to communicate effectively with the public, the community, media, NRAs, vaccine manufacturers, WHO and other stakeholders about the safety of COVID-19 vaccines being used; and — contribute to continuous updating of the safety profile of COVID-19 vaccines being used.	1. Inform the national AEFI committee about potential concerns for COVID-19 vaccines. 2. Consider which AESIs should be monitored using active surveillance. 3. Establish background rates for the selected AESIs. 4. Consider participation in regional and global safety surveillance data networks. 5. Countries could act as resource for neighbouring countries with less capacity. 6. Consider specific studies, e.g., plan to identify and evaluate VAED in the context of vaccine failure.

3.4 Specific provisions for additional national safety monitoring activities by COVID-19 vaccine manufacturers

COVID-19 vaccine manufacturers are also responsible for monitoring the safety of their COVID-19 vaccines introduced and for addressing any safety issues that occur. Additional safety surveillance activities should be carried out by vaccine manufacturers to continue collecting information on safety beyond that collected during pre-licensure COVID-19 vaccine trials.

The processes of engaging with the pharmaceutical industry, reviewing risk management plans and outlining the legal provisions and guidelines for COVID-19 vaccine safety are described in the engaging with the pharmaceutical industry module. Additional pharmacovigilance activities such as post-authorization safety studies (PASS) that should be performed to assess any identified risks or potential risks and provide important missing information are also described.

A comparison of passive surveillance, active surveillance for AEFIs and AESIs and for PASSs is presented in Table 3.

Table 3: A comparison of post-licensure pharmacovigilance with passive and active surveillance systems for AEFIs and AESIs and for post-licensure safety studies

	Passive surveillance for AEFIs	Active surveillance for AESIs	Post-authorization safety studies (PASS)
Purpose of information collection	To identify AEFIs, assess their severity and perform causality assessment	To identify predefined specific events and assess association with COVID-19 vaccination or actively follow up a vaccinated cohort	To provide safety information missing at the time of licensure
Relevant for	HCWs, NIP/EPI managers, NRAs, surveillance and information managers, epidemiologists, vaccine manufacturers, surveillance and information managers, media, vaccine safety partners, including the community	Sentinel site staff, NIP/ EPI managers, NRAs, epidemiologists, vaccine manufacturers, national AEFI committees, study teams	NRAs, NIPs/EPIs
Method for data collection	Through spontaneous reporting or detection by HCWs	As per specific protocols for AESIs by sentinel site surveillance of cases or electronic health records, using appropriate methods	As per study protocol designed by vaccine manufacturers and approved by relevant authorities
Initiated by	Pre-existing system	Countries or regions wanting to investigate significant knowledge gaps	Vaccine manufacturer
Responsibility	NIPs/EPIs, NRAs and MoHs	Principal investigator appointed by the country	Vaccine manufacturers with oversight from relevant authorities
Data sharing	NIPs/EPIs, NRAs, MoHs, WHO (VigiBase), vaccine manufacturers	NIP/EPI, NRAs, MoHs, WHO (VigiBase), vaccien manufacturerss	Vaccine manufacturers, NIP/ EPI, NRAs
Preparedness assessment	Preparedness checklist	Protocol reviewed by NITAG/ National AEFI committee	Based on criteria for site selection by NRA, NIP/EPI and vaccine manufacturers
Stakeholder training	All frontline immunization staff in health care facilities (public and private); and other relevant staff in reporting, investigation, data analysis, and causality assessment	Sentinel site staff, immunization staff and clinicians in sentinel sites and predefined active surveillance systems, NIP/EPI mangers, NRA, research staff, national AEFI committee	Principle investigator at study site

NITAG: National Immunization Technical Advisory Group

04 Serious AEFIs and AESIs

Serious AEFIs and AESIs are events that result in death, are life-threatening, require in-patient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, give rise to congenital anomalies or birth defects or are medically important events or reactions. In the event of serious AEFIs or AESIs all documentation generated during the management of the event, including hospitalization, should be appended to the investigation form and submitted as a dossier to the national AEFI committee for causality assessment.

The communication team should be made aware of the occurrence of a serious event as soon as possible in order to coordinate communication responses at the appropriate levels. This will be particularly important during the introduction of COVID-19 vaccines as misinformation may spread rapidly. Further details can be found in communication module.

05 Deaths following COVID-19 immunization

All countries should define specific protocols for investigating deaths following COVID-19 vaccination. Guidance on investigating deaths following vaccination is provided in the Global manual on surveillance of AEFI.[6] Individuals who die following COVID-19 vaccination, including those with any related diagnosis that is an AESI, should be included in the protocol for investigating deaths following COVID-19 vaccination. Due to the high number of deaths during a pandemic, coordination with all stakeholders handling deaths should be established for reporting deaths in persons with a history of COVID-19 vaccination. Specific protocols for autopsies of people with a suspected cause of death given as COVID-19 have been developed, and these could be used for the autopsy of COVID-19 vaccinated individuals who die.[7] If indicated, tissue samples should be collected for in-depth pathologic, virologic and genetic testing. If an autopsy is not done, a complete verbal autopsy using standard protocol should be conducted and the findings documented and sent to the national AEFI committee.

7 Carpenito L, D'Ercole M, Porta F, Di Blasi E, Doi P, Fagara GR, et al. The autopsy at the time of SARS-CoV-2: protocol and lessons. Ann Diagn Pathol. 2020;48:151562. doi: 10.1016/j.anndiagpath.2020.151562.

06 Appendix

Appendix 6.1: Preparedness checklist for vaccine safety during pandemics recommended tool for national programme managers

Need for minimum requirements checklist during a pandemic: During a pandemic, pre-existing systems need to be rapidly reviewed and assessed to determine if they are robust enough to address the anticipated unpredictable situations that may emerge during a pandemic that need decision making by ensuring that:

- tools and logistics are available to the appropriate safety focal persons and they know how to use them;
- availability of appropriate well trained, empowered manpower who have clearly defined roles and responsibilities with a balanced workload;
- access to data and ability to convert data to information for action rapidly is available;
- critical decisions can be made rapidly;
- multiple activities can be prioritized;
- communication is effective with relevant stakeholders involved in the response;
- the response is coordinated; and
- any crisis occurring is pre-empted and addressed appropriately.

Key considerations and managerial principles when using the pandemic preparedness checklist

- Ensure that high-quality training is available at all levels, and that vaccination staff (and staff monitoring safety) are knowledgeable, empowered and confident about making important decisions.
- Endeavour to be independent and find local solutions for local problems.
- Use existing tools and resources and 'adapt' them, if necessary, by making minimal essential and critical changes and modifications.
- Use existing staff and build capacity and enhance their roles and responsibilities rather than introducing new staff.
- Identify the existing data and information management systems and plan their upgrade, if necessary.
- Use innovative ideas and strengths from the health care sector and also from other sectors, including industry, businesses and private sectors.

- Harness the intellectual resources from multiple sectors and brainstorm and arrive at solutions that are more applicable to local content

These requirements have been streamlined to develop the minimum requirement preparedness checklist below. The checklist can be used to form a baseline assessment of the pre-deployment vaccine safety surveillance system to ensure that safe vaccines are administered and to identify how to prioritize and prepare the system to address the enhanced role it will have to play during the pandemic.

Preparedness checklist for vaccine safety during pandemics

#	Tasks	Not started	In progress	Completed	Responsibility assigned to
I	*Preparedness – managerial level*				
I-a	Has the NITAG and the MoH identified the vaccine to be used for the pandemic?				
I-b	Has the vaccination strategy been identified by the pandemic programme managers?				
I-c	Have the vaccine manufacturer submitted the vaccine safety dosser to the NRA for authorization for use in the country?				
I-s	Has the RMP submitted by the vaccine manufacturer been reviewed by the NRA?				
I-e	Has there been joint discussion with the NIP/EPI on operationalizing the RMP and aligning it with the vaccination strategy adapted by the country?				
I-f	Have specific funds been allocated in preparation to build vaccine safety capacity and manage safety issues?				
I-g	Have the national regulatory authority, NIP/EPI, NITAG, national AEFI committee, inter-agency coordinating committee, health sector coordinating committee, media committee and other relevant committees had a meeting to finalise the roll out plans?				
I-h	Has a decision been made about the passive AEFI system and the type of AESI active surveillance system(s) that the country will adopt for COVID-19 vaccine safety surveillance during the pandemic?				

#	Tasks	Not started	In progress	Completed	Responsibility assigned to
I-i	Have key national focal persons been identified and assigned responsibilities for AEFI and AESI surveillance?				
I-j	Have the frequency and dates for periodic vaccine safety reviews by the national AEFI committee, NITAG, NRA and EPI meeting ben finalized?				
I-k	Has the national AEFI committee been specially trained for the COVID-19 vaccine(s) to be used in the country? Has the training been comprehensive e.g., causality assessment, AEFI investigation?				
I-l	Has the investigation, management, response plan and the roles and responsibilities for vaccine safety crisis management (including deaths after vaccination) been defined?				
I-m	Is there a clear decision-making pathway at the national level to enable the MoH to operationalize the recommendations made by expert committees?				
II	***Communication strategy***				
II-a	Has the national coordination committee for communications been convened?				
II-b	Has the vaccine safety communications plan been included as a component of an overall vaccine rollout communication plan?				
II-c	Is there a vaccine safety media plan in place for crisis communication?				
II-d	Has the national communication spokesperson been trained on the vaccine safety aspects of the COVID-19 vaccine to be used during the pandemic?				
II-e	Does a system for the transparent dissemination of COVID-19 vaccine safety data to the public and stakeholders exist?				
III	***Data management strategy***				
III-a	Have the vaccine safety data management tools to be used for the collection, collation, transmission and processing of AEFI and AESI data been decided?				

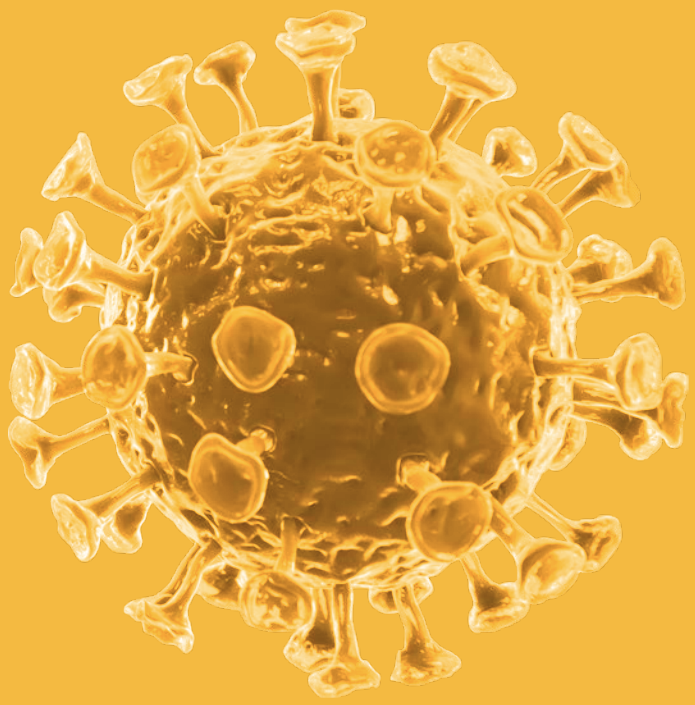
#	Tasks	Not started	In progress	Completed	Responsibility assigned to
III-b	Have the roles and responsibilities for the collection, collation, transmission and processing of AEFI and AESI data been finalized?				
III-c	Is there a clear strategy identifying the frequency and the content of the data to be shared with the relevant stakeholders (NRA, NIP/EPI pharmacovigilance centre and MoH)				
III-d	Have relevant stakeholders been trained on how to assess data coming from active surveillance systems for AESIs?				
III-e	Has the process for sharing data with the WHO programme for international drug monitoring been defined?				
IV	***Availability of tools and logistics***				
IV-a	Have the vaccine safety guidelines been reviewed and were they modified and adapted for the current COVID-19 pandemic context?				
IV-b	Have national tools for vaccine safety been reviewed and adapted for the COVID-19 pandemic context?				
	— AEFI reporting form				
	— AEFI linelisting form				
	— AEFI Investigation form				
	— AESI tools				
IV-c	Are these tools ready for use and have they been made available (shipped) and to institutions and stakeholders at:				
	— national level				
	— province level				
	— district level				
	— health centre level				
V	***Training and capacity building***				
V-a	Has a national training plan been developed for COVID-19 vaccine safety?				
V-b	Have train-the-trainer workshops been included in the national training plan for COVID-19 vaccine safety?				

#	Tasks	Not started	In progress	Completed	Responsibility assigned to
V-c	Has a clear COVID-19 vaccine safety training curriculum adapted to the COVID-19 vaccine(s) and vaccination strategy(ies) been developed for the local context?				
V-d	Have training timelines for different profiles of staff at all levels been defined?				
V-e	Has a specific budget been allocated for COVID-19 vaccine safety training?				
V-f	Is there a specific training plan for AEFI investigation for experts at the subnational level?				
V-g	Has AEFI investigation training been completed?				
V-h	Has specific training for active surveillance of AESIs based on approved protocols been completed?				

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

MONITORING AND RESPONDING TO ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIS)



Contents

Key points

- In the context of COVID-19 vaccination, surveillance systems need to be prepared for identifying and responding to both adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) as well as other safety events that may cause public concern, including incidents of substandard or counterfeit vaccines
- Specific funds should be allocated for identifying, reporting and responding to AEFIs and AESIs during the planning stage, before COVID-19 vaccination is implemented
- AEFIs are untoward medical events that follow immunization, and that do not necessarily have a causal relationship with the usage of the vaccine
- Clearly distinguishing genuine vaccine product-related events from coincidental events or concomitant medication-related AEs will be a challenge
- Immunization programmes should anticipate and prepare for clusters of AEFI following COVID-19 vaccination as the chances of immunization errors and Immunization anxiety-related reactions are much higher than that of routine immunization. Coincidental events can also occur as clusters
- AEFI detection primarily 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
- For COVID-19 immunization-related AEFIs, in addition to standard information, it is important to record the brand name, the manufacturer, as well as the batch numbers because it is possible that more than one COVID-19 vaccine will be in use simultaneously in a country
- All countries should establish a process for causality assessment prior to the introduction of COVID-19 vaccines
- AEFI causality assessment committees should pluri-disciplinary, including adult and elderly specialities, since COVID-19 vaccines will be administered to individuals of all ages
- The committee communication spokesperson will be responsible for communication about the AEFIs assessed by the committee, particularly with the media and other stakeholders
- AEFI causality assessment committees should anticipate an increase in reporting of serious AEFIs following the introduction of COVID-19 vaccines due to the novelty of COVID-19 vaccines, the high vigilance for AEFIs, and broad range of target populations
- Performing scientific causality assessments requires a comprehensive, completed AEFI investigation dossier, with all the necessary information including a 'valid diagnosis', details of the vaccine administered, information about medication being taken at the time of vaccination or prior to the occurrence of the AEFI and an independent AEFI causality assessment committee
- It is recommended to use existing data collection tools for data collection, collation and processing for AEFIs, that can be adapted, if necessary

01 Introduction

As outlined in the module on COVID-19 vaccine platforms, the unprecedented rapid development of the COVID-19 vaccines on novel platforms followed by their rapid deployment on a mass scale poses unique challenges for monitoring vaccine safety. Timely detection and reporting of adverse events following COVID-19 immunization is the first step in the continuous verification of vaccine safety. In the context of COVID-19 vaccination, surveillance systems need to be prepared for identifying and responding to both adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) as well as other safety events that may cause public concern, including incidents of substandard or counterfeit vaccines.

AEFIs and AESIs can be detected through passive and active surveillance, respectively. However, if countries do not implement active surveillance for AESIs, all AESI-like adverse events occurring following COVID-19 immunization should be considered as AEFIs and the standard procedure for AEFI response, described below, should be adopted. In addition, the separate module on AESIs and the WHO detailed guidance on AESI following COVID-19 vaccination (to be developed) provides detailed information on AESIs including a list of potential AESIs, their case definitions, study protocols, training requirements, data collection tools (including AESI confirmation forms), processing, transmission, analysis and response.

Specific funds should be allocated for identifying, reporting and responding to AEFIs and AESIs during the planning stage before COVID-19 vaccination is implemented. This is needed because there are likely to be a lot of unknown associations since COVID-19 is a new infectious disease with many of its manifestations are still unknown, a broad target population will be exposed to one of the many new vaccines being evaluated, produced by various manufacturers, and different immunization strategies will probably be adopted by different countries.

02 Standard vaccine safety definitions and their implications in vaccine safety in the COVID-19 context

2.1 Adverse events following immunization

AEFIs are any untoward medical events that follow immunization, and that do not necessarily have a causal relationship with the immunization. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.[1] The same definition will continue to be used to identify and report all AEFIs following COVID-19 immunization.

2.2 Cause-specific definitions of AEFIs and implications COVID-19 context

Vaccine product-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

- the identification of rare (occurring in 0.01% to less than 0.1% of immunized individuals) and very rare (occurring in <0.01% of individuals) adverse events is insufficient at the time of COVID-19 vaccine licensure and more information will be needed for which AEFI surveillance has to be strengthened.

Clearly distinguishing genuine vaccine product-related events from coincidental events or concomitant medication-related AEs will be a challenge.

Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the vaccine manufacturer.[2]

- Potential vaccine quality defects for new COVID-19 vaccine platforms might not be known at the time of authorization. Hence vaccine safety surveillance must be strengthened to be able to gather this knowledge.

1 Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Available from: https://cioms.ch/working_groups/vaccine-pharmacovigilance/. Accessed 16 November 2020.

2 For the purpose of this document, manufacturer also means marketing authorization holder.

- The rapid scaling up of vaccine production also poses additional potential risks and the identification of the exact substance in the vaccine formulation causing the adverse event will be needed.
- The likelihood of AEFIs being cause by a substandard or counterfeit version of COVID-19 vaccines should also be considered.

Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and so is preventable.

- It is anticipated that COVID-19 vaccines will be administered on a massive scale in a short time interval with minimum training and field preparation and larger number of Immunization error-related reactions are anticipated. Also, staff who are not familiar with immunization may be asked to perform immunization duties. Multiple vaccines with different specifications for storage, administration, dose etc, may be in use in a country simultaneously.

Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization.

- A larger number of Immunization anxiety-related reactions are anticipated due to numerous factors including older age groups, the different vaccination environments, the novelty of the vaccines and their administration modalities.

Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

- Because of real and potential underlying comorbidities in a large number of the potential vaccinees, it will be challenging to differentiate true coincidental events from COVID-19 vaccine product related reactions or drug reactions or interactions.
- Similar challenges will occur in healthy individuals without comorbidities, especially where a higher frequency is expected based on age, gender, geographic location or ethnic background. Knowing the population-based incidence (background rates) of pre-specified adverse events of special interest (AESI) will help to anticipate and respond to such events in order to identify those that are coincidental as and those that are vaccine product-related.

2.3 Serious AEFI

A serious AEFI is an event that results in death, hospitalization or prolongation of an existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or is life-threatening or is a medically important event or reaction.

- The types and characteristics of serious AEFI particularly rare and very rare adverse events that could occur following COVID-19 vaccines are currently unknown, particularly rare and very rare adverse events.

2.4 Cluster

A cluster is when two or more AEFIs related in time, place or by vaccine occur. Two or more cases of the same or similar events in an AEFI cluster are usually associated with a particular vaccine manufacturer, a health facility, a vaccine batch, or a vial of vaccine, when multidose presentations are used.

- When vaccines are administered on a massive scale, it is important for immunization programmes to anticipate and prepare for clusters of AEFI as the chances of immunization errors and Immunization anxiety-related reactions are much higher than that during routine immunization. Coincidental events can also occur as clusters.

2.5 Signal

A signal is information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verification.[3]

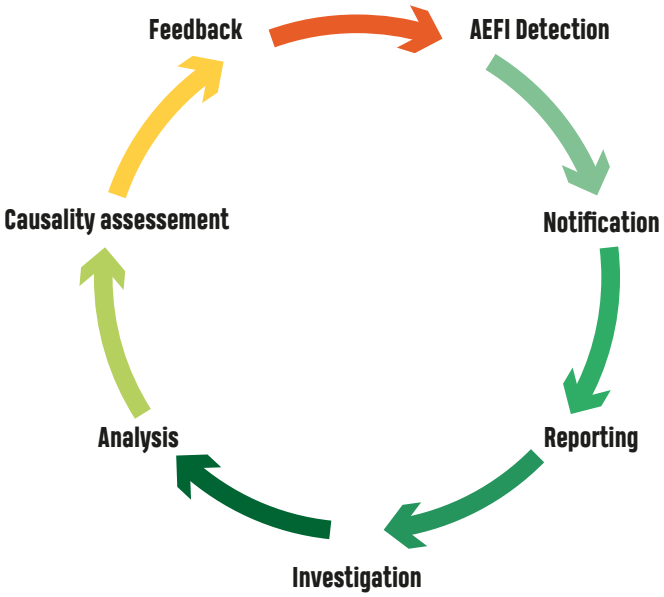
- Signal detection, verification and response is a key activity that has to be specifically addressed in the COVID-19 context. Signals can best be identified by pooling of data from multiple sources and analysing if the pooled data points to the occurrence of a new event that could be causally related to the vaccine.

3 CIOMS. Practical aspects of signal detection in pharmacovigilance. Report of CIOMS Working Group VIII. 2010. Available from: https://cioms.ch/publications/product/practical-aspects-of-signal-detection-in-pharmacovigilance-report-of-cioms-working-group-viii/. Accessed 21 November 2020.

03 AEFI surveillance in the context of COVID-19 vaccine introduction

At the time of vaccine introduction, all countries should at a minimum have an AEFI surveillance system in place as described in the *Global Manual on Surveillance of AEFI*.[4] The AEFI surveillance cycle (**Fig 1**) outlines the different steps in identification (detection), notification, reporting, investigation, data analysis, causality assessment and feedback following all AEFI, including AEFI following COVID-19 immunization.

Fig 1: AEFI surveillance cycle



3.1 AEFI detection, notification and reporting

AEFI detection primarily takes place primarily through routine passive surveillance (spontaneous reporting) in many countries. This 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 within the health care system. AEFIs can also be detected through active surveillance, via sentinel sites or through cohort event monitoring. In addition, AEFIs may be detected in phase IV clinical studies of COVID-19 vaccines where they should be independently reported, assessed and processed, in compliance with

4 World Health Organization. Global manual on surveillance of adverse events following immunization. 2014. Available from: https://www.who.int/vaccine_safety/publications/aefi_surveillance/en/. Accessed 21 November 2020.

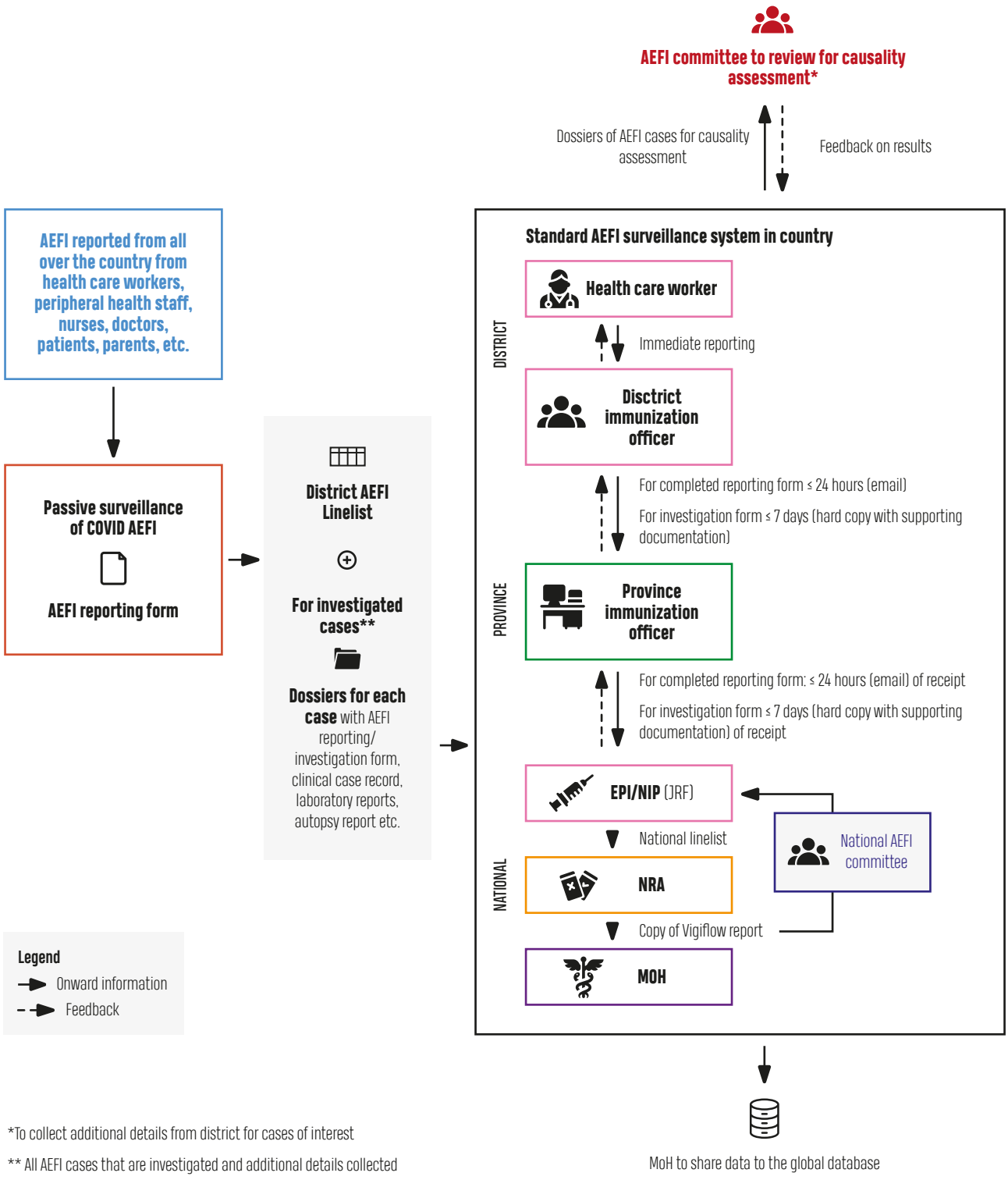
the study protocol and should not be reported through the passive reporting systems as described in this module.

3.1.1 Role of routine passive reporting systems for AEFI detection and notification

All AEFIs should be reported using the standard COVID-19 AEFI reporting form (**Appendix 5.1**) using the fastest means possible. When the AEFI is judged to be serious, reporting should also include a telephone call, direct conversation or notification via a specific application, depending on what is available in the country. AEFI reporting forms contain a minimum set of core variables in order to make the global evaluation of signals possible and thus help countries to evaluate the reported AEFIs.

For COVID-19 immunization-related AEFIs, in addition to standard information, **it is important to record the brand name, the manufacturer, as well as the batch numbers**, because vaccines in use in countries are likely to be manufactured on different platforms, with different antigen targets, adjuvants and dosage forms. A comprehensive complete AEFI report is the primary source for populating an AEFI linelist (**Appendix 5.2**) which, when processed, provides key descriptive epidemiological data (time, place and person) that are critical for identifying clusters and for signal detection. The AEFI reporting form also provides information on the quality of the passive surveillance system in terms of the completeness and timeliness of the reporting. This is important for monitoring the performance of pharmacovigilance systems. The primary reporter, i.e., the immunization provider or health care worker, are usually responsible for providing most of the information required in the COVID-19 AEFI reporting form. In some countries, vaccine recipients or their parents may complete the form themselves. AESIs may be reported spontaneously after COVID-19 immunization. These will be considered as AEFIs and will be processed through the standard AEFI surveillance system as described in this module (**Fig 2**).

Fig 2: In-country reporting and processing of AEFI



3.1.2 AEFI reporting

As outlined above, when a COVID-19 standard AEFI reporting form is received at the district, it should be reviewed for seriousness, decision taken on investigation and transmitted to the province and national levels as described in the *Global Manual on Surveillance of AEFI*.[5] If the

5 WHO. Global manual on surveillance of adverse events following immunization. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf. Accessed 28 October 2020

AEFI is considered to be minor or NOT serious, detailed investigation and causality assessment will not be required; this should be noted on the form. Detailed investigation and causality assessment will be required if the AEFI is considered to be:

- a serious AEFI, i.e., death, hospitalization, significant disability, life threatening, congenital anomaly, birth defect or a medically important event or reaction, or part of a cluster; or
- part of a group of events with an unexpected high rate or severity, or a suspected signal.

3.2 Investigating potential COVID-19 vaccine-related AEFIs

Chapter 6 of the *Global Manual on Surveillance of AEFI*[5] describes:

- why AEFIs should be investigated
- which AEFIs should be investigated
- who should investigate AEFIs
- when AEFIs should be investigate
- how to investigate AEFIs
- laboratory testing of specimen
- investigating AEFI clusters and investigation of deaths following immunization.

For AEFIs following COVID-19 immunization, the same processes and methodology should be followed, after the relevant staff have been trained. During the investigation, it is important to remember that, as for all other vaccines, attention should be paid to identify and rule out immunization (or programme) error-related AEFIs, immunization stress related responses and coincidental events that could manifest as a COVID-19 vaccine-related AEFI. Therefore, during AEFI investigations it will be necessary to obtain information on:

- concomitant medication, with indication and administration dates
- vaccine administration techniques
- vaccine transport, storage and handling
- immunization session environment and organization.

If the district authorities and experts feel that the AEFI investigation can be done locally, they can visit the patient and initiate the detailed investigation with appropriate members of the local health care team. If not, assistance should be solicited from the higher levels of the hierarchy. For deaths, national investigations should be led by a team from the National AEFI Committee, supported in the investigation by the Expanded Programme for Immunization (EPI) or National Immunization Programme (NIP), the National Regulatory Authority and other experts, as needed. During field investigations, the COVID-19 specific AEFI investigation form

(**Appendix 5.3**), the WHO AEFI investigation software[6] and aide mémoire[7] should be used to guide the process.

3.2.1 Causality assessment of potential COVID-19 vaccine-related AEFIs

Causality assessment is the systematic review and evaluation of available data about an AEFI to determine the likelihood of a causal association between the event(s) and the vaccine received. All countries must establish a process for causality assessment prior to the introduction of COVID-19 vaccines. In addition to having a functional post-marketing pharmacovigilance or AEFI surveillance system, there must be access to a functional expert group for causality assessment either at national, subnational, or regional levels. This step is critical for any country to ensure the scientific evaluation of potential COVID-19 vaccine-related AEFIs. Smaller countries who do not have enough experts may collaborate with neighbouring countries (or use regional resources), and larger countries may have committees at the subnational level.

The *Causality assessment of an adverse event following immunization (AEFI), user manual for the revised WHO AEFI causality assessment classification*[8] outlines the scientific basis for causality assessment and performing the assessment in a four-step process. The same causality assessment principles and process should be applied for the assessment of COVID-19 vaccine-related AEFIs.

However, because COVID-19 vaccines are novel vaccines, with multiple vaccine platforms, antigen targets and adjuvants produced by various manufacturers and will probably have differing implementation strategies adopted by different countries for broad target populations, information on risk of rare serious vaccine reactions will be limited at the time of regulatory assessment and authorization of the COVID-19 vaccines. The adaptation of causality assessment approaches must be envisaged to allow the efficient identification, monitoring and evaluation of suspected signals to ensure that the necessary regulatory and programmatic decisions are taken in a timely manner.

If phase III clinical trials are ongoing simultaneously with the widespread use of COVID-19 vaccines due to their emergency use listing, AEFI committees should have access to the periodic safety updated reports (PSURs). In addition, serious adverse events rates could be made available to the committee by the COVID-19 vaccine manufacturer. Global information and information from other regions should be available for the causality assessments, to help to identify signals and situations that could require collection of more detailed information.

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6 World Health Organization. AEFI investigation software. Available from: https://www.who.int/vaccine_safety/software-assistance-guiding-hq-AEFI-investigations/en/. Accessed 28 October 2020.

7 World Health Organization. AEFI investigation aide mémoire. Available from: https://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf?ua=1. Accessed 28 October 2020.

8 World Health Organization. Causality assessment of an adverse event following immunization (AEFI). Updated user manual for the revised WHO classification (Second edition). Available from: https://www.who.int/vaccine_safety/publications/gvs_aefi/en/. Accessed 28 October 2020.

3.2.2 Country preparedness and capacity required for causality assessment for COVID-19 vaccine-related AEFIs

The AEFI causality assessment committee should include experts from paediatrics, neurology, general medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. In addition, other external specific medical experts such as geriatricians, pulmonologists, cardiologists, nephrologists should be invited following the introduction of COVID-19 vaccines as they will be administered to individuals of all ages. If countries decide to use the AEFI committees to review AEFI cases to identify signals, the committees will need to be strengthened with additional expertise from statisticians and epidemiologists trained in research methodology. The committee communication spokesperson will be responsible for communication about the AEFI assessed by the committee, particularly with the media and other stakeholders.

The committee should be independent and should have secretarial support from both the immunization programmes (EPI or NIP) and the NRA. Alternatively, drug safety committees that evaluate adverse drug reactions could perform the causality assessment if training on AEFI causality assessments is provided. National pharmacovigilance centres play an important role in vaccine safety and their roles and responsibilities in causality assessment should be defined, taking into consideration the country context.

Countries with existing AEFI causality assessment committees do not need to establish a separate committee for COVID-19 vaccines. However, a refresher training course focusing on COVID-19 vaccine-specific AEFIs before COVID-19 vaccine introduction is warranted in the light of the unique challenges described above. Countries that do not have AEFI causality assessment committees should aim to establish such a committee prior to COVID-19 vaccine introduction to allow adequate time for training and preparation.

Decentralization should be considered in countries where the population and geographical territory are large. Sub-national AEFI causality assessment committees could be established, provided that the requisite expertise and other resources are available. This will enable timely AEFI causality assessment and reduce the workload for the national AEFI causality assessment committee. However, the sub-national committees should share all AEFI causality findings with the national committee. The sub-national level of AEFI causality assessment could also be considered as an interim stage of AEFI causality assessment for complex cases with national interest, for which the final assessment should be done by the national committee.

AEFI causality assessment committees should anticipate an increase in reporting of serious AEFIs following the introduction of COVID-19 vaccines due to the novelty of COVID-19 vaccines, the high vigilance for AEFIs, and broad range of target populations. Although this will increase their workload, the causality assessment must be performed in a timely manner to enable appropriate decision making and early response. This will be essential for maintaining the community's confidence and trust of the COVID-19 vaccines. The frequency of AEFI causality assessment committee meetings should be adjusted to meet this demand.

Countries requiring special technical expertise for causality assessment, such as specific training on COVID-19 AEFI causality assessment or advice for laboratory tests, should contact

their WHO national or regional office. Assistance is also available from WHO at the global level by contacting: gvsi@who.int.

Establishing a regional technical committee for causality assessment with collaborative mechanisms for a broader range of expertise and experience in causality assessment will support countries with limited internal expertise and resources. The success of this strategy will depend on the country willingness to share information, where necessary, while maintaining confidentiality. In addition, this regional committee could provide advice for Member States on the trends and patterns of safety signals for COVID-19 vaccines in use in the region.

3.2.3 Case selection and prerequisites for individual causality assessment

The selection of AEFI cases reported from passive surveillance systems for causality assessment should focus on the following situations:

- serious AEFIs in vaccinated patients that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability/incapacity, or result in a congenital anomaly or birth defect or is a medically important event or reaction;
- the occurrence of events with an unexpected high rate or unusual severity;
- signals generated as a result of individual or clustered cases;
- significant events of unexplained cause, occurring up to 1 year after COVID-19 vaccination (and that are not listed in the product information); or
- events causing significant parental, family or community concerns.

3.2.4 Key considerations during causality assessments for COVID-19 vaccine- related AEFIs

Performing scientific causality assessments requires a comprehensive, completed AEFI investigation dossier, with all the necessary information including a valid diagnosis, details of the vaccine administered, information about medication being taken at the time of vaccination or prior to the occurrence of the AEFI and an independent AEFI causality assessment committee. At the time of assessment, the AEFI case investigation should have been completed, all details of the case such as the COVID-19 AEFI report form, case investigation form, completed clinical case record, laboratory report, autopsy report, details of field investigations should be available.

Due to unique challenges associated with COVID-19 vaccines, the AEFI causality assessment committee should consider each of the following factors:

- *Evidence for causes other than COVID-19 vaccines*: Prior knowledge on background rates of the events in the population are essential to determine if the event is associated or not with the vaccine. This is important to support for the classification of coincidental events in adult population, particularly those with chronic diseases.
- *Known causal association between COVID-19 vaccines and vaccination*: Information available from clinical trials, information published for vaccine platforms and brand-specific AEFI

rates will be useful for the assessment. In addition, risk management plans and PSURs provided by the vaccine manufacturers will be useful.

- *Novel administration technologies and handling requirements:* Administration of some COVID-19 vaccines will require specific skills for storage conditions and handling of new technology. This could increase the risk of immunization-related errors.
- *Diverse age groups:* The use of COVID-19 vaccines for the immunization of adults and adolescents and in mass campaigns could increase the risk of reporting of immunization anxiety or immunization stress-related responses.
- *Other qualifying factors for classification:* These could include previous history of a similar event, background rates of pre-existing, present and past health conditions, medications, etc.
- *Vaccine- enhanced COVID-19 disease:* Vaccine-associated enhanced disease is known to be a AEFI associated with some live attenuated vaccines. COVID-19 vaccination may be associated with an increased risk of developing COVID-19-like disease or its complications. There is also a potential risk of individuals immunized with a COVID-19 vaccine could develop severe COVID-19 disease when exposed to wild-type COVID-19 virus. At present, there is no evidence that these risks exist for COVID-19 vaccines, but they cannot be excluded. It is important to keep in mind multisystem inflammatory syndrome in children and adults during causality assessment as the relationship is currently unclear.

04 Tools for AEFI

It is recommended to use the existing data collection tools, as described in the Global Manual on Surveillance of AEFI[5] for data collection, collation and processing for AEFIs. Some of the tools need to be amended and adapted to the context of the COVID-19 vaccine safety. The details of some available tools and how to access them are provided in **Table 1**.

Table 1: Tools recommended for COVID-19 vaccine-related AEFI reporting, investigation, management and causality assessments

Description	Purpose	Status for COVID-19	Electronic tool
AEFI reporting form	To collect basic reports of all AEFI cases that have been notified	COVID-19 standard AEFI reporting form that includes the name of the manufacturer and brand name	Use in-country tools if available; if not WHO recommends Vigiflow
AEFI linelist	To collate the details in the reporting form	COVID-19 standard linelist that includes the name of the manufacturer and brand name	WHO recommends Vigiflow
AEFI investigation form	To collect detailed information when serious AEFI cases are investigated	Adapted to include COVID-19 specific questions	WHO AEFI investigation assistance software
AEFI causality assessment (available here)	To determine case classification of serious AEFI cases	Remains unchanged	Global Vaccine Safety on-line causality assessment tool

05 Appendices

Appendix 5.1: Standard COVID-19 AEFI reporting form

AEFI reporting id number:

STANDARAD REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

***Patient name or initials*:** ***Patient's full Address*:** Telephone: Sex: ☐ M ☐ F (Pregnant ☐ Lactating ☐) ***Date of birth (DD/MM/YYYY)*:** _ _/_ _/_ _ _ _ *OR Age at onset :* ☐☐*Years* ☐☐ *Months* ☐☐☐ *Days* *OR Age Group:* ☐ 0 < 1 year ☐ 1- 5 years ☐ > 5 years - 18 years ☐ > 18 years – 60 years ☐ > 60 years	***Reporter's Name*:** Institution: Designation &Department: Address: Telephone & e-mail: Date patient notified event to health system (DD/MM/YYYY): _ _/_ _/_ _ _ _ Today's date (DD/MM/YYYY): _ _/_ _/_ _ _ _

Health facility (or vaccination centre) name:

Vaccine							*Diluent*		
Name of vaccine (Generic)	***Brand Name incl. Name of Manufacturer***	***Date of vaccination***	***Time of vaccination***	Dose (1st, 2nd, etc.)	***Batch/ Lot number***	Expiry date	***Batch/ Lot number***	Expiry date	Time of reconstitution

Adverse event (s): ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever≥38°C ☐ Other (specify)..... Date & Time AEFI started (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ ☐☐ Hr ☐☐Min	Describe AEFI (Signs and symptoms):
Serious: Yes / No ; ➔ If Yes ☐ Death ☐ Life threatening ☐ Disability ☐ Hospitalization ☐ Congenital anomaly ☐ Other important medical event (Specify_____)	
Outcome: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown ☐ Died If died, date of death (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ Autopsy done: ☐Yes ☐No ☐Unknown	
Past medical history (including history of similar reaction or other allergies), concomitant medication and dates of administration (exclude those used to treat reaction) other relevant information (e.g. other cases). *Use additional sheet if needed :*	

First Decision making level to complete:

Investigation needed: ☐ Yes ☐ No	If yes, date investigation planned (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

National level to complete:

Date report received at national level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	AEFI worldwide unique ID :
Comments:	

**Compulsory field*

Appendix 5.2: AEFI linelist

COVID19 AEFI linelist

Source	S. No	Patient Name/ Identifier	AEFI Reporting ID number	Patient Location (Village/Town)	Patient Location (District)	Sex (M/F)	Pregnant (Y/N)	Lactating (Y/N)	Age (Date of brith or age at onset)	Vaccine/s Brand	Manufacturer name	Dose	Vaccine Batch No	Diluent Batch No	Adverse Event	Place of vaccination	Date of Vaccination (DOV)	Date of onset (DOO)	Date of Notification (DON)	Date of Reporting (DOR)	Serious (Yes/No)	Reason for Serious	Outcome	Autopsy conducted in case of death (Y/N/NA)	Reported by	Reporter Location 1	Reporter Location 2	Investigation Planned (Y/N)	Date report recd. at Natl Level

Appendix 5.3: AEFI investigation form adapted for COVID-19 immunization

Oct 2020

AEFI FOLLOWING COVID 19 VACCINATION - INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A Basic details

Province/State **District** **Case ID**

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

Date of investigation: __ __ / __ __ / __ __ __ __
Date of filling this form: __ __ / __ __ / __ __ __ __

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐M ☐ F

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

OR *Age at onset: __ __ years __ __ months __ __ __ days*

OR *Age group:* ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years - 18 years* ☐ *> 18 years – 60 years* ☐ *> 60 years*

Patient's full address with landmarks *(Street name, house number, locality, phone number etc.)*:

Brand name of vaccines (including manufacturer) /diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom (*hh/mm):* __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐Unknown

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ (*hh/mm):* __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B Relevant patient information prior to immunization

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event?	Yes / No / Unkn	
Adverse event after any previous vaccination(s)?	Yes / No / Unkn	
History of allergy to vaccine, drug or food?	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unkn	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause?	Yes / No / Unkn	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unkn	
For adult women • Currently pregnant? Yes (weeks) _____ / No / Unknown • Currently breastfeeding? Yes / No		

For infants

The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

Section C Details of first examination** of serious AEFI case

Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy** ☐ **Other**_____ *If from verbal autopsy, please mention source* _____

Name of the person who first examined/treated the patient:_____

Name of other persons treating the patient: _____

Other sources who provided information (specify): _____

Signs and symptoms in chronological order from the time of vaccination:

Name and contact information of person completing these clinical details:	Designation:	Date/time

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports, prescriptions for concomitant medication) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day

Number immunized for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

a)	When was the patient immunized? (✓ the ☐ below and respond to ALL questions)	
	☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown	
	In case of multidose vials, was the vaccine given ☐ within the first few doses of the vial administered? ☐ within the last doses of the vial administered? ☐ unknown?	
b)	Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c)	Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d)	Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes* / No / Unable to assess
e)	Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes* / No / Unable to assess
f)	Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes* / No / Unable to assess
g)	Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes* / No / Unable to assess
h)	Number immunized from the concerned vaccine vial/ampoule	
i)	Number immunized with the concerned vaccine in the same session	
j)	Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k)	Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes* / No / Unable to assess
l)	Could this event be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes* / No / Unable to assess
m)	Is this case a part of a cluster?	Yes* / No / Unkn
	i. If yes, how many other cases have been detected in the cluster?	
	a. Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
	b. If no, number of vials used in the cluster (enter details separately)	

*__It is compulsory for you to provide explanations for these answers separately__

Section E Immunization practices at the place(s) where concerned vaccine was used

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn

If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____

Specific key findings/additional observations and comments:

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA

Specific key findings/additional observations and comments:

Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)	
• Correct dose and route?	Yes / No
• Time of reconstitution mentioned on the vial? (in case of freeze dried vaccines)	Yes / No
• Non-touch technique followed?	Yes / No
• Contraindications screened prior to vaccination?	Yes / No
• How many AEFI were reported from the centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If Yes, specify the date of last training _____)	Yes / No
Specific key findings/ additional observations and comments?	

Section F Cold chain and transport

(Complete this section by asking and/or observing practice)

Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

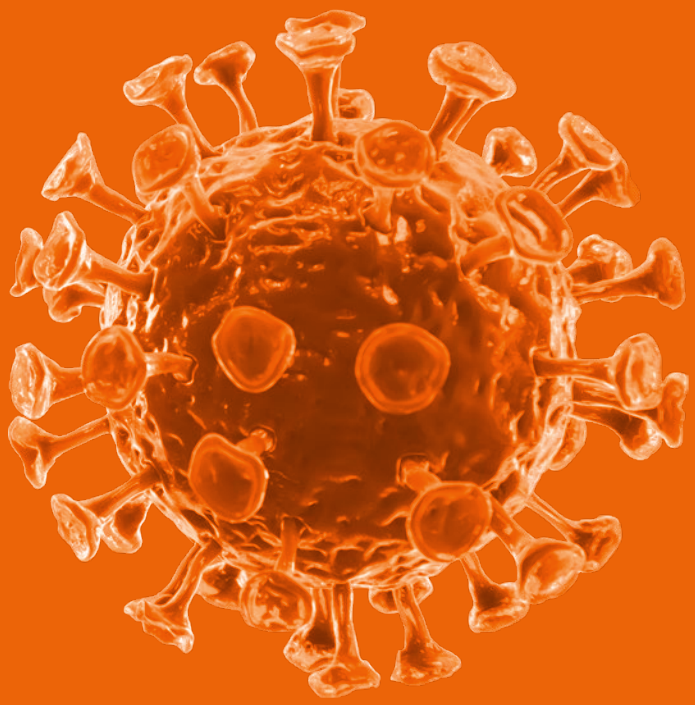
Other comments:

Section H Other findings/observations/comments

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

MONITORING AND RESPONDING TO ADVERSE EVENTS OF SPECIAL INTEREST (AESIS)



Contents

Key points

- Conventional vaccine safety pharmacovigilance and surveillance systems will need to be adapted rapidly in the context of COVID-19 vaccine introduction to ensure that the safety of the public is not put at risk.
- Shortlisting pre-specified adverse events of special interest (AESIs) before COVID-19 vaccine introduction will enable countries and regions to define events, ensure the availability of suitable tools, provide training for relevant staff and identify disease codes and estimate background rates.
- Before implementing active vaccine surveillance systems (AVSS) countries should have efficient passive surveillance systems for detecting AEFIs.
- AVSS can use different methods to monitor and assess COVID-19 vaccine-related AESIs including sentinel surveillance, data linkage and cohort event monitoring (CEM), depending on available expertise, resources and funding and type of data available for AVSS.
- The use of electronic tools such as m-Health and e-Health can facilitate the implementation of AVSS.
- AVSS can be used to detect delayed, AESIs, serious AESIs, AESIs in specific populations, and AESIs occurring during mass COVID-19 vaccination programmes.
- AESIs 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, identified via AVSS, for COVID-19 vaccinated and unvaccinated individuals will enable to ascertain if there is a link 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 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, 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.
- Appropriate communication with the community and all stakeholders at all stages of the process of investigation, causality assessment and the outcomes will be critical to maintain confidence in the vaccination programme, the health system and the health authorities.

01 Introduction

In the context of COVID-19 vaccine introduction, conventional vaccine safety surveillance systems will need to rapidly adapt to newer techniques of surveillance and ensure that post-vaccination safety and exposure information are collected and processed rapidly and responded to in near real time to ensure that the safety of the public is not put at risk.

Preparedness to address safety concerns rapidly is essential to counter real or perceived safety concerns particularly in the context of addressing adverse events following immunization (AEFIs) and adverse events of special interest (AESIs). For AEFIs, any event following immunization that is notified is reported and processed as outlined in the module on AEFIs; however pre-specified AESI should be identified through an active process and then reported, investigated and analysed to identify signals.

02 Adverse events of special interest and preparedness prior to COVID-19 vaccine introduction

2.1 Adverse events of special interest (AESIs)

The US Food and Drug Administration (FDA) defines an adverse event of special interest (serious or non-serious) as an event of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant 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.[1]

1 Guidance for Industry E2F Development Safety Update Report. Available from: https://www.fda.gov/media/71255/download. Accessed 22 November 2020.

Operational definition of an AESI: An AESI is a pre-specified medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies.

2.2 Identifying and shortlisting adverse events of special interest (AESIs)

AESIs are usually identified through active vaccine safety surveillance (AVSS) systems. Conditions commonly considered as AESIs include serious events that have followed other immunizations, for example:

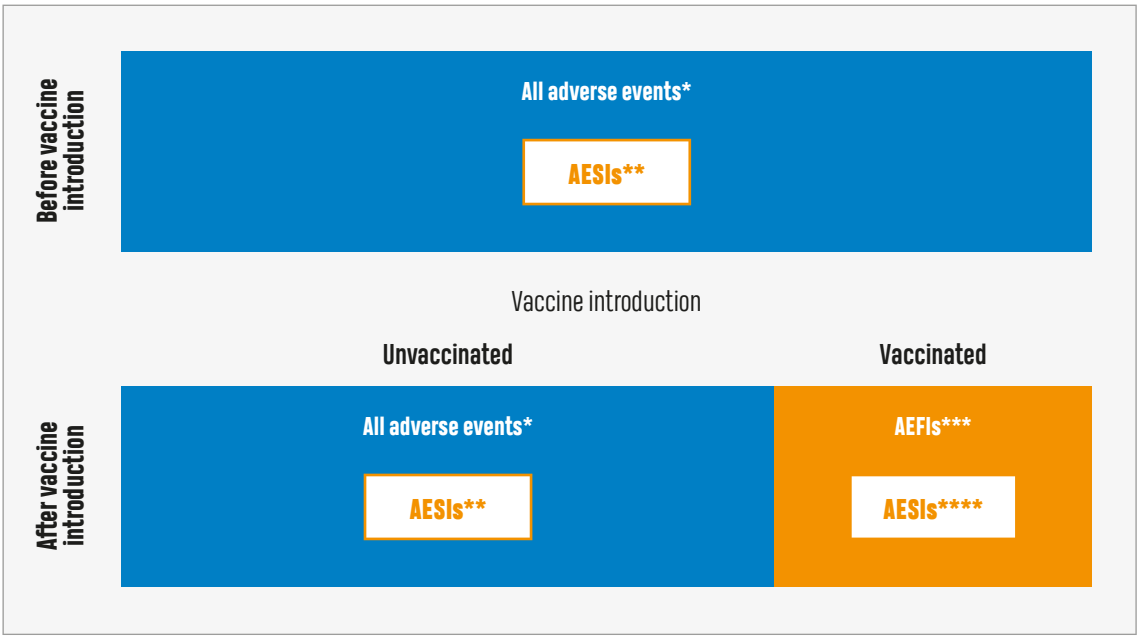
- Guillain-Barré syndrome (GBS);
- acute disseminated encephalomyelitis (ADEM);
- anaphylaxis;
- serious events potentially related to novel platforms;
- serious events potentially related to adjuvants;
- serious events related to vaccine failure/immunogenicity (vaccine-associated enhanced disease (VAED)); or
- events that are potentially important for specific populations.

Such conditions are shortlisted if there is a:

- proven association with immunization that is true for most, if not all, vaccines;
- proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine;
- theoretical concern based on immunopathogenesis of COVID-19 disease;
- theoretical concern related to viral replication during COVID-19 infection; or
- theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

The relationship between AEFIs and AESIs is shown schematically in **Fig 1** and the differences between AEFIs and AESIs and their practical implications are summarized in **table 1**.

Fig 1: Schematic representation of the relationship between AESIs and AEFIs.



** All events in a community that cause morbidity. Background rates provide information on the incidence of such events in the community*
*** Adverse events of special interest (AESIs) for a community defined prior to COVID-19 vaccine introduction. These events are of 'special interest' because although they are known to occur coincidently in the population, they have the potential to be associated with one or more of the COVID-19 vaccine platforms. It is important to estimate the background rates for these events and set up specific surveillance and training*
**** Adverse events following COVID-19 immunization (AEFIs)*
***** AESIs identified following COVID-19 immunization. In addition to following the requirements for AEFI management, there may be special requirements defined for AESIs, including investigation, follow-up and causality assessment activities*

Table 1: Differences between AEFIs and AESIs and practical implications

	AEFI	AESI in the context of COVID-19
What	Any untoward medical occurrence that follows immunization, and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.	A pre-specified event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies.
Purpose of collecting information	To identify all events after vaccination – determine if serious, investigate (serious) and do causality assessment.	To identify pre-specified specific events by a set criterion and determine if the event is associated with COVID-19 vaccination.
Identification method	Identified via spontaneous reporting by vaccine recipients or their parents, or health care workers or other persons who first notice the event.	Identified via an active surveillance system in sentinel sites or electronic health record (EHR-based cohort studies, CC, SCCS, rapid assessment e.g. VSD, VAC4EU, GVDN) by a health care worker or other staff in the system.
Case definitions	Important	Critical
Type of reporting	All events that follow immunization and are notified to the health care system.	All events identified through active surveillance that fit the case definition, irrespective of immunization status.
Training	All frontline immunization staff in health care facilities (public and private); and other relevant staff for reporting, investigation, data analysis, and causality assessment	Immunization staff and other health care workers in sentinel sites and predefined active surveillance systems, NIP/EPI mangers, NRA, research staff, national AEFI committee
Users	Health care workers, NIP/EPI managers, NRA, surveillance and information managers, epidemiologists, surveillance and information managers, vaccine safety partners including the community	Sentinel site staff, NIP/EPI managers, NRA, epidemiologists, national AEFI committees, study teams.

Abbreviations: CC: case-control; EPI: Expanded programme on immunization; NIP: national immunization programme; NRA: nal regulatory agency; SCCS: self-controlled cohort study

Shortlisting pre-specified AESIs before COVID-19 vaccine introduction will enable countries and regions to prepare for vaccine safety surveillance. This will involve defining the events, ensuring suitable tools are available to detect them, providing training for relevant staff and identifying the disease codes and estimating the background rates for the AESIs. This is important because AESIs are generally detected and reported through active vaccine safety surveillance (AVSS) systems as described below.

03 Active vaccine safety surveillance

Passive surveillance systems collect information on AEFIs and are useful for the identification of potential safety signals for adverse events that were unknown at the time of vaccine authorization or that are unexpected. However, these passive systems are unable to differentiate between a reaction following immunization and a coincidental event.

Active vaccine safety surveillance (AVSS) systems aim to collect complete, accurate information about adverse events following immunization (AEFIs) and their risk factors in a defined population via a continuous organized process. The information is collected with defined objectives which are to investigate one or more AEFIs that are pre-specified adverse events of special interest (AESIs).[2] AVSS, unlike passive surveillance systems, collect relevant data from all individuals within a defined population, thereby minimizing under-reporting.

AVSS systems can also be used for signal detection[3] (like passive surveillance systems) but they can also be used to determine:

- the rate of an event, in a defined population;
- the relative risk of the event:
  - the chance of the event occurring in those who were vaccinated with the specific vaccine, compared with those who were not or those who received a comparator vaccine;
  - the change in the event rate over time;
- the occurrence of events in both vaccinated and unvaccinated individuals in the defined population.

2 CIOMS. Guide to active vaccine safety surveillance. Available from: https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/. Accessed 28 October 2020.

3 In some countries AVSS is used for signal detection. Data linkage is used in the United States of America https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html and m-Health is used in Australia. https://www.westernalliance.org.au/2016/05/mhealth-using-mobile-technologies-to-improve-access-and-efficiency-in-health-care-delivery.

04 Key considerations for implementing AVSS systems

Countries should first establish efficient passive surveillance systems as the basic system for detecting AEFIs. AVSS systems should not be implemented to increase passive AEFI reporting rates. If passive AEFI reporting rates are below the recommended minimum WHO standard,[4] efforts should be made to improve AEFI reporting through strengthening the existing systems or implementing stimulated passive surveillance.

The COVID-19 surveillance and vaccine and vaccination landscape will vary markedly throughout the world and this will lead to different significant knowledge gaps. The CIOMS guide to active vaccine safety surveillance proposes an algorithm for determining when AVSS systems should be implemented.[2] At the time of COVID-19 vaccine authorization by a national regulatory agency, a risk management plan (RMP) should define any anticipated risks from the vaccine. At this point the AVSS algorithm can be used to determine what surveillance methods and post-authorization clinical trials or studies should be implemented.

4.1 Resources, governance and ethical considerations

AVSS systems will require more planning, resources (including funding) and expertise to set up than passive systems. They should be implemented using a collaborative approach, involving stakeholders, such as the vaccine manufacturer,[5] the Ministry of Health, the national immunization technical advisory group, multilateral and non-governmental organizations, the national regulatory authority and pharmacovigilance centres. Ethical and privacy clearances will be required to collect and analyse identifiable data, as described in the data management module.

4.2 Co-ordination of AVSS systems

Ideally there should be a global coordination of AVSS systems, as well as regional or national coordination, through the proposed or existing governance and research structures, as described in the module on stakeholders. This coordination will avoid duplication of effort

4 Lei J, Balakrishnan MR, Gidudu JF, Zuber PLF. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000-2015. Vaccine. 2018;36(12):1577-1582. doi: 10.1016/j.vaccine.2018.02.012.

5 For the purpose of this document, manufacturer also means marketing authorization holder.

and increase the size of the population under surveillance, thus enabling the assessment of very rare events and making comparisons.

4.3 Data collection for AVSS systems

Individual data, linked by a unique identifier, should be collected in the defined population for vaccination events, health events or outcomes and demographic characteristics. This identifier could be a national identification number, such as a social security number, a trial or study participant number, and if not, available linkage could be done using demographic identifiers, such as initials, date of birth or address.

The tools for data collection for AESI in AVSS systems are described below and provided in the Appendices. **Table 2** describes the core and complete data points to be collected for AVSS. Ideally electronic databases should be used for analysis.

Table 2: Core and complete data sets, linked through a unique individual identifier or initials, date of birth, address, to be collected for the AVSS system

		Vaccination data	Health events or outcomes	Demographic data
Complete data set	Core data set	Vaccine brand name	Adverse event(s)	Age at onset
		Lot number	Date of onset of symptoms	Gender
		Date of vaccination	Serious	Medical conditions
		Dose number	Outcome	Medication
		Site of vaccination	–	–
		Place of vaccination	Place of care	–
		Vaccine antigens	–	–
		Concomitant vaccines	–	–
		Route administration	–	–

4.4 Specific methods used for AVSS

The methods that can be used in AVSS systems for the collection of data on COVID-19 vaccine-related AESIs are described in **Appendix 7.1**. These methods include cohort event monitoring (CEM), sentinel surveillance and data linkage. Electronic tools, such as m-Health and e-Health, can facilitate the implementation of AVSS. The method selected will depend on factors such as available expertise, resources and funding and what data are needed and available for AVSS.

05 Implementing AVSS systems for COVID-19 vaccine-related AESIs

The implementation of COVID-19 vaccine-related AVSS systems for AESIs should:

- be considered when it is important to define the risk and risk factors in the population immunized with COVID-19 vaccines;
- be considered as complementary to existing passive surveillance systems;
- be considered when significant knowledge gaps cannot be addressed through enhanced passive surveillance;
- use harmonized protocols wherever possible;
- have sufficient funding and robust governance systems;
- operate independently without conflicts of interests; and
- have systems in place to share collected data widely and transparently.

Some of the types of AESIs that can be identified with AVSS systems are described below.

5.1 Delayed AESIs

Some AESIs, such as vaccine-associated enhanced disease (VAED) or those with an immunopathogenesis, may have delayed onset. For these events, passive surveillance is often subject to underreporting as events occurring closer to vaccination are more likely to be reported and those occurring at distance to vaccination are less likely to be reported. The type of specific AVSS systems that could be implemented for these delayed AESIs include CEM and sentinel surveillance. Data linkage could be used for hypothesis testing to establish if a causal relationship exists between a particular AESI and a COVID-19 vaccine.

5.2 Severe and serious AESIs

In many countries AEFI reporting by health care workers is inadequate because of poor knowledge of what defines an AEFI and barriers to reporting. Many of the COVID-19 vaccine-related AESI that have been identified for surveillance are severe or serious, or both, resulting in hospital visits or admissions. In addition, the COVID-19 vaccine-related AESIs that have been identified also occur at a background rate in unvaccinated individuals. For this situation, AVSS using sentinel surveillance could be used to identify all those having hospital visits or being admitted for one of the pre-specified AESIs. If electronic vaccination history and health event data are available for a large population, data linkage could be used.

5.3 Identified AESIs in priority target groups

It is likely that the authorized COVID-19 vaccines will have different reactogenicity profiles and will be used in populations with different ages, co-morbidities, concomitant medications and vaccine exposure. In the elderly, who are likely to be a priority vaccine target group, some of the COVID-19 vaccine-related AESIs, e.g., coronary artery disease, cerebrovascular disease, might be seen in the absence of COVID-19 immunization (background rate). Focused AVSS systems, using CEM should be considered for an elderly vaccinated cohort and sentinel surveillance could be used for conditions that are likely to result in hospital visits or hospitalization.

5.4 Surveillance of AESIs during mass COVID-19 immunization campaigns

If COVID-19 vaccines are delivered via mass immunization campaigns, many individuals will be exposed to the vaccines in a short time, with limited time for AEFI detection and analyses. Community concerns around vaccine safety are usually high when a new vaccine is introduced, particularly in the setting of mass immunization campaign (see module on communication strategies). In such situations, AVSS systems using tools such as m-Health or e-Health will help obtain near real-time surveillance data for all AEFIs, including AESIs.

5.5 Key resources for evaluating and processing COVID-19 vaccine listed AESIs

Additional unique resources are being developed for identifying and responding to AESIs, including protocols, case definitions, AESI confirmation forms, tabular checklists, automated tools for assessments, background rates and codes. Many of these can also be used in AEFI assessment and interpretation of signals are shown in **Table 3**. This will be consolidated as a separate document for countries and programmes seeking detailed guidance. Some of these resources are already available.

Table 3: Key resources available and being developed for evaluating and processing COVID-19 vaccine listed AESIs (can also be used for AEFIs)

Description	Purpose	Settings for use
Brighton case definitions	To provide a standard case definition so safety data are comparable	See https://brightoncollaboration.us/covid-19/ for latest list and definitions
AESI confirmation and interpretation forms	Detailed data form to facilitate standardized data collection and interpretation focused on the Brighton criteria to assess LOC.	— case investigation and assessment — AEFI signal / cluster investigation — outcome validation for analytic and epidemiological studies
Tabular checklist and algorithm to determine certainty	Abbreviated tabular form to summarize available case data and assign LOC	— same as above but where data have been collected and data abstraction is not needed
Automated tool to determine LOC for cases	To replace the previous Brighton online ABC tool	— training for LOC determination — causality assessment where first step is to determine LOC — any setting where LOC needs to be assessed
Background rates and risk factors of AESI	To provide summarized data on incidence of event as coincidental events by age, gender and geography	— epidemiologic studies where expected versus observed are compared — public reassurance in terms of 'expected' coincidental events
ICD and MedDRA codes	To assist in identifying or coding events from or for health care or pharmacovigilance databases	— AEFI MedDRA coding — coded database searches
Template protocols	Assess background rates, conduct active surveillance	

LOC: level of certainty

The resources shown in **Table 3** are being prepared for all the AESI listed in **Table 4** as well as for several others related to maternal, foetal and neonatal outcomes, narcolepsy and sudden unexpected death. These will be made available at the Brighton collaboration website (www.brightoncollaboration.us) at a specific site dedicated to COVID-19. From the COVID-19 webpage, links will be provided to a spreadsheet listing AESI in separate rows. The spreadsheet columns, will have embedded links for each AESI to enable access to the published or newly drafted case definitions, the data abstraction and interpretation forms, the tools for assigning level of certainty, background rates, risk factors, ICD and MedDRA codes and template protocols. For any tools not yet developed, the spreadsheet will provide a date by which it is planned to have a tool available.

06 Identifying, reporting and responding to COVID-19 vaccine-related AESIs

AESI detection can only start after the country finalizes the list of events that are considered as AESIs to be monitored in vaccinated and unvaccinated individuals. The list of AESI conditions should be developed based on the recommendations of their technical advisory group or from the list in **Table 4**. If possible, the background rates of these conditions should be known before COVID-19 vaccine introduction. Countries should have a national causality assessment committee with the necessary expertise. The members of this committee should be specifically trained to review population- based scientific data obtained from AESI cases and have the capacity to process them as outlined below.

At the 42nd meeting of the Global Advisory Committee on Vaccine Safety (GACVS) in May 2020, a list of potential AESIs were identified in collaboration with Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC).[6,7] It was recommended that available and newly generated Brighton Collaboration case definitions for AESIs and tools to assess certainty of cases should be shared widely for countries to use and to be aligned. **Table 4** lists the vaccine platform- and COVID-19 disease-related AESI from the May SPEAC list. Details are available at https://brightoncollaboration.us/covid-19/. As new information emerges this list will be updated.

The AESIs should be identified irrespective of the exposure to COVID-19 vaccine based on a pre-specified list, which will be unique for each country or region and diagnosis of each AESI case identified should match an approved case definition e.g., the Brighton Collaboration case definitions.

Depending on the AESI surveillance methodology (**Appendix 7.1**) and the protocol adopted by the country, AESIs can be detected through:

- prospective surveillance, which requires that health care workers are trained to detect AESIs, using simplified case definitions, as they occur;
- retrospective surveillance, which requires designated surveillance staff to conduct systematic searches for pre-specified AESIs, using a simplified case definition, in the target population by examining patient records at facilities; or
- other electronic methods.

6 Global Advisory Committee on Vaccine Safety, 27-28 May 2020 https://www.who.int/vaccine_safety/committee/reports/May_2020/en/

7 Safety Platform for Emergency vACcines (SPEAC). Available from: https://brightoncollaboration.us/speac/. Accessed 8 December 2020.

Master protocols are being developed to facilitate the implementation of active vaccine safety surveillance for AESIs with COVID-19 vaccines using harmonized methods and standardized tools. This will be posted on WHO website as they become available.

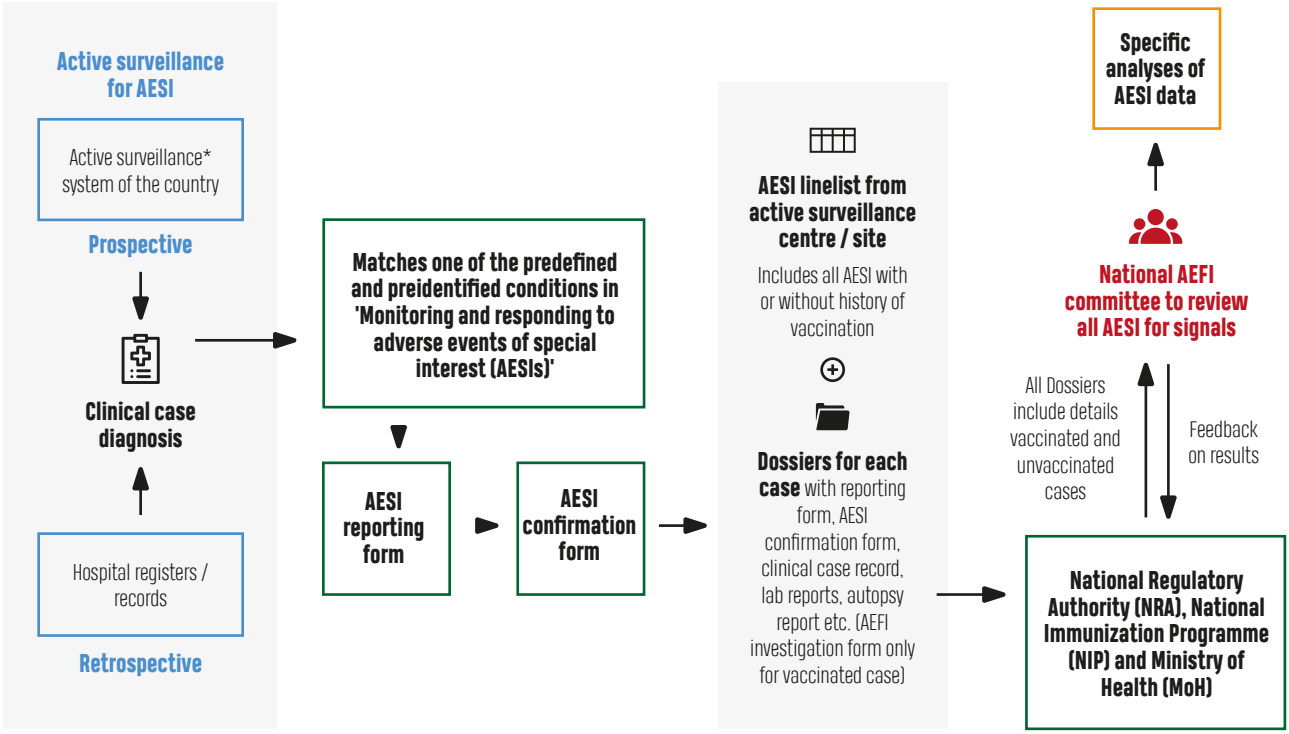
Table 4: List of AESI defined for COVID-19 vaccines (May 2020)

AESI
Vaccine-associated enhanced disease
Multisystem inflammatory syndrome in children
Acute respiratory distress syndrome
Acute cardiovascular injury (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia, myocarditis)
Coagulation disorder (thromboembolism, haemorrhage)
Acute kidney injury
Generalized convulsion
Guillain Barré Syndrome
Acute liver injury
Anosmia, ageusia
Chilblain – like lesions
Single organ cutaneous vasculitis
Erythema multiforme
Anaphylaxis
Acute aseptic arthritis
Meningoencephalitis
Acute disseminated encephalomyelitis
Thrombocytopenia

6.1 AESI reporting and response mechanisms in AVSS systems

Fig 2, below, shows a schematic representation of AESI reporting and response mechanisms in AVSS systems.

Fig 2: In-country reporting and processing of AESIs



* Data flow can be customized according to the active surveillance methods adopted by the country

6.1.1 AESIs detected though active vaccine safety surveillance systems

AESI cases can be detected through different modes of active surveillance such as cohort event monitoring (CEM), sentinel surveillance (SS) and data linkage (DL) using case definitions. Specific AVSS tools such as m-health (MH) and e-health (EH) are available for this purpose. Additional efforts should be made to obtain vaccine exposure information in AESIs identified through active surveillance to enable its association with the vaccine to be assessed. In such instances the AESI reporting form (**Appendix 7.2**), AESI confirmation form[8] for the specific AESI, detailed clinical records and results of additional tests must be collated and linelisted in an AESI linelist (**Appendix 7.3**) by the relevant centre or site responsible for AESI surveillance. Dossiers for each case in the AESI linelist should be submitted to the national level (NRA/NIP/EPI/MoH) in compliance with the country protocol and through them shared with the national AEFI committee that has been specifically trained for population-specific analyses of AESI data.

8 To be published in the AESI investigation guidance document that will be developed

6.1.2 Investigating AESI in patients exposed to COVID-19 vaccination

As mentioned above, any AESI matching the list of pre-specified AESI conditions should undergo detailed investigation, unless specified otherwise in the country's protocol. Since they are vaccinated, such cases are considered to be AEFIs and investigation should be done using the COVID-19-specific AEFI investigation form and causality ascertained as described in the AEFI module. When such cases from AEFI surveillance systems are being reviewed by the causality assessment committee, after confirming the absence of programmatic errors, Immunization stress related responses or coincidental events, vaccinated AESI cases will have to be categorised by the committee as '*B1 -Indeterminate' because the temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (it may be a new vaccine-linked event)* at the time of assessment. Details of the classification methodology are available in the AEFI causality assessment user manual for the revised WHO classification.[9]

6.1.3 Data analyses for AESI cases from active surveillance systems

Reviewing data from both vaccinated and unvaccinated AESI cases identified via the active AESI surveillance systems will enable to ascertain if there is a link between the AESI and the COVID-19 vaccine product and if there is need for further specific studies to confirm such an association. This can be done by comparing the incidence of the AESI among the COVID-19 vaccinated and unvaccinated individuals within a specific population and identification of signals for further characterization and investigation.

The causality assessment committee can perform these analyses if they have the necessary expertise and if they have been trained to review population-based scientific data arising from the specific types of studies in active surveillance systems. In this case, it is important that the committee also review the national, regional and global epidemiological data to determine if there is a pattern in the profile of reports received, e.g., clusters of similar events in space, time and vaccine administered.

In countries or regions that do not participate in AVSS systems for AESI, the routing of information about AESIs and response will follow the standard AEFI routing and response channels recommended in the country, as described in the AEFI Module.

6.2 Reconciling AESI data

Information about AESIs will be obtained from a passive AEFI surveillance system or from an AVSS system, as described above. These data cannot be collated because the data collection methods are different, and they represent different cohorts of individuals and should, therefore, be analysed separately. All documentation for the AESIs should be archived.

9 World Health Organization. AEFI causality assessment user manual for the revised WHO classification. Available from: https://www.who.int/vaccine_safety/CA_manual_second_edition/en/. Accessed 8 December 2020.

Signals are identified when a particular AESI occurs more frequently in the vaccinated population than in unvaccinated population (the background rate). When this occurs, 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.

The periodicity of AESI reports to the relevant administrative levels should be defined in the country's protocol. Countries may determine the profile of health care workers who will be responsible for reporting, when defining the active surveillance methods for AESI surveillance. Countries may establish a target for AESI reporting for all regions in the country, based on the background rates for the AESIs.

6.3 Tools for active surveillance of AESIs

Some of the existing tools as outlined in WHO's global manual on surveillance of adverse events following immunization can also be used for AESIs.[10] A summary of the available tools and how they can be accessed is given in **Table 5**.

6.4 Prioritizing preparedness for AESI

At the time of vaccine authorization, countries need to review the risk management plan (RMP) and discuss the risks and benefits with their respective in-country national immunization technical advisory groups (NITAGS) or regional immunization technical advisory groups (RITAGS). They need to determine if they have the capacity to implement active surveillance for AESIs as described in the module on establishing surveillance systems to supplement data obtained via the passive surveillance systems.

The many unknowns for COVID-19 vaccine use in a country and the limited knowledge about its safety profile make it difficult to set priorities for the AESIs that are most relevant to a given setting. In general, countries should prepare to address quickly signals for events that have the highest likelihood to derail a vaccination campaign. Several of the AESIs on the list in **Table 4** have been included because of a known association with vaccination. On this basis, generalized convulsions, thrombocytopenia and anaphylaxis would all be priority AESIs. Generalized convulsions would be an even higher priority for vaccines that induce a high frequency of fever and for those vaccines that will be used for children aged less 6 years of age. GBS should also be a priority, given its global occurrence, its known association with some vaccine platforms and its known increased frequency in older populations who are very likely to be in the priority target groups for COVID-19 immunization programmes.

Vaccine-associated enhanced disease, acute respiratory distress syndrome and multisystem inflammatory syndrome in children will all be of high priority although

10 World Health Organization. Global manual on surveillance of adverse events following immunization. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf. Accessed 28 October 2020.

they will be very difficult to assess and interpret in the context of active COVID-19 infection in the community. Priority should be given in surveillance systems to ensure that individual immunization records are readily available. Once immunization programmes finalise the type of vaccine(s) to be used, it will be essential to define the timeframe during which occurrence of COVID-19 infection would be considered evidence of vaccine failure. Vaccine-associated enhanced disease (VAED) could occur before a protective immune response is expected, particularly for vaccines that require more than one dose to Induce immunity. A non-protective immune response could be associated with VAED. These cases would occur closer to the time of immunization than cases that are caused by waning of neutralizing antibodies, which is why it is recommended to monitor for at least 1-year following immunization.

Table 5: Summary of tools recommended for AESI reporting investigations and causality assessment

Description	Purpose	Status for COVID-19	Hard copy
Detailed case definitions for AESI	To determine if clinical details comply with standard case definition by an expert	Available for some conditions and under development for others[11]	Being developed separately in additional guidance on AESI in preparation for COVID-19 vaccine introduction.
Simplified case definitions for AESI	To determine if clinical details comply with standard case definition by a frontline health care provider	To be developed (some available)	Being developed separately in additional guidance on AESI in preparation for COVID-19 vaccine introduction
AESI reporting form	To collect information for all AESI cases that have been notified in a standard common format for linelisting	Separate AESI reporting form developed for COVID-19	**Appendix 7.2**
AESI linelist	To collate the AESI details from AESI reporting forms	Separate AESI linelist format developed for COVID-19	**Appendix 7.3**
AESI confirmation form	To collect confirmation information when AESI cases are identified. Separate form for each condition	To be developed	Being developed separately for each condition and to be included in additional guidance on AESI in preparation for COVID-19 vaccine introduction
Investigation form for AESI cases that have history of COVID-19 vaccination	To collect detailed information when serious AEFI cases are investigated	Adapted to include COVID-19 specific questions	**Appendix 7.5.** This is the same as the COVID-19 AEFI investigation form

11 Brighton definitions: https://brightoncollaboration.us/category/pubs-tools/case-definitions/

Description	Purpose	Status for COVID-19	Hard copy
Causality assessment for AESI cases that have history of COVID-19 vaccination	To determine case classification of all AESI cases that have a history of COVID-19 vaccination reported from the passive surveillance system	Retain current method used for AEFI unchanged	Causality assessment of an adverse event following immunization (AEFI)
Detailed analysis format of AESI as per protocol	To determine if the incidence of the pre-specified AESI is higher in vaccinated individuals than unvaccinated individuals	Will depend on study protocol	Will depend on study protocol

Anosmia and ageusia are so common with acute COVID-19 infections that they have been proposed for the COVID-19 screening. It is recommended that relatively high priority should be placed on raising awareness about these conditions and determining their background rates, since they are also known to occur with other viral respiratory infections like influenza. This will be especially high priority in settings where there is ongoing community spread of COVID-19 disease.

Coagulation disorders should be of higher priority in settings where there are other infections that could present with bleeding, such as dengue. It will be important to have testing in place to establish if any observed coagulation disorders are coincidental to immunization or are caused by immunization.

Acute cardiac injury, acute liver injury and acute kidney injury would be of higher priority in settings and populations where there is a known high frequency of comorbid conditions (hypertension, chronic hepatitis, chronic renal failure).

Meningoencephalitis is an issue for live attenuated vaccines, especially in immunocompromised individuals. Although currently it seems unlikely that there will be live-attenuated COVID-19 vaccines in use, but if they are implemented, meningoencephalitis should be a higher priority in the AESI surveillance than for programmes that implement inactivated vaccines.

Acute aseptic arthritis is a priority where the vaccine platform involves vesiculostomatitis virus (rVSV).

Acute disseminated encephalomyelitis (ADEM) occurs rarely and has not been proven to be caused by immunization. Despite this, a single ADEM case could completely disrupt an immunization programme, which is why it has been identified as an AESI. It would be useful to have population prevalence data for ADEM if incidence data are not available or unobtainable.

Of lower priority would be chilblain-like lesions, erythema multiforme and single-organ cutaneous vasculitis.

6.5 AESI for special populations: pregnant women, neonates and immunocompromised individuals

The full impact of COVID-19 disease on pregnancy outcomes for mother and foetus as well as for new-borns is still unclear.[12,13] Vertical transmission appears to be rare. There have been reports of maternal deaths and foetal loss, but it is not yet known if the frequency is higher than expected during pregnancy. Increased frequency of caesarean section and premature delivery have been observed among pregnant women who developed COVID-19 infection in the third trimester. Neonatal COVID-19 infections have been reported including some with fatal outcome, but most infants have survived infection without any apparent long-term sequalae.

To date, AESI specific to obstetric outcomes have not been identified by SPEAC, because trials rarely include pregnant women. This could change as more evidence is published. However, in the post-introduction phase it will be essential to plan to follow pregnancy outcomes with, for example, a registry of all such occurrences so follow-up can be maintained for any adverse outcomes to the mother, foetus or new-born. Pregnancy registries are important tools to determine pregnancy outcomes when vaccines are likely to be used inadvertently or intentionally during pregnancy or for women who may become pregnant post-vaccination. Furthermore it is recommended to determine the background rates of obstetric and neonatal outcomes, such as maternal mortality, stillbirth, miscarriage, neonatal mortality and congenital anomalies, using standardised case definition prior to initiation of COVID-19 immunization programmes. The COVAX Maternal Immunization Working Group is developing guidance for approaches for the evaluation of COVID-19 vaccine safety for pregnant women and their infants for the post-licensure period.[14]

It is not yet clear whether vaccination will be recommended for pregnant or immunocompromised individuals. As a general rule, live vaccines are contraindicated for both, but there should be several inactivated vaccines available.

6.6 Sudden unexpected death as an AESI

Without question, sudden unexpected death occurring within days of immunization is a major threat to immunization programmes. Sudden death has not yet been added to the AESI list. While it has been observed in association with COVID-19 infection, such occurrences are rare and are related to thromboembolic phenomena such as stroke, pulmonary embolus and coronary thrombosis.[15] However, it will be essential to be prepared for such occurrences to enable rapid response in terms of investigation and communication to the public.

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12 Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521-531. doi: 10.1016/j.ajog.2020.03.021.

13 Castro P, Matos AP, Werner H, Lopes FP, Tonni G, Araujo Júnior E. Covid-19 and pregnancy: an overview. Rev Bras Ginecol Obstet. 2020;42(7):420-426. doi: 10.1055/s-0040-1713408.

14 To be published soon.

15 Avila J, Long B, Holladay D, Gottlieb M. Thrombotic complications of COVID-19. Am J Emerg Med. 2020 Oct 1:S0735-6757(20)30860-3. doi: 10.1016/j.ajem.2020.09.065.

Selected events that could result in death,[16] although rare, have been identified as cause-specific AEFIs that could be seen following immunization including:

- vaccine product related reaction: anaphylaxis;
- vaccine quality defect: wild type disease following incompletely attenuated live viral vaccine as occurred with the Cutter incident with polio vaccination;[17]
- immunization-error: sepsis following contamination of multidose vials; use of a drug (e.g. anaesthetic drug, insulin) to reconstitute vaccine; instead of the diluent supplied;
- anxiety-related reaction: fatal head injury associated with syncope in settings where post-immunization safety is not assured;[18] and
- coincidental reaction: likely to be the underlying cause of the majority of sudden deaths following immunization, including but not limited to, sudden infant death syndrome, sudden cardiac death, sudden unexpected death in epilepsy (SUDEP), anaphylaxis related to food, insects, environmental toxins, overwhelming sepsis.

To assess the cause of any unexpected death following immunization, a thorough field investigation should be conducted without delay, and an autopsy performed according to the protocol developed for people with a suspected COVID-19 cause of death.[19] Knowing regional and age-specific background incidence of sudden deaths as well as relevant risk factors will be essential to inform the causality assessment. Appropriate communication with the community and all stakeholders at all stages of the process of investigation, causality assessment and its outcomes will be critical to maintain confidence in the vaccination programme, the health system and the health authorities.

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16 Gold MS, Balakrishnan MR, Amarasinghe A, MacDonald NE. An approach to death as an adverse event following immunization. Vaccine 2016;34:212-217. doi: 10.1016/j.vaccine.2015.

17 Fitzpatrick M. The Cutter incident: How America's first polio vaccine led to a growing vaccine crisis. J R Soc Med. 2006;99(3):156.

18 Woo EJ, Ball R, Braun MM. Fatal syncope-related fall after immunization. Arch Pediatr Adolesc Med. 2005 Nov;159(11):1083. doi: 10.1001/archpedi.159.11.1083.

19 Carpenito L, D'Ercole M, Porta F, Di Blasi E, Doi P, Fagara GR, et al. The autopsy at the time of SARS-CoV-2: protocol and lessons. Ann Diagn Pathol. 2020;48:151562. doi: 10.1016/j.anndiagpath.2020.151562.

07 Appendices

Appendix 7.1: Summary of methods that can be used for active vaccine safety surveillance systems for AESIs

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19-related surveillance
Cohort event monitoring (CEM)	CEM is a prospective, observational, cohort study of adverse events associated with a medication or vaccine.[20] A vaccinated cohort is established and followed for any predefined AEFIs (Including AESIs) that occur over a defined period. Demographic data are collected to enable risk factors to be characterized.	**Vaccination history** Details of COVID-19 vaccine or other vaccines collected at the time of enrolment **Health event(s)** Pre-specified COVID-19-related AESIs and constitute the health outcome under surveillance. **Demographic data** Data collected that could be relevant to outcome, for example, those factors associated with severe COVID-19 disease (diabetes, obesity, medication).	**Advantages** Data from CEM can be used to define AESI rates, within a vaccinated cohort, but is dependent on the rate of the AESI and the size of the observational cohort. CEM may not require extensive resources and may not require the infrastructure for more sophisticated forms of AVSS (such as data linkage). **Disadvantages** Data from CEM cannot be used to estimate relative risk of AESIs compared with an unvaccinated population but is able to define a relative risk if more than one COVID-19 vaccines are under surveillance. To define the rate of a rare AESI a large observational cohort would be required.

20 World Health Organization. A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis. Available from: https://www.who.int/medicines/publications/Pharmaco_TB_web_v3.pdf. Accessed 22 November 2020.

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19-related surveillance
Sentinel surveillance (SS)	SS involves identifying sentinel sites, usually a health facility. The population is defined as patients attending or admitted to the health facility. AVSS involves systematically ascertaining if an individual has attended the facility with symptoms, signs or laboratory information that meet a specific case definition (for example those of a COVID-19-related AESI). If the case definition is met further data are collected, for example, vaccination status, outcome and demographic data.	**Vaccination history** Details of COVID-19 vaccination is collected only if the patient meets the case definition of the AESI, AEFI or condition under surveillance. **Health events** COVID-19 related AESI, AEFI, or a specific health condition is specified. Every patient attending or admitted to the sentinel facility is screened to see if the definition is met, regardless of vaccination status. **Demographic data** Demographic data are collected only if the patient meets the case definition of the condition under surveillance. The data collected could include possible risk factors.	**Advantages** It is possible to collect detailed data on the health event, outcome and demographics. It may be possible to estimate the relative risk for events where the post-vaccination onset time is clearly defined using a self-controlled case-series analysis. **Disadvantages** It is not possible to estimate the rate of the health event under surveillance. Data collection can be costly and time consuming. Vaccination data for the patient with the AESI may not be readily available.

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19-related surveillance
Data linkage (DL)	DL involves linking electronic data, from different data collections, where the data have usually been collected prior to linkage. Vaccination, health event and demographic data, often from many thousands of individuals which are stored in different databases can be linked by a unique identifier or based on matching according to other identifiers such as name, date of birth, and address.	**Vaccination history** Usually obtained from pre-existing electronic databases such as a national vaccine register or an administrative database. Databases would need to capture COVID-19 vaccines for the age group under surveillance. **Health events** Health events under surveillance (e.g., COVID-19 related AESIs) need to be coded (ICD coding) and stored electronically. **Demographic data** Demographic data are collected only if the patient meets the case definition of the AESI under surveillance Data collected that could be relevant to outcome, for example, those factors associated with severe COVID-19 disease (diabetes, obesity, medication)	**Advantages** Can be used to examine associations between vaccination and rare or very rare events. This method would be ideally suited for hypothesis testing of the causal relationship between COVID-19 vaccination and an AESI. If linked databases are established, DL can be used for regular rapid review of safety signals. **Disadvantages** Few countries have the capacity and ready access to large established databases containing vaccination, health event and demographic data that can be linked. DL can be resource intensive in terms of the cost and expertise required for linkage. In many countries there are significant barriers to data access, because of privacy and confidentiality laws. DL is most often used to link to hospital events and is more difficult to use for conditions that do not lead to hospitalization.

Method of AVSS	Description	Data to be collected	Advantages and disadvantages for COVID-19-related surveillance
Example of tools for CEM: m-Health (MH) and e-health (EH)	MH and EH are evolving ways to monitor for health events following immunization or medication use. They become more feasible because of the increasing use of mobile phones and access to the internet. MH and EH can target individuals for surveillance via various methods such as SMS, reporting apps, direct telephone calls, emails and on-line surveys.	**Vaccination history** Details of COVID-19 vaccine or other vaccines collected at the time of enrolment **Health event** COVID-19 related AESIs or other surveillance conditions could be predefined and occurrence of the event ascertained by a survey administered through an electronic platform. **Demographic** Limited demographic data collected through a survey.	**Advantages** Low cost and can target individuals (vaccinees or their parents) directly. Can be used for 'real-time' surveillance and for vaccine safety signal generation. Rates of AEFIs can be estimated but large samples may be required. **Disadvantages** Network coverage, mobile phone and internet costs maybe a barrier to reporting. Significant resources could be required to verify reports.

Appendix 7.2: COVID-19 AESI reporting form

AESI reporting id number:

REPORTING FORM FOR SUSPECTED ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

***Patient name:**	***Reporting source:** ☐ ***Hospitalised** ☐ ***outpatient (e.g. clinic)***
***Patient's full Address:**	***Process of detection:** ☐ ***Patient-reported** ☐ ***Part of active surveillance***
	AESI Reporter's Name:
	Institution:
Telephone:	*Designation & Department:*
Sex: ☐*M* ☐ *F*	*Address:*
***Date of birth:** _ _/_ _/_ _ _ _	*Telephone & e-mail:*
OR Age at onset : ☐☐*Years* ☐☐ *Months* ☐☐☐ *Days*	*Date patient notified event to health system* _ _/_ _/_ _ _ _
OR Age Group: ☐*< 1 Year* ☐ *1 to 5 Years* ☐ *> 5 Years*	*Today's date (DD/MM/YYYY):* _ _/_ _/_ _ _ _

Adverse event(s) of special interest:		*Describe AESI (Signs and symptoms):*
☐ *Acute aseptic arthritis*	☐ *Coagulation disorder (Thromboembolism, Haemorrhage)*	
☐ *Acute cardiovascular injury*	☐ *Enhanced disease following immunization*	
☐ *Acute disseminated encephalomyelitis*	☐ *Erythema multiforme*	
☐ *Acute liver injury*	☐ *Generalized convulsion*	
☐ *Acute kidney injury*	☐ *Guillain Barré Syndrome*	
☐ *Acute respiratory distress syndrome (Microangiopathy, Heart failure, Stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis)*	☐ *Meningoencephalitis*	
☐ *Anaphylaxis*	☐ *Multisystem inflammatory syndrome in children*	
☐ *Anosmia, ageusia*	☐ *Single Organ Cutaneous Vasculitis*	
☐ *Chilblain – like lesions*	☐ *Thrombocytopenia*	
☐ *Other (specify).....*		

***Date & Time AESI started:** __ __ /__ __ /__ __ __ __ ☐☐ *Hr* ☐☐*Min*

***Did this AESI cause?** ☐ *Death* ☐ *Life threatening* ☐ *Disability* ☐ *Hospitalization* ☐ *Other important medical event (Specify_____)*

***Outcome at the time of reporting:** ☐ *Recovering* ☐ *Recovered* ☐ *Recovered with sequelae* ☐ *Not Recovered* ☐ *Unknown*

☐ *Died If died, date of death:* __ __ /__ __ /__ __ __ __ *Full Autopsy done:* ☐*Yes* ☐*No* ☐*Unknown*

If No, Verbal Autopsy Done? ☐*Yes* ☐*No*

Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases). Use additional sheet if needed:

***Did this patient receive COVID19 Vaccine?** ☐*Yes* ☐*No* ☐*Unknown;* ***If Yes,** Complete the table below*

Health facility (or vaccination centre) name:

COVID19 Vaccine								***Diluent***	
*Brand Name	Manufacturer	Dose	*Date of vaccination	Time of vaccination	Immunization record No.	*Batch/ Lot number	Expiry date	*Batch/ Lot number	Expiry date
		1							
		2							
		3							

***Details of Non-COVID19 vaccines received in the last 1 year** (please use the next page if there are more vaccines)*

*Brand Name	Manufacturer	*Date of vaccination	Time of vaccination	Dose (1st, 2nd,..)	Batch/ Lot number	Expiry date	Batch/ Lot number	Expiry date

First Decision making level to complete – for ALL AESI cases including COVID19 vaccinated and unvaccinated:

AESI Confirmation initiated: ☐ *Yes* ☐ *No* ***If Yes,** Confirmation done by Dr/ Mr/Ms_____ Date of Confirmation:*

Is this AESI Linelisted? ☐*Yes* ☐ *No*

For COVID 19 vaccinated cases: Field investigation planned with AEFI investigation form? ☐*Yes* ☐*No If yes, date planned* _ _/_ _/_ _ _ _

**Mandatory fields to be completed*

Appendix 7.3: COVID-19 AESI linelisting form

COVID19 AESI linelist

Source	S. No	Reporting source	Detecting process	Patient Name/ Identifier	AESI Reporting ID number	Patient Location (Village/Town)	Patient Location (District)	Sex (M/F)	Age (Date of birth or age at onset)	AESI	Date of onset (DOO)	Date of Notification (DON)	Date of Reporting (DOR)	Manifestation	Outcome	Autopsy conducted in case of death (Y/N/NA)	Vaccine/s	Manufacturer	Dose	Vaccine Batch No	Diluent Batch No	Place of vaccination	Date of Vaccination (DOV)	Reported by	Reporter Location 1	Reporter Location 2	AESI Confirmation initiated? (Y/N)	Field investigation planned? (Y/N)

Appendix 7.4: COVID-19 AESI confirmation forms (under development)

- Acute aseptic arthritis
- Acute cardiovascular injury
- Acute disseminated encephalomyelitis
- Acute liver injury
- Acute kidney injury
- Acute respiratory distress syndrome (microangiopathy, heart failure, stress cardiomyopathy, Coronary artery disease Arrhythmia, Myocarditis)
- Anaphylaxis
- Anosmia, ageusia
- Chilblain – like lesions
- Coagulation disorder (thromboembolism, haemorrhage)
- Enhanced disease following immunization
- Erythema multiforme
- Generalized convulsion
- Guillain Barré Syndrome
- Meningoencephalitis
- Multisystem inflammatory syndrome in children
- Single organ cutaneous vasculitis
- Thrombocytopenia

Appendix 7.5: AEFI investigation form adapted for AESI following COVID-19 immunization

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AEFI FOLLOWING COVID 19 VACCINATION - INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A Basic details

Province/State **District** **Case ID**

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

Date of investigation: __ __ / __ __ / __ __ __ __
Date of filling this form: __ __ / __ __ / __ __ __ __

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐M ☐ F

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

OR *Age at onset: __ __ years __ __ months __ __ __ days*

OR *Age group:* ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years - 18 years* ☐ *> 18 years – 60 years* ☐ *> 60 years*

Patient's full address with landmarks *(Street name, house number, locality, phone number etc.)*:

Brand name of vaccines (including manufacturer) /diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ Time of first symptom (*hh/mm):* __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): ☐ Died ☐ Disabled ☐ Recovering ☐ Recovered completely ☐Unknown

If died, date and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ *(hh/mm):* __ __ / __ __
Autopsy done? (✓) ☐ Yes (date)_____ ☐ No ☐ Planned on (date)_____ Time_____
Attach report (if available)

Section B Relevant patient information prior to immunization

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event?	Yes / No / Unkn	
Adverse event after any previous vaccination(s)?	Yes / No / Unkn	
History of allergy to vaccine, drug or food?	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unkn	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause?	Yes / No / Unkn	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unkn	
For adult women • Currently pregnant? Yes (weeks) _____ / No / Unknown • Currently breastfeeding? Yes / No		

For infants
The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

Section C Details of first examination** of serious AEFI case

Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy**
☐ **Other**_____ *If from verbal autopsy, please mention source* _____

Name of the person who first examined/treated the patient:_____
Name of other persons treating the patient: _____
Other sources who provided information (specify): _____

Signs and symptoms in chronological order from the time of vaccination:

Name and contact information of person completing these clinical details:	Designation:	Date/time

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports, prescriptions for concomitant medication) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day

Number immunized for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

a)	When was the patient immunized? (✓ the ☐ below and respond to ALL questions)	
	☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown	
	In case of multidose vials, was the vaccine given ☐ within the first few doses of the vial administered? ☐ within the last doses of the vial administered? ☐ unknown?	
b)	Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c)	Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d)	Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes* / No / Unable to assess
e)	Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes* / No / Unable to assess
f)	Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes* / No / Unable to assess
g)	Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes* / No / Unable to assess
h)	Number immunized from the concerned vaccine vial/ampoule	
i)	Number immunized with the concerned vaccine in the same session	
j)	Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations: _____	
k)	Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes* / No / Unable to assess
l)	Could this event be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes* / No / Unable to assess
m)	Is this case a part of a cluster?	Yes* / No / Unkn
i.	If yes, how many other cases have been detected in the cluster?	
a.	Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
b.	If no, number of vials used in the cluster (enter details separately)	

*__It is compulsory for you to provide explanations for these answers separately__

Section E Immunization practices at the place(s) where concerned vaccine was used

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn

If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled disposable ☐ Other _____

Specific key findings/additional observations and comments:

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA

Specific key findings/additional observations and comments:

Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)	
• Correct dose and route?	Yes / No
• Time of reconstitution mentioned on the vial? (in case of freeze dried vaccines)	Yes / No
• Non-touch technique followed?	Yes / No
• Contraindications screened prior to vaccination?	Yes / No
• How many AEFI were reported from the centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If Yes, specify the date of last training _____)	Yes / No
Specific key findings/ additional observations and comments?	

Section F **Cold chain and transport** *(Complete this section by asking and/or observing practice)*	
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

Section G Community investigation (Please visit locality and interview parents/others)

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality? Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

Of those effected, how many are
- Vaccinated:_____
- Not vaccinated:_____
- Unknown:_____

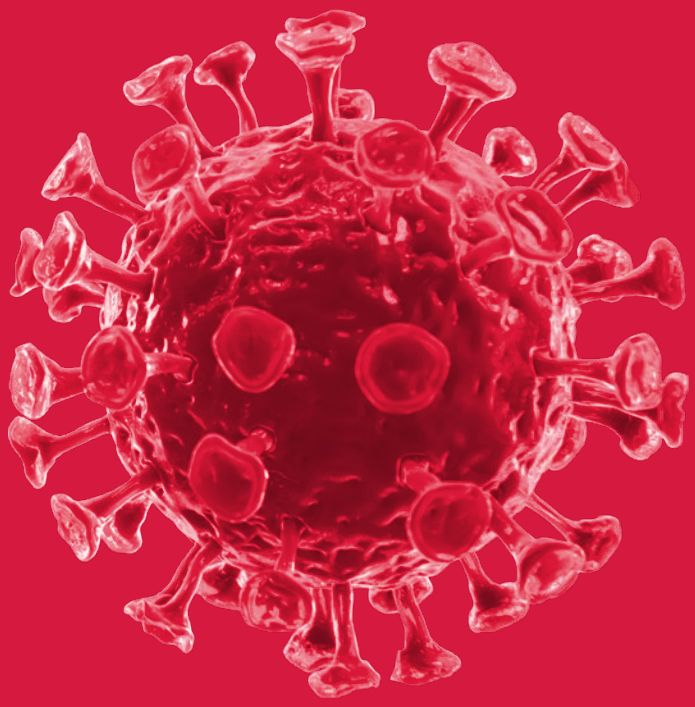
Other comments:

Section H Other findings/observations/comments

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

SAFETY DATA MANAGEMENT SYSTEMS, METHODS OF POST-INTRODUCTION EVALUATION AND ASSESSING PERFORMANCE IN COUNTRIES USING COVID-19 VACCINES



Contents

Key points

- Data sharing at all levels is important to increase knowledge rapidly that can inform decisions about COVID-19 vaccine introduction and continuation strategies
- Key ethical considerations for data sharing include data confidentiality, data security, autonomy, sovereignty and benefits for those providing and sharing data
- Vaccine safety surveillance systems are for all vaccines, not just the COVID-19 vaccine and that routine vaccination will continue during COVID-19 deployment
- The WHO global database VigiBase, which contains ICSRs for adverse events following immunization (AEFIs) from all Member States in the WHO Programme for International Drug Monitoring, can be used to detect signals and safety concerns at national, regional and global levels
- Safety data will be also be available as aggregated data from various local data bases and from ad hoc research
- Data will have to be stored using agreed international standards or data transformation will have to performed to ensure compatibility for successful data sharing
- There are many examples of repositories that are collecting and processing information on AEFIs that can be used for data necessary for decision making at national, regional and global levels
- Counties should verify the performance of their safety data collection and assessments using either adaptations of existing indicators or COVID-19-specific immunization indicators

01 Introduction

WHO's global manual on surveillance of adverse events following immunization (AEFIs)[1] provides guidance on the purpose of data analysis at different levels. For example, who should analyse data, how it should be analysed and interpreted and its use for estimating relative and attributable risks. In the context of COVID-19 vaccine AEFI surveillance, the same principles and approaches should be applied, with some adaptation to allow for different vaccination strategies, vaccine target populations, types of vaccines and the surveillance systems available in different countries.

Guidance on vaccine safety surveillance systems and responding to AEFIs and adverse events of special interest (AESIs) to address the unique challenges from COVID-19 vaccine introduction is given in separate modules (AEFI and AESI modules). Once surveillance systems are operational, the efficiency and effectiveness of the system will be determined by the outputs and outcomes from the system. First, the raw data generated by the system needs to be collated, then transmitted, processed and interpreted and, finally, responded to systematically and scientifically. This module will provide guidance on how COVID-19 vaccine safety data should be processed and made actionable.

02 Sharing COVID-19 vaccine safety data

To guarantee the integrity and validity of the generated COVID-19 vaccine safety data, data loss and duplication should be minimized. This can be achieved through data sharing between stakeholders such as national immunization programmes (NIPs) and expanded programmes on immunization (EPIs), national regulatory agencies (NRAs), pharmacovigilance centres, Ministries of Health (MoHs), AEFI committees, private sector, vaccine manufacturers.[2] Data in some countries will be reported through multiple channels, with programmes obtaining data from the same patients and sometimes via the same health care worker, but with different goals and pathways.

1 World Health Organization. Global Manual on Surveillance of AEFI. Available from: https://www.who.int/vaccine_safety/publications/Global_Manual_on_Surveillance_of_AEFI.pdf. Accessed 29 October 2020.

2 For the purpose of this document, manufacturer also means marketing authorization holder.

At regional and global levels, data sharing maximizes resources and capacity to enable efficient responses and decision-making. Data sharing also increased signal detection capacity and the ability to detect and analyse very rare adverse events. Data transformation is usually required to facilitate data sharing from different sources.

2.1 Rationale for data sharing

Data sharing at all levels is important to increase knowledge rapidly that can inform decisions about COVID-19 vaccine introduction and continuation strategies. Uncertainty about the frequency AEFIs and clinical presentation will be expected due to the fast-track development processes for COVID-19 vaccines, with short time frames for data collection and regulatory review. The rationale for sharing data from four main sources is outlined below:

- **Data from passive and enhanced passive AEFI surveillance systems:** to detect signals, monitor safety aspects of immunization programme activities, monitor events that could be related to defective, non-authorized or counterfeit COVID-19 vaccines.
- **Data from active surveillance systems:** to verify and confirm the post-authorization safety profiles of COVID-19 vaccines, test hypotheses (epidemiologic associations between AEFIs and COVID-19 vaccines), detect signal with an accelerated time frame from reporting to detection.
- **Data from COVID-19 vaccine manufacturers:** bi-directional sharing[3] of data with COVID-19 vaccine manufacturers will help ensure that data collection is complete and will avoid double counting of events. In addition, the manufacturers may be aware of data from other countries or sources that can help in the evaluation of AEFIs.
- **Data from other sources such as disease surveillance data, vaccine distribution and utilization data:** can help generate rapid alerts to trigger common responses from a geographical territory, provide knowledge about the implementation level and the quality of surveillance at the national level to plan for improvement strategies, understand the distribution of different COVID-19 vaccines and to compare with distribution of the disease for interpreting patterns observed during data analysis.

2.2 Ethics in safety data sharing and collaboration

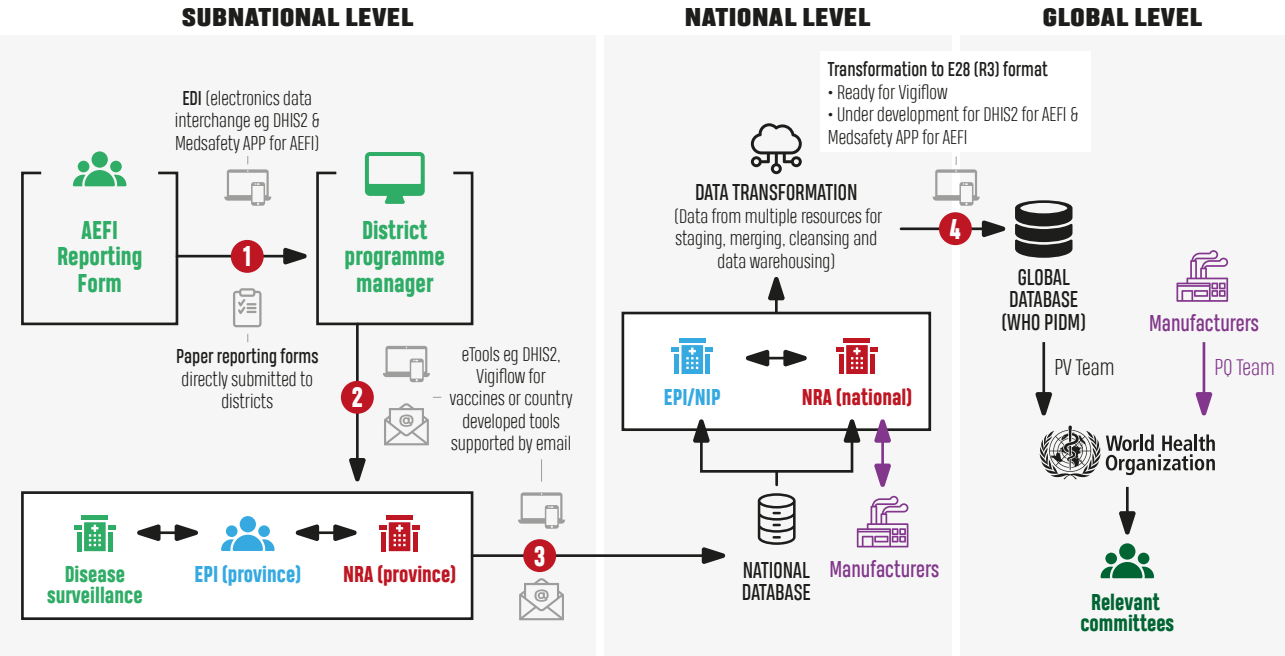
The key ethical considerations for data sharing include data confidentiality, data security, autonomy, sovereignty and benefits for those providing and sharing data.

3 Vaccine manufacturers inform the NRAs of the AEFI occurring in other parts of the world and the NRA needs to share AEFI data from their country with the vaccine manufacturers.

2.3 Generic data sharing model

Fig 1 shows a schematic representation of the structure of a generic model for data sharing at the local, subnational, national and global levels. Each country must adapt the generic systems to their local context.

Fig 1: Schematic representation of the structure for data sharing at the subnational, national and global levels



AEFI: adverse event following immunization; DB: database; EPI/NIP: expanded programme for immunization/national immunization programme; NRA: national regulatory authority.

2.4 Stakeholder mapping for AEFI data sharing

The potential stakeholder mapping is summarized in **Table 1**. It is important to consider who will be producing or managing COVID-19 vaccine AEFI data when a data sharing strategy will be developed.

Table 1: Potential stakeholder mapping of COVID-19 vaccine AEFI data sharing

Stakeholder	Current data mapping (variable depending on context)
Subnational level	
Health care institutions	— Individual Case AEFI reports — Case Report Forms for ad-hoc studies
Disease surveillance offices	— Investigation information to complete Individual Case AEFI reports — Data on local epidemiological behaviour of infectious diseases

Stakeholder	Current data mapping (variable depending on context)
Immunization programme offices	— Data on immunization activities — Individual Case AEFI reports
National level	
Disease surveillance responsible	— Data on infectious and non-infectious diseases — Data on AEFI surveillance
National immunization programmes / expanded programmes on immunization	— Data on immunization activities: administrative data and distribution activities — Data on AEFI surveillance.
National regulatory authorities	— Data on AEFI surveillance from primary health care workers and citizens — Data on AEFI surveillance from manufacturers — Data on adverse event reports from clinical trials — WHO global database of ICSRs including adverse drug reactions and AEFIs
Health information systems units	— Data from all sources in the country
Research institutions/clinical research organization	— Individual case safety (adverse events) reports from clinical trials — Data on diseases considered as AESI/AEFI
Vaccine manufacturers	— Individual Case AEFI reports — Periodic safety update reports
Clinical research sponsors	— Suspected unexpected serious adverse reactions (SUSAR) from clinical trials
Regional and global levels	
WHO regional offices	— WHO/UNICEF Joint Reporting Form (JRF)[4] — Individual case reports on infectious disease surveillance — Access to WHO global database of individual case safety reports (ICSRs) including adverse drug reactions (ADRs) and AEFIs[5]
WHO headquarters	— WHO-UNICEF JRF — Individual case reports on infectious disease surveillance — Access to WHO global database of ICSRs[5] including ADRs and AEFIs
WHO Programme for International Drug Monitoring /VigiBase (maintained by UMC)	— Individual Case AEFI reports — WHO global database of ICSRs including ADRs and AEFIs

4 WHO/UNICEF Joint Reporting Process. Available from: https://www.who.int/immunization/monitoring_surveillance/routine/reporting/en/. Accessed 9 December 2020.

5 VigiBase. Available from: https://www.who-umc.org/vigibase/vigibase/. Accessed 9 December 2020.

2.5 Data sources

There are different data sources with different data formats that can be used in COVID-19 vaccine pharmacovigilance. Some considerations for country capacity for data sharing include:

- timely availability of individual AEFI case reports with at least the 25 core variables;
- data centralization in a database with variables coded using a pre-defined data standard;
- completeness and accuracy of data (quality);
- technology available to implement safe data transfer; and
- data governance frameworks that define rules for data sharing with external institutions.

2.5.1 Individual case safety reports (individual AEFI case reports)

Different levels of information systems exist in different countries. This information is usually collected from passive AEFI surveillance systems, however, it could also be collected from active sentinel surveillance sites. Individual reports could also come from COVID-19 vaccine trials that would be assessed by a specific study scientific committee established for the purpose. The WHO global database VigiBase, contains ICSRs and AEFIs from all Member States in the WHO Programme for International Drug Monitoring (PIDM). The source can be used to perform quantitative calculations at national, regional and global levels to detect signals and safety concerns.

2.5.2 Aggregated safety data from different sources

All countries routinely share aggregated safety data to help characterize vaccine safety e.g. WHO-UNICEF JRF, situation reports (SITREPs), integrated disease surveillance and response (IDSR), networks reports from regulatory authorities and academic initiatives.

2.5.3 Ad-hoc research

Ad hoc research projects or specific studies could be performed by networks of health care institutes using data transferred to national institutes and to the data warehouse of the institute doing the final analysis. The platform selected by the study coordination and described in the study protocol will have an impact on the database. It is necessary to assess the data available for the event and its quality, and the availability of information about the vaccination status of the patients to be included in the study before initiating ad-hoc studies. Patient diagnosis registration systems and vaccination registries should be available.

2.6 Data standards

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standardizes the definition of the data elements used in electronic transmission of different types of Individual Case Safety Reports (ICSRs), regardless of source

and destination. The standard adopted by the ICH for electronic transmission of ICSRs is described in the ICH E2B(R3) message standard. Additional information is available at https://www.ich.org/page/electronic-standards-estri.

Data should satisfy agreed international standards for successful data sharing, so that both the transmitter and the receiver have identical information. Multiple data standards are available for specific coding and for whole database structures and data formats. For clinical diagnosis coding, some standards have been developed e.g. Medical Dictionary for Regulatory Activities (MedDRA) and ICD. It is important to use a standard for identifying the specific vaccine that is being evaluated. Whenever available, the anatomical therapeutic chemical (ATC) standard[6] should be used. For active surveillance systems, data standards are defined by the study protocols.

2.7 Data transformation

If the database used by the country does not comply with a standard as outlined above, data transformation is essential before data can be shared. The ICH E2B(R3) message standard should be used for data transformation and transmission in a standard transmission format. This requires coding as outlined in MedDRA and Identification of Medicinal Products (IDMP). Data science techniques should be applied for converting the source database format into the target format of the international database, using tools such as, ETL (extract, transform and load). Countries are encouraged to contact WHO country offices for guidance if needed.

2.8 Repositories

The following are examples of repositories that are collecting and processing information on AEFIs and enabling decision making at national, regional and global levels:

- examples of national databases: Vaccine Safety Datalink (US), Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) and Vigiflow, maintained by UMC;
- example of regional databases: EudraVigilance;
- example of global databases:
  - for aggregate data: the WHO/UNICEF Joint Reporting Process;
- example of national, regional and global datasets:
  - for case-based data, the WHO global database of individual case safety reports, Vigibase, maintained by UMC.

6 World Health Organization. The ATC/DDD Methodology. Available from: https://www.who.int/medicines/regulation/medicines-safety/toolkit_methodology/en/. Accessed 29 October 2020.

03 Methods for rapid post-introduction evaluation of COVID-19 vaccine safety

Before regulatory approval, results from randomized clinical trials will be used for the initial evaluation of the safety of any COVID-19 vaccine. These trials will have limited sample size, duration of follow-up and certain populations may be missing or underrepresented (e.g., elderly, people with chronic conditions, pregnant women). It is also possible that some vaccines may be introduced under an emergency use listing authorization, further limiting the data available prior to introduction. It is critical, therefore, to conduct post-introduction safety surveillance to ensure appropriate monitoring to allow rapid signal detection and assessment to evaluate the benefit-risk profile of COVID-19 vaccines. Here we propose a set of post-introduction analyses and points for consideration in the assessment of COVID-19 vaccine safety that can be applied both for signal detection or for assessment of signals detected in other data sets.

3.1 Study population

Studies should include all vaccinees for the primary analyses to provide maximum statistical power, with subgroup analyses of:

- children under the age of 19,
- elderly patients over the age 64, and
- pregnant women.

Studies should be conducted in the whole vaccine-eligible population of the country or region or in a representative sample. If the delivery of COVID-19 vaccines is initially limited (due to supply constraints) to high-risk groups such as health care workers, then the target study population for safety surveillance should be defined accordingly.

3.2 Signal detection

When we ascertain or quantify adverse events (AEs), the occurrence of the event is compared in vaccinated and non-vaccinated individuals or in exposed versus unexposed time periods for the same individual, using different types of methodologies.

For signal detection the observed AE rate is compared with the 'expected' rate which is generally inferred from data from:

- historical controls using data from the same (or a similar) population during an earlier time period;
- cohort studies which compare event rates in specific risk windows; controls may be other individuals during the same time period who did not receive the targeted vaccine but who are otherwise similar to those vaccinated;
- self-controlled studies, using a case-series, case-crossover or risk interval design, in which all data would be obtained from vaccinated individuals, comparing a post-exposure risk window with either a pre-exposure control window or with a post-exposure control window that occurs after the risk window;
- case-based studies where the vaccination rate among cases who had the AE of interest is compared with that among individuals that did not have the AE of interest, in a case-control or case-coverage design.

In most anticipated post-introduction settings, self-controlled designs will be promising and efficient study designs as they automatically adjust for between-person confounding that can be present in other study designs. However, one disadvantage of the self-controlled study design with pre-exposure control windows is potential bias due to vaccine indication or contraindications, in situations where having the adverse event increases or decreases the likelihood of being vaccinated. The most extreme form of vaccine contraindication is death, since dead people will not be vaccinated. To overcome this limitation, a post-exposure control window, occurring after the risk window, may be defined. One disadvantage of this approach is that a signal will not be detected if the risk of the AE is constant during the post-vaccination period. Moreover, AEs are not informative, and cannot contribute to a safety 'signal', until data from the post-exposure control window are available, delaying the timeliness of the analysis. This is further complicated if vaccination requires two doses of the vaccine, e.g. if a second dose is recommended 30 days after the first dose it could be difficult to specify an appropriate post-vaccination control window. Finally, for signal detection, a traditional self-control design has limited utility for diseases with a long latency, but this could be overcome by using a post-vaccination control window that occurs before the risk window. When a risk window cannot be well defined, it is possible to use the self-control temporal scan statistic, simultaneously evaluating hundreds of potential risk windows, while automatically adjusting for the multiple testing inherent in such an approach.

While automatically adjusting for between person bias, it is important to recognize that self-control designs are still subject to time-varying confounders. Examples of such confounders are concomitant vaccines, seasonal variation in the adverse event, changing diagnosis coding, and for infants, increasing age.

In a cohort design, the key challenge is to identify a control group that minimizes between person bias. The priority target groups for COVID-19 vaccines are likely to be similar to those for seasonal influenza vaccines (health care workers, the elderly, and potentially pregnant women), therefore, the use of time-varying propensity scores analysis for COVID-19 vaccine recipients and seasonal influenza recipient controls could minimize health care seeking and risk group biases in studies assessing the safety of COVID-19 vaccine. This approach could be used if seasonal influenza and COVID-19 vaccine campaigns are overlapping, providing not all individual get both vaccines at the same time. It would allow for matching on propensity scores

as well as the epidemiological week of exposure, to simultaneously control for presence of circulating wild-type virus. Another alternative would be to use influenza vaccine recipients from an earlier period. If the COVID-19 vaccine is given at times outside the influenza vaccination season, adjustment for any seasonal variation in the AE rates must be made.

Each vaccine safety study design has its different strengths and weaknesses, therefore it is often advisable to use multiple designs for the investigation of the same AE.

3.3 Vaccine exposure

Given the large variety of vaccine platform technologies used to develop COVID-19 vaccines, It is important to be able to perform vaccine-specific safety analyses. For this will be important to have complete information about the COVID-19 vaccine, such as manufacturer, brand name and batch number. While there are hopes that at least some of the new COVID-19 vaccines will be equipped with 2D barcodes which can be scanned to record this information, this is not guaranteed. Also, pilot projects with 2D barcodes in the US have revealed several hurdles slowing down that acceptance.[7] Plans for alternative 'lower tech' means to capture the essential vaccine exposure information must therefore be made. For example, a standard data dictionary for each COVID-19 vaccine introduced for use could be maintained by Brighton Collaboration or WHODrug Global.

3.4 Analytic approaches for signal detection on electronic health record data

3.4.1 Rapid cycle analyses for suspected adverse events

Outcomes: Standard vaccine AEs following immunization (AEFI) during relatively brief post-vaccination risk intervals, or adverse events of special interest (AESIs) such as Guillain-Barré syndrome (GBS), Kawasaki disease and seizures. Serious outcomes from clinical trials, even if only one event was observed. AESI lists developed by the Safety Platform for Emergency vACcines (SPEAC)[8] or provided by WHO.[9]

Frequency: Weekly data feeds and analyses.

Statistics: Maximized sequential probability ratio test.

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7 Centers for Disease Control and Prevention. Summary report. Reporting for the adoption strategies for 2D barcode project (page 36). Available from: https://www.cdc.gov/vaccines/programs/iis/2d-vaccine-barcodes/downloads/summary-report.pdf. Accessed 9 December 2020.

8 Brighton Collaboration. Safety Platform for Emergency vACcines (SPEAC). Available from: https://brightoncollaboration.us/speac/. Accessed 9 December 2020.

9 Global Advisory Committee on Vaccine Safety, 27–28 May 2020, WER. 2020;95(28):331:325-336.

Model: Can be used with any study design., e.g.:

- Poisson model with age- and sex-adjusted expected counts from the general population, with a fixed X to Y day risk interval, where X and Y depend on the outcome;
- Poisson model with day zero as the risk window, with age- and sex-adjusted expected counts from general population;
- Self-controlled Bernoulli model, with a 1 to 14 day risk window and a pre-vaccination control window of between 15 to 42 days; and
- Self-controlled temporal scan model, with 1 to 42 days[10] post-vaccination follow-up and a temporal scan statistic as the risk window. A post-vaccination control period (e.g. 21 to 34 days) may also be considered to address the possibility that it may not be appropriate to use a pre-vaccination period. If this is done, then the analysis will be delayed until the end of the post-vaccination control period. An adjustment to allow for delays in recording of AEs in the database should be considered.

Case-centered logistic regression could also be used with a sequential test (either a likelihood ratio test or a Wald test, with a flat Pocock-style threshold for controlling one-sided alpha-spending at 0.05), regardless of whether the 'expected' proportion of vaccinees who experience an AEFI during a risk window is inferred from historical controls, contemporaneous controls, or other comparison windows (in self-controls).

Sample size: Analyses should start immediately with the first week of post-authorization vaccinees, even if there are only a few exposed individuals. The sequential analyses should continue until there are at least one million individuals for the primary analysis, and 200,000 for the subgroup analyses.

3.4.2 Time-to-onset analysis

Time-to-onset analysis, using Kolmogorov–Smirnov tests,[11] has been used in spontaneous reporting system databases to compare time-to-event distributions for AESIs with:

- the time-to-event distributions for other events following exposure to the same vaccine; and
- the time-to-event distributions of AESIs after exposure to other vaccines.

The approach has been tested in a prospective observational setting but has not yet been used for signal detection in routine health care data. If influenza vaccination occurs in late 2020 in the northern hemisphere, prior to deployment of COVID-19 vaccines, this will provide an opportunity to construct time-to-event distributions for AESIs following influenza vaccine exposure to be used to compare with corresponding distributions following COVID-19 vaccine exposure.

10 The 42-day window would have to be censored when the second vaccine dose for a two-dose regimen is received.

11 Van Holle L, Zeinoun Z, Bauchau V, Verstraeten T. Using time-to-onset for detecting safety signals in spontaneous reports of adverse events following immunization: a proof of concept study. Pharmacoepidemiol Drug Saf. 2012;21(6):603-10. doi: 10.1002/pds.3226.

3.4.3 Ecological methods

Ecological analyses may also be informative if COVID-19 vaccination uptake is high and over a short period, in a demographic group that can easily be selected, such as the elderly. A simple interrupted-time series analysis comparing rates of selected AESIs in the pre- and post-vaccine deployment periods may be able to detect a signal for an event with a brief onset-to-event interval in a subpopulation with high vaccine coverage, assuming wild-type virus circulation is relatively stable over these periods. It may also be possible to assess time effects by comparing changes in the incidence of AESIs in vaccination targeted groups with changes in non-targeted groups. However, it is important to take into consideration the potential changing patterns in health care due to the COVID-19 pandemic.

3.4.4 Data mining for unexpected adverse events

In addition to evaluating the risk of a predetermined list of AEFIs or AESIs, it will also be necessary to search for unexpected AEFIs or AESIs. To do this, a different approach is required:

Outcomes: Would include most ICD-10 (or ICD-9) codes with removal of those for elective events, such as well-care visits, pregnancies or for conditions not of interest such as cancer.

Frequency: Monthly data feeds and analyses.

Statistics: Sequential tree-based scan statistics, using ICD-9 or ICD-10 hierarchical coding structure.

Model: Self-controlled Bernoulli model, with days 1 to 21 as the risk window, and in separate analyses, days 22 to 42 post-vaccination and days 22 to 42 pre-vaccination as control windows.

Sample size / length of surveillance: Analyses should start immediately after authorization and ideally continue until there are one million doses for the primary analysis, 200,000 each for children under the age of 19 and elderly patients over the age 64 subgroups, and 50,000 for pregnant women subgroup.

3.4.5 Signal evaluation

Any signals must be thoroughly evaluated. Steps to be considered are:

1. data quality check:
    a. examination of electronic health record linelist of all outcomes for the patients generating the signal (i.e. who have the AE); and
    b. examination of temporal trends for both the vaccination and the outcome.
2. medical record review to confirm cases with the outcome, if not for all, at least for a sample, to assess the positive predictive value of the case identification algorithm;
3. COVID-19 vaccine brand- and platform-specific analyses with comparison with COVID-19 vaccines of a different brand or using a different platform;

4. adequate control for confounding, using study design, matching or adjustments, as necessary; and

Following this evaluation, any signals that remain of concern should be assessed further in a full appropriately-designed epidemiological study, which ideally should be done using a different dataset to the one in which the signal was detected.

3.5 Ongoing surveillance while signals are being evaluated and refined.

Regulators and public health agencies will not necessarily stop delivering vaccines when a safety signal exceeds a pre-defined statistical threshold. However, if this threshold is exceeded, the information will contribute to an overall analysis of vaccine's benefit-risk profile. These analyses should provide information on the magnitude of the risk and the attributable risk.

Although pre-signal statistical tests are sequential, ongoing surveillance after a signal can report nominal p-values and confidence intervals, in addition to the sequentially adjusted test that initially generated the signal. The multiplicity of outcomes under surveillance and the multiplicity of analyses of the accumulating data should continue to be reported.

3.6 Impact of change in health care use and provision on AESI identification and temporal trends

The pandemic has led to changes in health care use and provision and these changes are likely to continue into the vaccine deployment period. This may be reflected in observational data as an excess or a deficit of code counts for some AESIs or their proxies in the pandemic period. To understand these changes to the data available for analysis, it is recommended that counts and rates of both individual codes used in any AESI case-identification algorithm as well as the set(s) of codes used to identify each event be described over time both within and between databases, taking into account the type of database and the type of health care encounters typically captured (e.g. general practice vs. hospitalization). These counts and rates should be compared graphically to help to interpret the study results. It may also be possible to use historical periods to generate projected expected counts and rates in the absence of changes to health care use and provision.

3.7 Vaccine-associated enhanced disease

It has been suggested that individuals who receive a COVID-19 vaccine might be at increased risk of experiencing enhanced or more severe disease following vaccination or vaccine-

associated enhanced disease (VAED).[12] This has been suggested as a potential problem because of results in animal models with SARS-CoV-1 and MERS vaccines. Importantly, it has not been reported in animal models or in humans for any COVID-19 vaccine in advanced development. To be classified as a case of VAED, the individual would have to be a vaccine failure and also exhibit either a specific histopathology associated with advanced disease or have a specific biomarker. Unfortunately, none of the proposed patterns of histopathology have been confirmed and there is currently no known biomarker. Hence, diagnosis of VAED will require the demonstration that vaccinated individuals who develop COVID-19 disease have a higher risk of developing severe disease than non-vaccinated individuals. This assessment is further complicated by the fact that a higher risk of VAED could be expected as the levels of antibody wane with time, i.e. distant from vaccination. For this reason, it is being recommended that vaccinees be followed for an extended period, possibly for several years. A registry to follow-up participants from clinical trials who were in the control (unvaccinated) group and who choose to remain unvaccinated after vaccine introduction may be useful. It would be even more useful if they could have periodic blood draws that could be stored in biobanks for the future identification of potential biomarkers should VAED be recognized as a real AESI. It will not be possible to use of SCCS study design due to an indeterminate risk window following vaccination, therefore, a case-control design will probably be the most suitable for a study using standardized severity assessment scores for the multiple possible disease outcomes associated with COVID-19 disease to assess if the cases (vaccinated individuals with COVID-19 disease) are more likely to have severe disease than controls (unvaccinated individuals with COVID-19 disease).

12 Lambert PH, 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):4783-4791. doi: 10.1016/j.vaccine.2020.05.064.

04 Performance indicators

Indicators have been adapted from existing immunization indicators, where possible, so that all counties can verify that their safety assessments for COVID-19 vaccines, but some specific indicators have been developed to respond to the current COVID-19 situation. Programme managers should take into consideration the fact that vaccine safety surveillance systems are for all vaccines, not just the COVID-19 vaccine and that routine vaccination will continue during COVID-19 deployment.

This section describes indicators obtained by extracting data on COVID-19 vaccines from pharmacovigilance monitoring and evaluation systems. The objectives of these indicators specific to COVID-19 vaccines are:

- at the national level:
  - help national AEFI committees, NRAs and NIPs/EPIs to identify any subnational programmatic issues, vaccine safety signals or any crisis in a timely manner and to make decisions for correction;
  - identify if the country's vaccine safety system is sensitive enough to identify signals and respond to them;
  - improve the quality of reporting, investigations and causality assessment; and
  - enable comparison of national safety performances with regional and global standards.
- at the subnational level:
  - help provincial governments to identify districts where surveillance is poor (low reporting);
  - identify and respond to programme and immunization errors early;
  - identify capacity gaps in specific districts, particularly those with vulnerable populations; and
  - allocate resources for building local training capacity.
- at the local level:
  - Identify zones with high COVID-19 coverage but poor AEFI reporting.

Since COVID-19 vaccines are novel, it has been suggested that a separate report should be generated monthly, based on:

- key COVID-19 vaccine pharmacovigilance indicators (**Table 2**):
  - total AEFI rate/100,000 COVID-19 vaccine doses administered/distributed;
  - serious AEFI (SAE) rate per 100,000 doses of COVID-19 vaccine administered/distributed;

- six indicators for monitoring the functionality of pharmacovigilance systems in the COVID-19 context (**Appendix 5.1**):
  - % of districts with silent COVID-19 AEFI reporting (i.e. no reports received);
  - % of districts not submitting monthly reports;
  - % of districts with >10 COVID-19 related AEFI reports / 100,000 doses of COVID-19 vaccines doses administered;
  - % of serious AEFI after COVID-19 vaccination investigated;
  - % of serious AEFI after COVID-19 vaccination investigations initiated within 2 days of notification; and
  - % of identical AEFI reports available with the NRA and the NPI/EPI (i.e. NRA reports =EPI reports).

- five indicators for monitoring the quality of pharmacovigilance systems in the COVID-19 context (**Appendix 5.2**):
  - % of case based AEFI reports shared between NRA and EPI <7 days of receipt;
  - % Completeness of AEFI reporting forms with the critical variables;
  - % of AEFIs reported within 48 hours of notification;
  - % of serious AEFI cases with causality assessed within 14 days of investigation; and
  - % of AEFI cases with causality assessment done where feedback was provided within 7 days of case classification.

Table 2: Key COVID-19 vaccine safety surveillance indicators

Indicator	Calculation	Information source	Measures	Primary collector
Total AEFI rate per 100,000 doses of COVID-19 vaccine doses administered / distributed*	No of AEFI reported at xx level / no of doses of COVID-19 vaccines administered or distributed at the same level X 100,000	Numerator: Case based AEFI reports from linelist or reporting forms Denominator: Vaccination records at the local level	If the reporting rate of AEFI differs from the ones available in clinical trials	Numerator: health care workers reporting AEFI Denominator: District immunization programme manager
Serious AEFI rate per 100,000 doses of COVID-19 vaccines doses administered / distributed*	No of serious AEFI reported at xx level / no of doses of COVID-19 vaccines administered or distributed at the same level X 100,000	Numerator: Case based serious AEFI reports from linelist or reporting forms Denominator: Vaccination records at the local level	If the reporting rate of serious AEFI differs from the ones available in clinical trials	Numerator: health care workers reporting serious AEFI Denominator: District immunization programme manager

**To consider the type of vaccine at the time of calculation.*

05 Appendices

Appendix 5.1: Indicators and targets for monitoring the performance of pharmacovigilance systems in COVID-19 context

Indicator	Target	Calculation	Information source	Measure	Main responsible
% of districts with silent (i.e. no reports received) COVID-19 AEFI reporting.	<10%	Number of districts where COVID-19 related AEFI was zero in the month of XX / No of Districts X 100	Reports submitted with zero AEFIs. during the previous month.	Identification of silent districts / areas within a province	District immunization programme manager sending periodic reports
% of districts not submitting monthly Reports	<10%	Number of districts where monthly COVID-19 related reports AEFI was not sent for a particular month / No of Districts X 100	Monthly (including zero) reports submitted by districts	Identification of delinquent reporting districts in a province	District immunization programme manager sending periodic reports
% of districts with >10 COVID-19 related AEFI reports/ 100,000 doses of COVID-19 vaccines doses administered	>80%	No of districts with > 10 AEFI reported for 100,000 doses of COVID-19 vaccines Administered / No of Districts X 100	Calculated from AEFI reporting form submitted by the districts following COVID-19 vaccination and Immunization registries	District performance on AEFI monitoring	District immunization programme manager sending AEFI reporting form and data on administered doses
% of serious AEFI after COVID-19 vaccination investigated	100%	Number serious AEFI investigated / Number of serious AEFI X 100	AEFI reporting form and AEFI investigation form	The quality of investigation of serious AEFI	District immunization programme manager coordinating the AEFI investigation

Indicator	Target	Calculation	Information source	Measure	Main responsible
% of serious AEFI after COVID-19 vaccination investigations initiated within 2 days of notification	>80%	Number serious AEFI investigations initiated within 2 days of notification / Number of serious AEFI X 100	AEFI reporting form and AEFI investigation form	The timeliness of investigation of serious AEFI	District immunization programme manager coordinating the AEFI investigation
Proportion of identical AEFI reports available with the NRA and the EPI (i.e. NRA reports =EPI reports).	1 for all months	No of AEFI reports with NRA in the month of XXXX / No of AEFI reports with EPI in the month of XXXX	AEFI reporting forms available with EPI or NRA following COVID-19 vaccination	Data sharing between the immunization programme and the regulators	Regulators and NIP/EPI programme managers

Appendix 5.2: Indicators and targets for monitoring the quality of pharmacovigilance systems in COVID-19 context

Indicator	Target	Calculation	Source of information	Measure	Main responsible
% of case based AEFI reports shared between NRA and EPI <7 days of receipt	100%	Number AEFI reports shared between NRA and EPI within 48 h of receipt / Number of AEFI reports X 100	AEFI reporting forms available with NRA and EPI or matching number of cases in linelist	Quality of data sharing	NRA and NIP/EPI programme managers
% Completeness of AEFI reporting forms with the critical variables	>80%	Number AEFI reports with complete critical variables* / Number of AEFI reports X 100	AEFI reporting forms	Quality of AEFI data collected	NIP/EPI programme managers
% of AEFIs reported within 48 hours of notification	>80%	Number AEFI reports sent to next level within 48 hours of notification / Number of AEFI reports X 100	AEFI reporting forms	Speed of response to AEFI notification	NIP/EPI programme managers

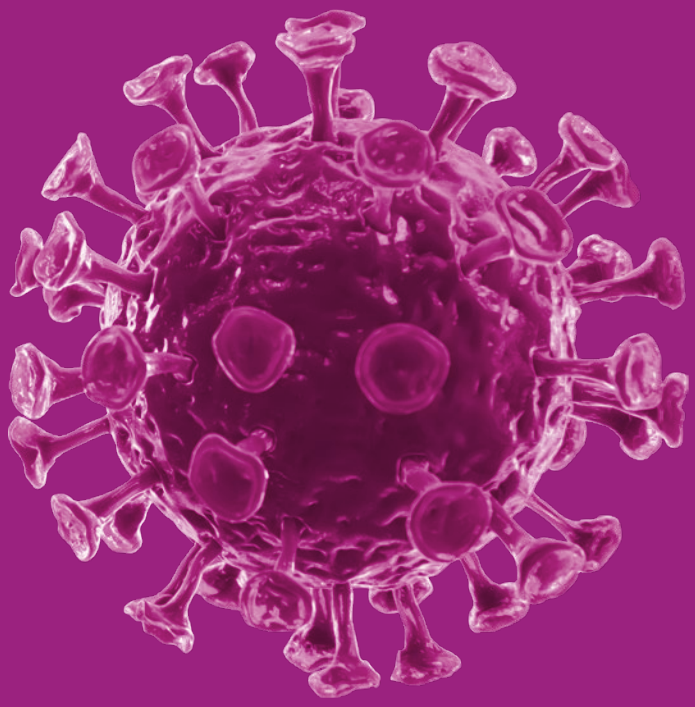
Indicator	Target	Calculation	Source of information	Measure	Main responsible
% of serious AEFI cases with causality assessed within 14 days of investigation	>80%	Number serious AEFI reports with causality assessed within 14 days of investigation / Number of serious AEFI reports X 100	AEFI reporting forms	Speed of response to AEFI investigation	NRA and NIP/EPI programme managers
% of AEFI cases with causality assessment done where feedback was provided within 7 days of case classification	>80%	Number causality assessed cases with feedback provided within 7 days of case classification / Number of AEFI reports with causality assessment done X 100	Documentation of feedback of AEFI causality assessment	Speed of response to AEFI causality assessment	NRA and NIP/EPI programme managers

** Italics in reporting form*

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

ENGAGING WITH THE PHARMACEUTICAL INDUSTRY FOR COVID-19 VACCINE SAFETY SURVEILLANCE



Contents

Key points

- The pharmaceutical industry plays a critical role in the accelerated development of vaccines and therapeutics
- They also have an essential role in verifying the safety of COVID-19 vaccines through vaccine safety surveillance activities described in risk management plans for licensed vaccines particularly via periodic safety update reports
- Vaccine manufacturers are encouraged to adopt existing formats for risk management plans, which contain essential elements, such as a safety specification section, pharmacovigilance activities, risk minimization activities, and evaluation of the effectiveness of the risk minimization measures
- Both routine and additional pharmacovigilance activities, which are integrated in the RMP, contribute to the maintenance of a positive benefit-risk balance for a vaccine
- There should be global, regional and national oversight of the RMPs for COVID-19 vaccines
- National regulatory agencies (NRAs) and the WHO prequalification team should consider making data sharing a condition of marketing authorization or prequalification for COVID-19 vaccines during the pandemic, particularly in countries
- Effective data flow should be established between NRAs or the WHO prequalification team and the vaccine manufacturer while respecting data security and patient privacy
- Training to enhance pharmacovigilance competencies and to enable regional coordination should be coordinated and existing training materials and programmes should be leveraged as much as possible

01 Introduction

The private sector plays an essential role in the development and introduction of vaccines, as well as in on-going pharmacovigilance activities to ensure efficacy, quality and safety throughout the vaccines' life cycle. Under the current pandemic, it plays a critical role in accelerated development of vaccines and therapeutics. Although diverse players make up the private sector, this module will focus on the vaccine manufacturers[1] and their role in ensuring the safety of COVID-19 vaccines through pharmacovigilance activities, as described in risk management plans and more specifically in providing periodic safety update reports (PSURs).

02 Legal provisions and guidelines regarding COVID-19 vaccine safety

In countries where the regulatory authority is a member[2] or an observer of the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH), ICH technical guidelines and requirements will guide the vaccine manufacturers in meeting their obligations for COVID-19 vaccine registration and continued monitoring of safety when the vaccine is on the market. Two ICH guidelines set out common standards for pharmacovigilance activities to ensure the safety of new drugs and those already on the market: *ICH E2E Pharmacovigilance Planning*,[3] and *ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER).*[4]

1 For the purpose of this document, manufacturer also means marketing authorization holder.
2 ICH Members & Observers. Available at: https://www.ich.org/page/members-observers. Accessed 25 October 2020.
3 ICH E2E Guideline: Pharmacovigilance Planning 2004. Available at: https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed 25 October 2020.
4 ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report (PBRER) 2012. Available from: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf. Accessed 25 October 2020.

All national regulatory authorities (NRAs) are encouraged to follow ICH guidelines. However, in settings where ICH guidelines have not yet been implemented, existing legislation governing pharmacovigilance should be interpreted under the COVID-19 pandemic situation, to provide clear guidance and directives on pharmacovigilance requirements to the vaccine manufacturers. A risk management plan (RMP) is a key document in the marketing authorization submission dossier. The RMP describes the current knowledge about the benefits and the risks of the vaccine or medicinal product, providing key information on plans for studies and other activities to gain more data on missing information, more knowledge about the safety profile of the product, and plans for risks minimization. Depending on their complexity, some RMPs may require special measures for their implementation, especially in low- and middle-income countries (LMICs). Hence there is a need to coordinate efforts by stakeholders and partners at national, regional, and global levels and the following key considerations should be included in specific directives and guidelines for COVID-19 vaccine safety:

- specific conditions when relevant authorities might request the vaccine manufacturer to provide a regional annex to the RMP, to reflect local situations such as epidemiological characteristics, medical practice, ethnicity, limitations of logistics and regional health and regulatory systems;
- requirements for PSURs/periodic benefit risk evaluation reports (PBRERs);
- specifications of routine and additional pharmacovigilance activities to be carried out during the pandemic as well as the periodicity for updating safety information. These activities may include:
  - monthly safety summaries in addition to routine PSURs;
  - post-authorization safety studies;
  - the establishment of sentinel sites, as part of an active surveillance system for COVID-19 vaccine safety; and
  - provision of educational materials and implementation of tracking system of vaccine administered e.g., barcode stickers.
- requirements for the vaccine manufacturer launching a COVID-19 vaccine in a country to designate a qualified person responsible for pharmacovigilance (QPPV) (or a global QPPV for international vaccine manufacturers) for monitoring its safety; and to clearly present the contact information and qualifications of the QPPV.

03 Risk management plans

The short timelines under which COVID-19 vaccines are being developed and ultimately deployed present challenges for guaranteeing their safety. Lessons learnt and best practices from past pandemics, such as those from 2009 H1N1 pandemic[5], should be used to guide current procedures for the safety of COVID-19 vaccines.

As with the H1N1 vaccines, more information about the immunogenicity, effectiveness, and safety of COVID-19 vaccines will only become available during their use in the field. Hence, the risk management plan for COVID-19 vaccines will be an evolving document and should be amended when new significant information, such as a change in the profile of adverse events, results from safety studies, changes in benefit-risk balance, becomes available.

3.1 Format and components of RMPs for COVID-19 vaccines

The vaccine manufacturer is encouraged to adopt existing formats, such as the European Union RMP format, which contain essential elements such as a safety specification section, pharmacovigilance activities, risk minimization activities, and evaluation of the effectiveness of the risk minimization measures.[6] RMPs in alternative formats, such as a global or core RMP, are also acceptable provided they contain the essential elements mentioned above.

In addition, when requested, a region-specific annex (referred to as a regional annex hereafter) to the core RMP that takes into consideration additional context specific to the region where the vaccines are to be deployed, should be provided. Similar annexes are routinely implemented by certain regulatory authorities to ensure adaptation to local context, e.g. Australia-specific annex required by the Australian Government Therapeutic Goods Administration (TGA)[7]. In general, the regional annex for COVID-19 vaccines in the RMPs should highlight any differences in safety concerns in the regions where the COVID-19 vaccines are launched, e.g., differences in the frequency, severity or nature of safety concerns, resulting from differences in the epidemiology of COVID-19 and the target population. It should also confirm that the pharmacovigilance (PV) and risk minimization activities are compatible with the safety concerns specified.

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5 CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine adopted by CHMP in November 2006. Revision 1.1 adopted by CHMP on 24 September 2009 (EMEA/359381/2009).

6 Guideline on good pharmacovigilance practices (GVP) Module V – risk management systems (Rev 2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf. Accessed 25 October 2020.

7 Risk management plan for medicines and biologicals– Australia-Specific Annex. Available from: https://www.tga.gov.au/book-page/risk-management-plan-australia-specific-annex. Accessed 4 October 2020.

3.2 Routine pharmacovigilance plan as part of the RMP

Both routine and additional PV activities contribute to the maintenance of a positive benefit-risk balance for a vaccine. They form part of the RMP, along with further PV measures that are appropriate for the evaluation of efficacy and safety of vaccines.

For COVID-19 vaccines, as part of routine PV activities, the vaccine manufacturer should describe in the RMP:

- specific activities for the collection, compilation, assessment, and reporting of adverse reactions to the NRA
- format, content and periodicity of the PSURs/PBRERs
- other requirements defined in the regional annex.

Challenges related to restrictions during the pandemic (e.g. due to social distancing or limited medical resources) or to the volume of reports of adverse events following immunization (AEFIs) to be processed (e.g., associated with a mass vaccination campaign) should be considered and reflected in the planning document. The reporting patterns following mass vaccination campaigns during a pandemic are likely to differ qualitatively from routine reporting, and this needs to be taken into account when performing the analyses.

During the pandemic, the usual 6-month reporting cycle may be too long for the assessment of COVID-19 vaccine safety because it is expected that there will be high levels of exposure within a short period of time. Therefore, it is recommended that monthly safety summaries are provided focusing on adverse events of special interest (AESIs), at a minimum. The monthly safety summaries are intended to complement the regular 6-monthly PSURs for COVID-19 vaccines during the pandemic period and should include:

- a summary of vaccine distribution (number of doses, locality of distribution, etc.);
- global numbers (with country of origin) and analyses of AESIs reported in individuals following immunization, following the Brighton Collaboration recommendations for COVID-19 vaccines;[8] and
- numbers of deaths and relevant case histories, including observed over expected analyses.

In addition to the monthly safety summaries, a 6-monthly cumulative PSUR/PBRER should be submitted following the PBRER ICH E2C (R2) format3. This provides a cumulative overview of all available information which provides the vaccine's overall benefit-risk profile. Following the first 6-month report, and as experience with the vaccine evolves, the periodicity of the monthly summaries and of the PSURs/PBRERs should be reviewed by the regulator.

8 Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project (WHO slide deck presentation by Robert T Chen, Scientific Director Brighton Collaboration). Available from: https://www.dcvmn.net/IMG/pdf/8._cepi_speac_presentation_bob_chen.pdf. Accessed 7 October 2020.

3.3 Additional pharmacovigilance activities

If ongoing or planned clinical trials or routine activities will not provide sufficient data for the complete characterization of important identified and potential risks, then additional PV activities, such as post-authorization safety studies (PASSs) should be considered and reflected in the RMP (Guideline on good pharmacovigilance practices (GVP) Module V; Risk management plan for medicines and biologicals– Australia). If an observational study is proposed, it should be on a cohort of individuals who have comparable ethnic and geographic origins and appropriate study protocols that are specifically designed for LMICs should be used.

The pandemic COVID-19 pharmacovigilance plan will terminate when national competent authorities decide that it is no longer necessary.

3.4 Specific considerations under different scenarios

The NRA should provide clear guidance on PV requirements for different scenarios, as many different COVID-19 vaccines are likely to be introduced to the market, through different channels. For example, the NRA should specify conditions and types of AEFIs and AESIs that should be included in the monthly safety summaries for each vaccine type. Penalties and sanctions for non-compliance should also be clearly defined and communicated. Two possible scenarios, depending on if the vaccine has been submitted for WHO prequalification (PQ) or emergency use listing (EUL) are described below.

Scenario 1: COVID-19 vaccines submitted for WHO prequalification or emergency use listing

Vaccines submitted for WHO PQ or EUL are likely to be developed by established companies who have submitted well-defined RMPs for stringent review by regulatory authorities. However, the vaccines can be introduced outside of the country where they were originally authorized, in countries where additional activities may be required. In this case, WHO PQ could request that an annex is included in the original RMP to cover any additional considerations and PV activities in the country where the vaccine will be introduced. As far as possible, a regional annex will be the preferred option, valid for all countries in a specific region (e.g., for the WHO African region).

The details of the monthly safety summaries and any PASS will be agreed as part of the WHO PQ / EUL procedure. The vaccine manufacturer will be responsible for compiling and submitting the monthly summaries and PSURs/PBRER to the local competent authority and WHO PQ.

Planned PASSs should be carried out by the vaccine manufacturer or its local representatives or distributors. Ideally, multi-country collaborative PASSs could be considered, with the PASS implemented in selected, representative sites across a few countries in a region. Study

sites should be selected in countries with the best capacity,[9] or with previous experience of participating in PASSs.

When available, PASS protocols such as those developed by WHO, should be used when such studies are to be conducted in LMICs.

Scenario 2: COVID-19 vaccines not submitted for WHO prequalification or emergency use listing

This scenario may include smaller companies that implement COVID-19 vaccines in LMICs. In this case, the vaccines may not have undergone stringent review for authorization by a regulatory authority. In this scenario, regional and coordinated approaches will be critical to ensure the safety monitoring of these COVID-19 vaccines. Additional considerations in this scenario include the following:

- the smaller vaccine manufacturers may consider collaborating with other manufacturers to prepare a common RMP for the region where the vaccine will be introduced;
- regional or global cooperation and coordination should be adopted, wherever feasible, and may include:
  - joint review of RMPs through regulatory reliance or works-sharing (more information in the regulatory reliance module;
  - leveraging existing regional networks, such as, the African Vaccine Regulatory Forum (AVAREF), the Western Pacific Regional Alliance of NRAs (WPRA) and the Pan American Network for Drug Regulatory Harmonization (PANDRH);
  - supporting multi-country safety studies to evaluate the real-world safety profile of the vaccines, especially in populations not represented in clinical trials, such as children and pregnant women;
- training to be provided to the smaller vaccine manufacturers on:
  - common core RMP components and any region-specific requirements;
  - regulatory obligations for vaccine PV for the region, including review of PSURs and analysis of AEFIs.

9 WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Available from: http://www.who.int/medicines/regulation/benchmarking_tool/en/. Accessed 25 October 2020.

04 Oversight

Oversight should be at different levels:

- at the national level, the NRA is responsible for providing clear guidance on the PV requirements for COVID-19 vaccines as described previously and should also:
  - provide input to WHO PQ on RMP assessments, to help define special considerations or annexes for the RMPs;
  - contribute to establishing criteria for PASS study site selection;
  - provide oversight for study implementation, including study sites inspections;
  - provide clear guidance to the vaccine manufacturer on requirements for routine communication of study findings, monthly safety summaries, and ad hoc communications for any urgent emerging issues;
  - implement a coordinated routine communication plan with stakeholders such as the national immunization programme or expanded programme for immunization (NIP/EPI) and the vaccine manufacturer; and
  - ensure that a national committee is ready to review any national PASS data as they become available.

- at the regional level, a regional review committee with scientific and regulatory expertise should be established to:
  - participate in WHO PQ assessments of RMP for COVID-19 vaccines, to bring the regional-specific perspectives to the review;
  - advise when a regional annex to the RMP would be justified;
  - develop and communicate clear guidance on criteria for study site selection in multi-country collaborative PASSs in the region for vaccine manufacturers;
  - review results from multi-country collaborative PASSs in the region;

- at the international level, an international review committee should be established to:
  - review PASS protocols;
  - review and analyse multi-country study data across continents;
  - provide support to the WHO PQ team for the analyses of RMPs and PSURs/PBRERs.

05 Data sharing

Data sharing is essential for generating reliable evidence on the safety of COVID-19 vaccines which will facilitate timely regulatory actions and effective public health interventions. Spontaneous AEFI reporting systems, active surveillance systems for AESIs, and PASSs are all important sources of data. To be successful at sharing data in a timely manner, while respecting data security and patient privacy, close collaboration between national stakeholders, such as the NRA and the EPI or NIP is critical.

Effective data flow needs to be established between the NRA and the WHO global database of individual case safety reports, Vigibase, and between the NRA and the vaccine manufacturer. In countries where current legislation does not mandate data sharing, NRAs should consider making data sharing a condition of marketing authorization. Alternatively, a data sharing agreement or memorandum of understanding could be established between the vaccine manufacturer and the NRA. Similarly, the WHO PQ programme should consider making data sharing a condition of inclusion of a vaccine on the EUL.

Data sharing and data sharing platforms are discussed in detail in the module on data sharing. In the context of coordinated regional review of RMPs and evaluation of multi-country PASSs, a data-sharing platform is critical for:

- enabling data pooling from multi-country sites to facilitate meaningful interpretation;
- enabling review committees to review PASS outcomes; and
- identifying patterns and safety issues of regional importance.

06 Training

Many training needs to enhance pharmacovigilance competencies and to enable regional coordination have been identified:

Training needs	Training Target				Potential training providers
	NRA/PV review staff	*National AEFI Committee*	*Regional Review Committee*	*Vaccine manu-facturer / subsidiary*	
Legislation and legal obligations for pharmacovigilance	✓			✓*	DCVMN*, IFPMA*, ISoP, NRA
RMP review: common core elements, regional annex, PSUR core elements	✓		✓		WHO, NRA
Ethics review of study protocols	✓	✓	✓		CIOMS, WHO
Review of safety study outcomes		✓	✓		WHO, GACVS, AACVS
Pharmacovigilance for vaccine safety	✓			✓*	DCVMN*, IFPMA*

** Training to manufacturer/subsidiary to be provided by DCVMN, IFPMA.*

AACVS: African Advisory Committee on Vaccine Safety; CIOMS: Council for International Organizations of Medical Sciences; DCVMN: Developing Countries Vaccine Manufactures Network; GACVS: Global Advisory Committee on Vaccine Safety; IFPMA: International Federation of Pharmaceutical Manufacturers and Associations; ISoP: International Society of Pharmacovigilance; NRA: national regulatory authority; WHO: World Health Organization

In LMICs, vaccine manufacturers may also require training to understand NRA's requirements and how to compile, summarize and analyse data from COVID-19 vaccine safety studies.

Coordination will be critical for the efficient provision of all levels of training. Existing training materials and programmes should be leveraged as much as possible. Stringent regulatory authorities can contribute their technical expertise to help LMICs strengthen their regulatory systems. It is equally critical to ensure that designated QPPVs and local subsidiaries of large vaccine manufacturers can set up efficient in-country PV systems. Existing networks, such as DCVMN (Developing Countries Vaccine Manufacturers Network) and IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) could play a key role in coordinating and delivering training to the vaccine manufacturers in anticipation of the introduction of COVID-19 vaccines, as they have a good understanding of the needs and capacity of these companies.[10]

10 Hartmann K, Pagliusi S, Precioso A. Landscape analysis of pharmacovigilance and related practices among 34 vaccine manufacturers' from emerging countries. Vaccine. 2020;38(34):5490-7. doi: 10.1016/j.vaccine.2020.06.016.

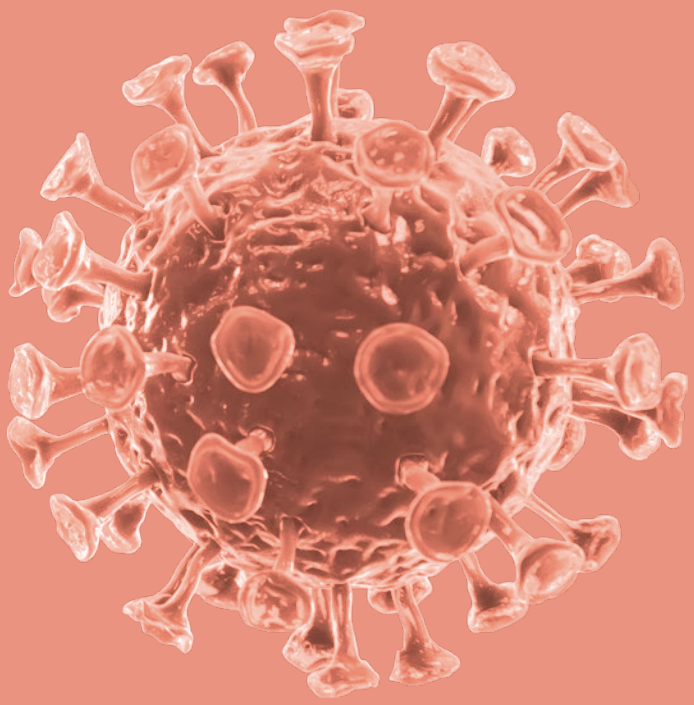
07 Funding

Post-authorization safety studies, carried out by the vaccine manufactures, may be supported financially through COVAX, the vaccine pillar of the ACT Accelerator. Training could be co-funded by several stakeholders. GAVI, the Vaccine Alliance, and WHO could potentially provide funding to train the NRAs, with stringent regulatory authorities potentially providing technical expertise or financial support or both. Industry networks such as DCVMN and IFPMA should support the training needs of vaccine manufacturers by providing funding and scientific expertise. Funding needs for monitoring systems, and platforms for data sharing between the NRAs or the WHO PQ team and vaccine manufacturers at the regional level are discussed in the module on data sharing.

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

REGULATORY RELIANCE AND WORK-SHARING



Contents

Key points

- Levels of regulatory reliance between national regulatory authorities (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.
- Reliance and work-sharing are important for countries with limited regulatory capacity.
- Regulatory reliance can be used for various regulatory activities across the product life cycle, including post-authorization pharmacovigilance activities, and lead to increased efficiency and improvement to regulatory capacity.
- In the context of the current COVID-19 pandemic, regulatory reliance should be considered wherever possible, to improve regulatory efficiency, thereby facilitating timely access to COVID-19 vaccines, as well as effective monitoring of safety issues and implementation of risk minimization measures.
- Work-sharing at the regional level will be an important mechanism to perform regulatory oversight effectively and will require identifying the similarities between the countries that would make them suitable for pharmacovigilance work-sharing.
- Activities that could be shared include review of risk management plans, common template for post-authorization safety studies (PASSs), joint review of post-authorization safety data and pharmacovigilance inspections.

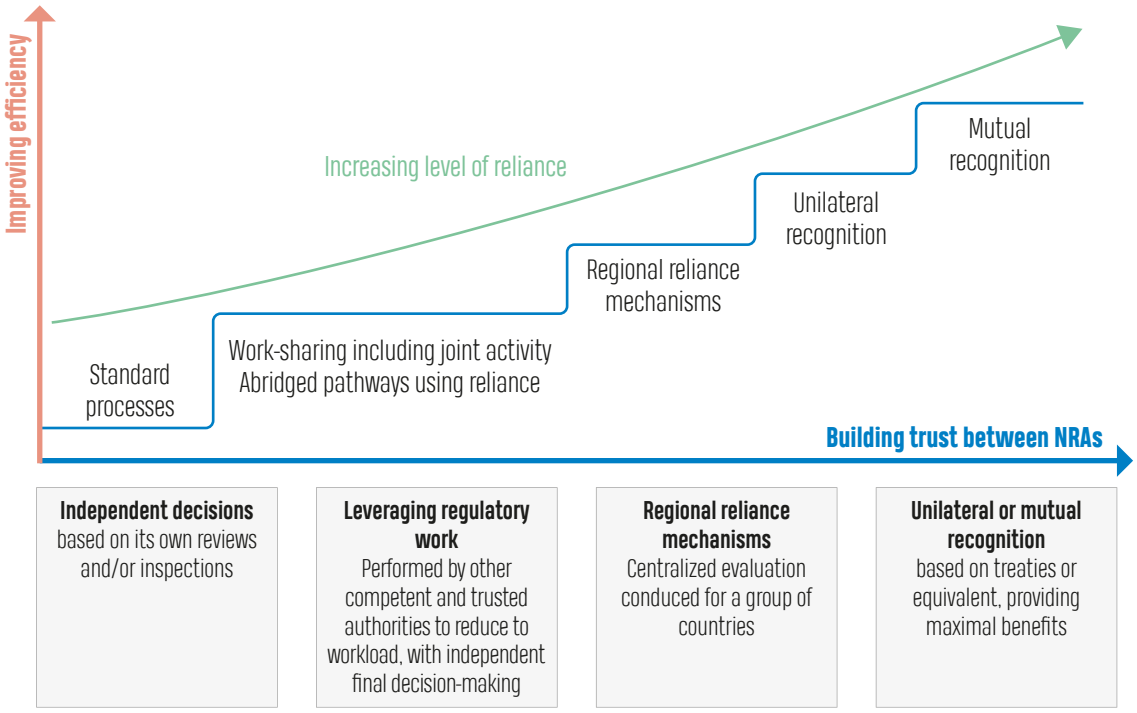
01 Introduction

1.1 Definition of regulatory reliance

Regulatory reliance is defined in the WHO draft guideline on good reliance practice standards[1] as "*the act whereby the national regulatory authority (NRA) in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.*".

The levels of reliance between NRAs can range from independent decisions by NRAs (no reliance) to mutual recognition (full reliance) (**Fig 1**). Recognition is a formalized process for reliance, based on legal provisions whereby one regulatory authority recognizes the decisions of a reference regulatory authority, without additional regulatory assessment. Recognition may be unilateral or mutual and several NRAs may participate in the same recognition agreement.

Fig 1: Schematic representation of increasing levels of regulatory reliance and the increasing benefits from this process



1 WHO Working document QAS/20.851/Rev.1, August 2020. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_Rev_1_Good_Reliance_Practices.pdf?ua=1. Accessed 26 October 2020. [NOTE: The GRelP document has been adopted at the 55th ECSPP (12-16 October 2020) and will be published in the TRS. Reference to be revised].

While regulatory reliance is widely used for initial authorization of medical products, it is equally important to consider reliance for pharmacovigilance and other post-marketing activities. It is useful to distinguish between two types of activities:

1. Reliance on processes, tools and methods developed by others. This involves regulatory authorities adopting common processes and standards, e.g. templates for safety reporting, templates for study protocols and reports, signal detection methods, platforms for epidemiological studies.
2. Reliance on product-specific regulatory activities. These activities can cover the entire life cycle of the product. Product-specific reliance may include participation in a joint assessment committee for marketing authorization approval and variations and for safety assessments. Also, it can include reliance on product information approved by another NRA or reliance on the assessment of post-authorization safety study protocols and results by others. This level of reliance requires assurance that the products concerned are the same or are sufficiently similar in terms of composition, indications, conditions of use, etc.

The decision to practice reliance should take into consideration the context and characteristics of the national health and regulatory system, the availability of an authority that the NRA can rely on, and how reliance can complement existing capacities to drive efficiencies and optimization of resources. The general principles under which reliance should operate are discussed in the WHO working document for good reliance practice (WHO working document QAS/20.851/Rev.1). It is particularly important to note that reliance does not mean a decrease in level or quality of evidence for safety and efficacy or lowering of the quality of regulatory activities. It should be viewed as a more efficient form of regulatory oversight that is based on constructive regional and international collaboration.

1.2 Definition of work-sharing

Work-sharing is defined in the WHO draft guideline on good reliance practice standards (WHO working document QAS/20.851/Rev.1) as "*a process by which NRAs of two or more jurisdictions share activities to accomplish specific regulatory tasks. The opportunities for work-sharing include, but are not limited to:*

- *jointly assessing applications for authorization of clinical trials;*
- *marketing authorizations or good practices inspections;*
- *joint work in the post-marketing surveillance of medical product quality and safety;*
- *joint development of technical guidelines or regulatory standards, and collaboration on information platforms and technology.*

Work-sharing also entails the exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other NRAs.".

02 Examples of regulatory reliance in pharmacovigilance

Regulatory reliance approaches have been applied for various regulatory activities across the product life cycle and have led to increased efficiency and improvements to regulatory capacity (WHO working document QAS/20.851/Rev.1). Several of them are presented in the WHO working document. Some examples of its application in pharmacovigilance are presented here.

2.1 Processes, tools, and methods

Around 140 Member States participate in the WHO Programme for International Drug Monitoring (PIDM)[2] and contribute to the WHO global database of individual case safety reports, VigiBase, developed and maintained by the Uppsala Monitoring Centre (UMC), which is the WHO Collaborating Centre for International Drug Monitoring. Member States share their safety data, rely on this resource (and thereby, on each other's data) as a single point of pharmacovigilance information, to confirm or validate signals of adverse events with medical products. Regional pharmacovigilance databases, already available as a subset of VigiBase, can also help regulators from specific regions to share and use safety data on products of mutual interest and for products that are specific for their region/groups of countries.

In Europe, under Article 57 of Regulation (EC)726/2004 of the European Union (EU) pharmaceutical legislation, manufacturers[3] of medicines in the EU and the European Economic Area (EEA) are required to submit and update a standard set of information on authorized medicines to the European Medicines Agency (EMA).[4] This information enables the regulators of all EU Member States to access the same information on the characteristics of authorized medicinal products and identify the company's qualified person for pharmacovigilance (QPPV), which facilitates coordinated enquiries from regulators to companies, and the organization of other regulatory functions such as joint pharmacovigilance inspections.

2 World Health Organization. Programme for International Drug Monitoring. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/. Accessed 3 October 2020.

3 For the purpose of this document, manufacturer also means marketing authorization holder.

4 European Medicines Agency. Data submission of authorised medicines (Article 57). Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/data-submission-authorised-medicines-article-57#:~:text=All%20holders%20of%20marketing%20authorisations,information%20up%2Dto%2Ddate. Accessed 01 October 2020.

2.2 Product-specific activities

Under the Article 58 of Regulation (EC)726/2004 procedure, the EMA provides scientific opinions on high priority medicines, including vaccines, that are intended exclusively for markets outside of the EU. The evaluations are carried out in cooperation with WHO and relevant 'target' non-EU NRAs. The same rigour and standards required for marketing authorization in the EU are applied, while the benefit-risk assessment is focused on the intended non-EU population and indication(s). The relying regulatory authorities can use the risk management plan (RMP) proposed by EMA for specific products and adapt it for relevance, feasibility, and implementation for use in their own countries**.** Hence, regulatory decisions for licensing and post-authorization requirements are taken by the regulators where the medicines or vaccines will be used. The Article 58 procedure facilitates patient access to essential medicines in low- and middle-income countries (LMICs), including improved treatment options for unmet medical needs and diseases of major public health interest, which include vaccines used in the WHO Expanded Programme on Immunization (EPI), medicines for protection against diseases such as HIV/AIDS, malaria and tuberculosis.

03 Regulatory reliance for COVID-19 vaccines

In the context of the current COVID-19 pandemic, regulatory reliance should be considered wherever possible, to improve regulatory efficiency, thereby facilitating timely access to COVID-19 vaccines, as well as effectively monitor safety issues and implement risk minimization measures.

Reliance is important for countries with limited regulatory capacity. Thus, for LMICs, a regional approach should be considered and implemented, especially in regions where the countries share common cultural values, languages, and health care system models.[5] The Caribbean Regulatory System (CRS) provides an example of a regional reliance mechanism, where many small states in the Caribbean Community (CARICOM) that lack the resources and capacity to provide full regulatory oversight of medical products rely on the CRS for marketing authorization processes.[6] CARICOM member states also submit in-country adverse reaction reports to VigiBase thereby leveraging the regional capacity for post-market surveillance.

5 Preston C, Chahal HS, Porrás A, Cargill L, Hinds M, Olowokure B, et al. Regionalization as an approach to regulatory systems strengthening: a case study in CARICOM member states. Rev Panam Salud Publica. 2016;39(5):262-268.

6 Preston C, Freitas Dias M, Peña J, Pombo ML, Porrás A. Addressing the challenges of regulatory systems strengthening in small states. BMJ Glob Health. 2020;5(2):e001912. doi: 10.1136/bmjgh-2019-001912.

Some regional reliance mechanisms involve the regional decisions being made for the participating members (e.g. EU processes), while in others they serve as the basis of consideration and the participating members make their own regulatory decisions (e.g. CRS, the Gulf Health Council (GHC)). Ideally, the application of reliance should be anchored in the regional strategy, with detailed procedures and integrated processes to avoid discrepancies in reliance decision and to be able to justify diverging decisions.

3.1 Pharmacovigilance for COVID-19 vaccines

Reliance for product-specific activities and for processes, tools and methods can be implemented for pharmacovigilance of COVID-19 vaccines. Examples of four specific aspects of pharmacovigilance, where reliance approaches can be implemented, are described below.

3.1.1 Example 1: Review of risk management plans at regional and WHO prequalification levels

Reliance for the review of risk management plans (RMP) submitted by vaccine manufacturers using a common format could be agreed with regional regulatory authorities or with the WHO prequalification programme to facilitate their assessment and the decision-making on the need and methods for additional pharmacovigilance or risk minimization activities. This process could also reduce the regulatory burden for the vaccine manufacturer and accelerate patient access to COVID-19 vaccines. Existing formats with essential sections, such as safety specification, pharmacovigilance activities, risk minimization activities, and evaluating effectiveness of risk minimization measures could be considered, e.g. the EU RMP format.[7] If justified, the RMP should be accompanied by a regional annex that takes into consideration the specific context of the region where the vaccine(s) will be deployed. If country-specific characteristics exist that are significantly different from the regional characteristics and this could have an impact on the safety profile of the COVID-19 vaccine(s), the NRA should request that the vaccine manufacturer includes the regional annex in the RMP.

Practically, a group of countries, or an economic community could identify a reference country to lead the assessments of RMPs or pharmacovigilance documents. For example, representatives from the reference LMIC could participate as assessors for the WHO prequalification/emergency use listing of COVID-19 vaccines, to review the RMPs submitted by applicants to the WHO prequalification process. This would facilitate reliance for the countries represented in the WHO prequalification process. A good example is the East African Community (EAC)'s Medicines Regulatory Harmonization (MRH) initiative.[8] Within the EAC-MRH, each national regulatory authority has the lead on one regulatory aspect, e.g. Kenya leads pharmacovigilance, Burundi leads clinical trials and Uganda leads joint GMP inspections.

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7 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf. Accessed 4 October 2020.

8 Arik M, Bamenyekanye E, Fimbo A, Kabatende J, Kijo AS, Simai B, et al. (2020) Optimizing the East African Community's Medicines Regulatory Harmonization initiative in 2020–2022: a roadmap for the future. PLoS Med 17(8): e1003129. https://doi.org/10.1371/journal. pmed.1003129.

3.1.2 Example 2: Post-authorization safety study protocol template

Post-authorization safety studies (PASS) may be required to address issues that are specific to LMICs, either identified in the RMP or at the time of RMP-assessment, for example, to compare safety profiles and highlight differences in specific populations, such as ethnic groups. Where possible, protocol templates specifically developed for LMICs should be used by the vaccine manufacturer and agreed with the reference national or regional regulatory authorities to facilitate implementation of multi-country PASS. This template could be used for the development of country-specific protocols following study site selection. In addition, information sheets for PASS participants could be developed at the regional level to provide consistent messaging and transparency about COVID-19 vaccines.

3.1.3 Example 3: Regulatory review through work-sharing

Pharmacovigilance of COVID-19 vaccines could be conducted by a regional regulatory system or by a group of NRAs. Work-sharing at the regional level should be adopted wherever feasible in countries with limited regulatory resources and capacity. In this context, a regional review committee should be established to facilitate cooperation and coordination, as well as oversee the process in reaching valid regulatory decisions that will serve as a reference for relying NRAs. Activities that could be carried out through work-sharing include:

- joint review of periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs);
- joint review of safety data from regional multi-centre studies; and
- collaborations between NRA and national immunization programme (NIP) or EPI staff on activities such as signal investigation, calculation of AEFI rates (i.e., obtaining denominator data on doses delivered or administered).

3.1.4 Example 4: Pharmacovigilance inspections

Mutual recognition agreements have been developed by NRAs in different regions to enable regulatory authorities to rely on each other's inspection outcomes, thus avoiding duplication of efforts and making best use of resources. The Pharmaceutical Inspection Co-operation Scheme (PIC/S), a non-binding co-operative arrangement between regulators, has issued guidance on inspection reliance that outlines a process for remote (desk-top) assessment of GMP compliance.[9] The reliance approach could be used for pharmacovigilance (PV) inspections. For COVID-19 vaccines where mutual recognition agreements exist, the reliance approach could be used also for PV inspections. For WHO prequalified emergency use listed vaccines, WHO inspection outcomes should be used.

9 PIC/S Guidance: GMP inspection Reliance. Available from: https://picscheme.org/users_uploads/news_news_documents/PI_048_1_Guidance_on_GMP_Inspection_Reliance_1.pdf. Accessed 4 October 2020.

As reliance is increasingly used for PV, especially during public health emergencies such as the current COVID-19 pandemic, it is important to specify PV activities that should be performed at the national level (and not through reliance on another NRA), such as:

- management of national data on adverse events of special interest (AESIs) and disease epidemiology in specific populations;
- national spontaneous reporting systems, assessment of AEFIs and adverse drug reactions reported nationally, and reporting to VigiBase;
- risk communication to the public and to health care workers;
- information on the distribution system and statistics on vaccine exposure; and
- some risk minimization measures specific to the national context.

3.2 Specific considerations under different scenarios for COVID-19 vaccine introduction

As it is likely that several different COVID-19 vaccines will be introduced in different parts of the world, with a phased roll-out plan targeting initially front-line health care workers and other vulnerable populations, two likely scenarios should be considered for regulatory reliance for vaccine safety and PV activities.

3.2.1 Scenario 1: First introduction of a new COVID-19 vaccine

If a new COVID-19 vaccine is introduced in a group of LMICs with limited PV capacity, work-sharing at the regional level will be an important mechanism to carry out regulatory oversight effectively. In this case, it will be important to identify the similarities between the countries that would make them suitable for PV work-sharing. It will also be important to identify any unique features of each country that could have an impact on the safety profile of the vaccine, such as ethnicity, epidemiological characteristics, medical practice, and health and regulatory framework. Joint reviews of submissions related to COVID-19 vaccine safety, e.g. PSURs and RMPs, could be carried out collaboratively by the target countries through an agreement on a collaborative approach, e.g. joint assessment with a representative from each country, or shared review of different sections or modules by participating NRAs. If a unique local characteristic could have an impact on the safety profile of the new vaccine being introduced, the NRA should ask the vaccine manufacturer to reflect these characteristics in their PV plans.

3.2.2 Scenario 2: Introduction of a COVID-19 vaccine that has already been introduced elsewhere

If the COVID-19 vaccine being introduced into a particular country has already been introduced in other countries, and the vaccine was authorized by a reference regulatory authority using stringent regulatory requirements or the WHO prequalification emergency use listing programme, the country could rely on:

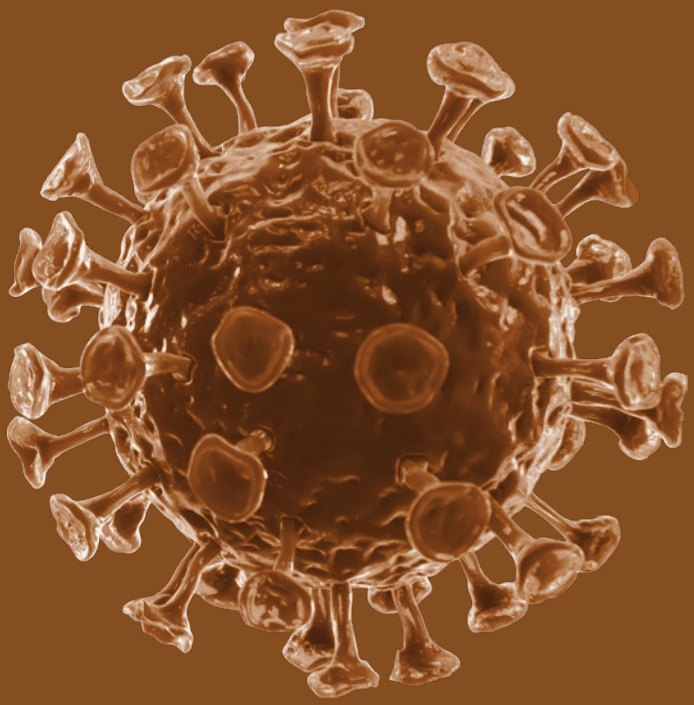
- the assessment from the reference regulatory authority for marketing authorization decisions;
- batch release by the reference regulatory authority;
- the assessment of updated safety information from the reference regulatory authority during the pandemic;
- safety signals from the phase 1 roll-out to health care workers and vulnerable populations that have been identified in the reference country(ies); and
- assessments of the effectiveness of the risk minimization measures made by the reference regulatory authority.

Routine surveillance may be sufficient to monitor the safety of the new COVID-19 vaccine being introduced in the relying country, unless there are significant differences between the local populations and the population of the reference country that could have an impact on the safety profile of the COVID-19 vaccine. If this is the case, the relying NRA should request that PV plans, specific to the local context, are submitted by the vaccine manufacturer.

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

COVID-19 VACCINE SAFETY COMMUNICATION



Contents

Key points

- Effective communication about COVID-19 vaccine safety, which will play a key role in maintaining the public's confidence in vaccination, will require planning and resources, that should be in place as early as possible, prior to deployment of COVID-19 vaccines.
- Vaccine safety perceptions are influenced by multiple factors, such as individual knowledge, attitudes and beliefs, social networks, messages about vaccine safety, 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 people to make evidence-informed choices about COVID-19 vaccination, to encourage trust in health authorities and those delivering vaccines and to facilitate access to timely, accurate and credible information about COVID-19 vaccination safety.
- Messages should be tailored to suit specific audiences, barriers and enablers, to ensure they are relevant and engaging.
- Messages should be pre-tested to assess their impact with people, even just a small group, who are representative of the target audience.
- The communications team should be integrated into vaccine safety planning and decision-making activities to facilitate appropriate and proactive communication activities.
- Partnerships should be established with other vaccine safety stakeholders to ensure coordinated information sharing and dissemination.
- It is important to identify and monitor for potential threats as a poorly managed incident concerning a COVID-19 vaccine safety issue will attract negative public attention.
- Establishing relationships with journalists and engaging with them regularly is important e.g., briefing them regularly and supporting their information needs around vaccine safety issues and concepts; this may help 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 but the level and scale of response adopted should take into consideration resources and opportunity costs and the potential impact of the claim.

01

COVID-19 vaccine safety communication

Communication about COVID-19 vaccine safety will play a key role in maintaining the public's confidence in vaccination. Effective communication will require planning and resources, which need to be in place as early as possible before COVID-19 vaccines are available. This module provides guidance on communicating about COVID-19 vaccine safety from a programme perspective. It includes:

- a description of factors that influence people's perceptions of vaccine safety,
- case studies of past experiences with previous pandemics and vaccine safety issues,
- a synthesis of evidence and recommendations for communication from risk communication,
- hypothetical scenarios that apply these recommendations to the COVID-19 vaccine context, and
- criteria for prioritising responses to vaccine safety issues.

For more detailed, in-depth guidance, links to further resources, and answers to frequently asked questions about COVID-19 vaccine consult the appendices at the end of this document (see **Section 5**).

This module concerns communication at a programmatic level. It does not cover communication to support vaccine acceptance and uptake more generally; guidance is available here [placeholder for WHO acceptance and uptake doc]. Provider-patient communication is also not the focus of this document; guidance is available here.

02 Factors influencing vaccine safety perceptions

Vaccine safety perceptions are influenced by multiple factors, such as individual knowledge, attitudes and beliefs, social networks, messages about vaccine safety, communication environment, cultural and religious influences, organization of health services and expectations created by political leaders.

2.1 Individual intentions towards COVID-19 vaccination

Understanding individuals' perceptions of COVID-19 vaccine safety is fundamental for effective communication as this will strongly influence their intention to be vaccinated. Adults are most likely to be the focus of early COVID-19 vaccination efforts in most countries, particularly those in high-risk professions, such as health care workers (HCWs). They will have diverse views on vaccination, ranging from those advocating for, or demanding, COVID-19 vaccines, through to those who reject them and a small group of anti-vaccine activists who will oppose COVID-19 vaccines. Table 1 provides descriptions of these groups, and the related goals for vaccine safety communication. See **Appendix 5.1** for additional resources about these factors.

Results from early population-based polls and surveys during this COVID-19 pandemic showed that intentions to have a hypothetical COVID-19 vaccine among adults ranged from 87% in Australia to 37% in Poland.[1] Intentions *not* to be vaccinated ranged from 44% in Turkey to 2.6% in China. Individual factors associated with lower vaccination intentions include lower education and health literacy levels,[2] lower income and younger or older age.[3] People are likely to shift their intentions over time as new information about COVID-19 vaccines becomes available. Interactions between groups, for example between activists and hesitant people, can also trigger changes in views on vaccination. Hence, individuals may change their intention over time.

1 Feleszko W, Lewulis P, Czarnecki A, Waszkiewicz P. Flattening the curve of COVID-19 vaccine rejection—a global overview (June 20, 2020). Available at SSRN: https://ssrn.com/abstract=3631972 or http://dx.doi.org/10.2139/ssrn.3631972.

2 Dodd RH, Cvejic E, Bonner C, Pickles K, McCaffery KJ; Sydney Health Literacy Lab COVID-19 group. Willingness to vaccinate against COVID-19 in Australia. Lancet Infect Dis. 2020:S1473-3099(20)30559-4. doi: 10.1016/S1473-3099(20)30559-4.

3 COCONEL Group. A future vaccination campaign against COVID-19 at risk of vaccine hesitancy and politicisation. Lancet Infect Dis. 2020 Jul;20(7):769-770. doi: 10.1016/S1473-3099(20)30426-6.

Table 1: Descriptions of the range of COVID-19 vaccination intentions

Vaccination intention	Communication goals	Vaccine safety perceptions
Anti-vaccine activism	Reduce impact on other groups.	Activists may oppose all vaccination or just COVID-19 vaccination and engage in related activities such as protests. They are a small but vocal group and may attract public attention. They may source and share misinformation about vaccine safety, particularly via social networks. It is not possible to stop anti-vaccination activism, but its impact can be affected by the environment (see below).
Rejection	Minimize the size of this group by good management of vaccine safety issues.	A minority will reject COVID-19 vaccination, primarily based on safety concerns. However other factors such as experience, perceptions and values could be involved.
Hesitation	Listen to and address safety concerns transparently and effectively to support well-informed decisions. Facilitate access to reliable, evidence-based digital information at a country level (support from VSN*).	Some people will be hesitant to accept COVID-19 vaccination[2,4,5,6] due to factors such as the newness of the disease, use of novel vaccine platforms and uncertainty surrounding vaccine safety. This may change as they become more familiar with COVID-19 vaccination programmes. Hesitancy is dynamic and can be influenced by communication with a trusted health care worker.
Acceptance**	Address questions during vaccination encounters. Provide vaccine safety resources to share via social networks.	Most people will accept COVID-19 vaccines. Acceptance will depend on individual motivation to be vaccinated, social and professional influences and the availability of, and access to, a vaccine. Acceptors may have questions about potential side effects. Some, but not all, may want to understand the risk of more rare and serious potential adverse events by age or co-morbidity status.
Demande	Address questions during vaccination encounters.	Some people will absolutely want a COVID-19 vaccine. This has implications for vaccine programmes, prioritization, and health care worker interactions. High demand with low supply could lead to conflict and perceptions of 'favouritism' that may diminish trust in the overall programme.
Advocacy	Support constructive advocacy with tools that accurately and transparently address safety concerns.	Some people will be strong advocates for COVID-19 vaccination, motivated by a personal experience with COVID-19, or strong support of vaccination more generally. Advocates can be a key asset in safety communication, sharing information rapidly via their social networks, some of which can be large.[7]

**VSN: Vaccine Safety Net, a global network of websites facilitating the access to reliable vaccine safety information[8];*
*** to maintain this intention, access and other practical aspects should be facilitated.*

4 Wong LP, Alias H, Wong PF, Lee HY, AbuBakar S. The use of the health belief model to assess predictors of intent to receive the COVID-19 vaccine and willingness to pay. Hum Vaccin Immunother. 2020;16(9):2204-16. doi: 10.1080/21645515.2020.1790279.

5 Barello S, Nania T, Dellafiore F, Graffigna G, Caruso R. 'Vaccine hesitancy' among university students in Italy during the COVID-19 pandemic. ***Euro J Epidemiol***. 2020;35(8):781-3. doi: 10.1007/s10654-020-00670-z.

6 Palamenghi L, Barello S, Boccia S, Graffigna G. Mistrust in biomedical research and vaccine hesitancy: the forefront challenge in the battle against COVID-19 in Italy. Euro J Epidemiol. 2020;35(8):785-8. doi: 10.1007/s10654-020-00675-8.

7 Dunn AG, Leask J, Zhou X, Mandl KD, Coiera E. Associations between exposure to and expression of negative opinions about human papillomavirus vaccines on social media: an observational study. J Med Internet Res. 2015;17(6):e144. doi: 10.2196/jmir.4343.

8 Vaccine Safety Net. Available at: https://www.vaccinesafetynet.org/. Accessed 23 October 2020.

2.2 Negative messages

Negative messages about vaccine safety can influence the public, particularly when shared in their social networks by people they trust. WHO is undertaking work on social listening to identify circulating messages about the safety of COVID-19 vaccines. Types of negative messaging include:

- misinformation – false or misleading information[9]
- disinformation – false information, purposely shared to mislead others[9,10]
- conspiracy theories – explanations that allude to the hidden influence of powerful people[11]
- fake news – fictitious information that imitates genuine news.[9]

Exposure to these types of negative messages, as well as negative opinions about vaccines, both in traditional and social media, has been associated with decreases in vaccine confidence and vaccine uptake.[12,13,14,15,16] Viewing content that is critical of vaccines (even briefly) has been shown to increase people's perceptions of vaccines as risky;[17] and exposure to negative claims has been shown to decrease people's certainty about vaccine safety.[18] However, the environment can also influence how people respond to negative messages. See **Appendix 5.2** for detailed guidance on managing negative messaging.

2.3 Environmental influences

The 'environment' refers to the social, political and historical contexts that influence how people perceive vaccine safety issues. The wider contexts that influence vaccine hesitancy

9 Lazer DMJ, Baum MA, Benkler Y, Berinsky AJ, Greenhill KM, Menczer F, et al. The science of fake news. Science. 2018;359:1094-6. doi: 10.1126/science.aao2998.

10 Wardle C, Derakhshan H. Information disorder: toward an interdisciplinary framework for research and policy making, Council of Europe; 27 September 2017.Available from: https://rm.coe.int/information-disorder-toward-an-interdisciplinary-framework-for-researc/168076277c. Accessed 24 October 2020.

11 Sunstein CR, Vermeule A. Conspiracy theories: causes and cures. J Polit Philos. 2009;17:202–227. doi: 10.1111/j.1467-9760.2008.00325.x.

12 Larson HJ, Hartigan-Go K, de Figueiredo A. Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. Hum Vaccin Immunother. 2019;15(3):625–7. doi: 10.1080/21645515.2018.1522468.

13 Suppli CH, Hansen ND, Rasmussen M, Valentiner-Branth P, Krause TG, Malbak K. Decline in HPV-vaccination uptake in Denmark – the association between HPV-related media coverage and HPV-vaccination. BMC Public Health. 2018;18(1):1360. doi: 10.1186/s12889-018-6268-x.

14 Gortz M, Brewer NT, Hansen PR, Ejrnæs M. The contagious nature of a vaccine scare: how the introduction of HPV vaccination lifted and eroded MMR vaccination in Denmark. Vaccine. 2020;38(28):4432–9. doi: 10.1016/j.vaccine.2020.04.055.

15 Dunn AG, Surian D, Leask J, Dey A, Mandl KD, Coiera E. Mapping information exposure on social media to explain differences in HPV vaccine coverage in the United States. Vaccine. 2017;35(23):3033–40. doi: 10.1016/j.vaccine.2017.04.060.

16 Hansen PR, Schmidtblaicher M, Brewer NT. Resilience of HPV vaccine uptake in Denmark: decline and recovery. Vaccine. 2020;38(7):1842-1848. doi: 10.1016/j.vaccine.2019.12.019.

17 Betsch C, Renkewitz F, Betsch T, Ulshofer C. The influence of vaccine-critical websites on perceiving vaccination risks. J Health Psychol. 2010;15(3):446–55. doi: 10.1177/1359105309353647.

18 Dixon G, Clarke C. The effect of falsely balanced reporting of the autism–vaccine controversy on vaccine safety perceptions and behavioral intentions. Health Educ Res. 2013;28(2):352–9. doi: 10.1093/her/cys110.

have been described extensively.[19] Vaccine safety fears and subsequent rejection may be vehicles for the expression of deeper tensions. These may arise in situations where previous experiences may have compromised trust in governments and other institutions that promote and deliver vaccine programmes.[20]

Some of the factors that may affect safety perceptions of COVID-19 vaccines are presented below.

Social, cultural, community and religious influences. Social norms and networks can greatly influence motivation to be vaccinated.[21,22,23] People with shared values and beliefs may exist in tight-knit communities where ideas spread readily. For example, religious or community leaders with negative views on COVID-19 vaccine safety could be capable of changing the beliefs of those in their network.[24] Certain aspects of vaccines may clash with people's moral foundations.

Historical issues affecting trust. Lack of equity in health authorities' responses to the COVID-19 pandemic, or in previous immunization situations, could affect trust in COVID-19 vaccines among some historically disenfranchised groups. Groups most at risk may include people living on a low-income; ethnic, racial, indigenous, religious, sexual, and gender minorities; disabled; migrant; or members of communities with inadequate health service access or who have been disproportionately affected by the COVID-19 pandemic.[25,26] Previous safety events related to other vaccines or vaccination programmes - whether real or rumours - may also impact on trust.

Organizational influences. Some individuals, such as HCWs, may be reached through workplace vaccination programmes. In some countries, mistrust has emerged among HCWs as a result of workplace COVID-19 infections and a perception of having been unsupported by governments in the face of overwhelming COVID-19 case numbers. This may reduce trust in communication about vaccine safety not only from governments but also from other community groups such as partners (UN agencies and NGOs) or schools.

Vaccination services. Previous negative experiences with health services may influence acceptance in adults.[27] Delivery of vaccination in large-scale clinics increases the chance of a clustered immunization stress-related response, where two or more vaccinees experience

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19 Larson HJ, Jarrett C, Eckersberger E, Smith DMD, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. Vaccine. 2014;32(19):2150-9. doi: 10.1016/j.vaccine.2014.01.081.

20 Wiley KE, Leask J, Attwell K, et al. Parenting and the vaccine refusal process: a new explanation of the relationship between lifestyle and vaccination trajectories. Soc Sci Med. 2020;263:113259. doi: 10.1016/j.socscimed.2020.113259.

21 Brewer NT, Chapman GB, Rothman AJ, Leask J, Kempe A. Increasing vaccination: putting psychological science into action. Psychol Sci Public Interest. 2017;18(3):149-207. doi: 10.1177/1529100618760521.

22 Leask J, Chapman S, Hawe P, Burgess M. What maintains parental support for vaccination when challenged by anti-vaccination messages? A qualitative study. Vaccine. 2006;24(49-50):7238-45. doi: 10.1016/j.vaccine.2006.05.010.

23 The Sabin-Aspen Vaccine Science and Policy Group. Meeting the challenge of vaccine hesitancy. 2020. Available from: https://www.sabin.org/sites/sabin.org/files/sabin-aspen-report-2020_meeting_the_challenge_of_vaccine_hesitancy.pdf. Accessed 24 October 2020.

24 Hussain RS, McGarvey ST, Fruzzetti LM. Partition and poliomyelitis: an investigation of the polio disparity affecting Muslims during India's eradication program. PLoS One. 2015;10(3):e0115628. doi: 10.1371/journal.pone.0115628.

25 Shadmi E, Chen Y, Dourado I, et al. Health equity and COVID-19: global perspectives. Int J Equity Health. 2020;19(1):104. doi: 10.1186/s12939-020-01218-z.

26 Reiter PL, Pennell ML, Katz ML. Acceptability of a COVID-19 vaccine among adults in the United States: how many people would get vaccinated? Vaccine. 2020;38(42):6500-7. doi: 10.1016/j.vaccine.2020.08.043.

27 Wheelock A, Parand A, Rigole B, et al. Socio-psychological factors driving adult vaccination: a qualitative study. PLoS One. 2014;9(12):e113503. doi: 10.1371/journal.pone.0113503.

the same adverse event at the same place and time, with the same vaccine. See hypothetical scenario 5 for guidance on communicating in such a scenario.

Political influences. Leaders may create high expectations of COVID-19 vaccines. Over-confident communication could lead to mistrust if expectations are not met.[28,29] Vaccine safety concerns may be a form of expression for wider political divisions and tension and thus, politicization of vaccination programmes is likely to do more harm than good.

28 Betsch C, Sachse K. Debunking vaccination myths: strong risk negations can increase perceived vaccination risks. Health Psychol. 2013;32(2):146-55. doi: 10.1037/a0027387.

29 Sandman PM, Lanard J. Part 2: Effective COVID-19 Crisis Communication. In COVID-19: The CIDRAP Viewpoint May 6, 2020. Available from https://www.cidrap.umn.edu/sites/default/files/public/downloads/cidrap-COVID-19-viewpoint-part2.pdf. Accessed 24 October 2020.

03 Recommendations for a vaccine safety communications approach

This section provides a summary of recommendations for communicating about COVID-19 vaccine safety, informed by risk communication principles. More detailed guidance is available in **Appendix 5.3.**

The goal of vaccine safety communication should be to empower people to make evidence-informed choices about COVID-19 vaccination. Any communication approach must encourage trust in health authorities and those delivering the vaccine, facilitate access to timely, accurate and credible information about COVID-19 vaccination safety via trusted channels and provide people with a means of asking questions and having their concerns addressed. The Vaccine Safety Net (VSN), established by WHO, is a worldwide network of websites that provide reliable information on vaccine safety online.[8] VSN was established to counterbalance websites that published unbalanced, misleading and unreliable vaccine safety information. It aims to facilitate access to reliable, understandable, evidence-based information on the safety of vaccines for online users in various geographical locations and speaking different languages.

3.1 Plan and prepare prior to vaccine introduction

Planning and preparing to communicate about COVID-19 vaccine safety should take place as early as possible, ideally well in advance of the vaccines being deployed. Planning should include integration of the communications team (or equivalent) into any vaccine safety planning and decision-making activities to facilitate appropriate and proactive communication activities.

Establishing partnerships with other vaccine safety stakeholders will help coordinate information sharing and dissemination. Developing a communications plan — including activities such as designating responsibilities, nominating spokespeople, defining audiences or population groups, and developing materials — will help preparation for likely scenarios and develop mitigation measures. See **Appendix 5.3** and **Appendix 5.4** for more detailed guidance.

3.2 Set up lines of communication

Preparations should include setting up lines of communication, via trusted channels, with influencers and mobilizers, such as community, religious or cultural leaders, HCW associations, trusted journalists and other influential people. Engaging with them will help to identify and meet their information needs and offer opportunities to encourage

promotion of positive vaccination behaviour. Planning for and creating multiple forums for the public to ask questions or raise concerns, such as public meetings, website feedback forms, email, telephone hotlines, online chat, or a social media platform, should also be part of the preparation of communication pathways. See **Appendix 5.4** for more detailed guidance.

Case study: Setting up lines of communication with local field workers—Sierra Leone, 2015

The use of local field workers can give credibility to engagement and help build public health capacity. Local field workers, who will remain part of a community long after external involvement has ceased, are accountable to local populations and understand the nuances of local needs and situations. During Ebola vaccine trials in Sierra Leone in 2015, researchers adopted a two-team approach, with both teams consisting primarily of local staff. One team liaised with the community, and their responsibilities included monitoring community concerns and addressing rumours. The other team undertook social science activities, such as assessing community perceptions, and their responsibilities included understanding trial participants' experiences by providing opportunities for them to give feedback. This feedback was then used to tailor and improve the vaccine trial processes.[30]

3.3 Identify potential threats to confidence in COVID-19 vaccine safety

Various COVID-19 vaccine-related events could occur that may negatively influence perceptions of vaccine safety. These could include publication of new data on COVID-19 vaccines, and information about events such as a temporary vaccine suspension or recall, adverse events, negative messaging in the media, and community attitudes and beliefs. A poorly managed incident, for example a substandard or counterfeit vaccine, will also attract negative public attention. Identifying potential threats and monitoring for them will help to plan how, when and what to communicate and to whom. It is essential to communicate early and often (see case study below). See **Appendix 5.4** for more detailed guidance.

30 Dada S, McKay G, Mateus A, Lees S. Lessons learned from engaging communities for Ebola vaccine trials in Sierra Leone: reciprocity, relatability, relationships and respect (the four R's). BMC Public Health. 2019;19(1):1665. doi: 10.1186/s12889-019-7978-4.

Case study: Communicate early, often, and with transparency—Sweden, 2010

The H1N1 vaccine, Pandemrix, was used in approximately 20 European countries but primarily in Finland, France, Germany, Ireland, Norway, Sweden and United Kingdom. Studies conducted in these countries confirmed an association between Pandemrix vaccination and narcolepsy.[31] A meta-analysis of the studies showed that during the first year after vaccination, the relative risk of narcolepsy was increased 5- to 14-fold in children and adolescents and 2- to 7-fold in adults.[32] Subsequent investigations indicated a possible genetic basis in affected individuals for this adverse event.[33,34]

In Sweden, the country with the highest number of narcolepsy cases reported, Pandemrix vaccination coverage rates were high, with 60% of the population vaccinated against H1N1.[35] Initial communications about the vaccine had strongly emphasized vaccination for all Swedes as a measure to protect themselves and others, unless there were individual medical contraindications to vaccination. There was comparatively little communication around possible side effects in this newly developed vaccine.[36]

There were several key lessons learned from these events in terms of communication. To maintain trust in a vaccination programme it is important to communicate early about possible side effects, listen to and involve those who are affected, rapidly investigate cases and transparently communicate results, as well as correct misleading information as soon as possible.[39] In addition, the Swedish investigation concluded that a glossary of key terms should be made available, e.g. via Internet, to allow people understand technical information.[36,37]

3.4 Listen proactively

Listening proactively to the public, using multiple data sources, is essential to formulate tailored and targeted communications. Listening can help to:

- identify audiences and provide insights into what they are thinking, their concerns and questions;

31 European Medicines Agency. Twenty-second pandemic pharmacovigilance update - 19 August 2010. Available from: https://www.ema.europa.eu/en/documents/report/twenty-second-pandemic-pharmacovigilance-update_en.pdf. Accessed 24 October 2020.

32 Sarkanen TO, Alakuijala AP, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: systematic review and meta-analysis. Sleep Med Rev. 2018; 38: 177-186. doi: 10.1016/j.smrv.2017.06.006.

33 Partinen M, Komum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet Neurol. 2014;13(6):600-13. doi: 10.1016/S1474-4422(14)70075-4.

34 Hallberg P, Smedje H, Eriksson N, Kohnke H, Daniilidou M, Öhman I, et al. Pandemrix-induced narcolepsy is associated with genes related to immunity and neuronal survival. EBioMedicine. 2019;40: 595–604. doi: 10.1016/j.ebiom.2019.01.041.

35 Lundgren B. 'Rhyme or reason?' Saying no to mass vaccination: subjective re-interpretation in the context of the A(H1N1) influenza pandemic in Sweden 2009–2010. Med Humanit. 2015;41(2):107–12. doi: 10.1136/medhum-2015-010684.

36 Fahlquist JN. Vaccine hesitancy and trust. Ethical aspects of risk communication. Scand J Public Health. 2018;46(2):182–8. doi: 10.1177/1403494817727162.

37 Feltelius N, Persson I, Ahlqvist-Rastad J, Andersson M, Arnheim-Dahlström L, Bergmanet P, al. A coordinated cross-disciplinary research initiative to address an increased incidence of narcolepsy following the 2009–2010 Pandemrix vaccination programme in Sweden. J Intern Med. 2015;278(4): 335–53. doi: 10.1111/joim.12391.

- identify community influencers and trusted sources; and
- detect negative messaging and anti-vaccine activity.

These insights may be specific to contexts and locations. Listening should be a continuous activity, as concerns and information needs will change as the pandemic evolves and as vaccines are deployed. Social listening may provide an additional avenue for surveillance for real or perceived AEFIs. Not listening proactively may result in incomplete or incorrect understanding of audiences and missed opportunities to respond to issues such as emerging misinformation or public outrage over a perceived vaccine safety issue.

Ways to listen to the public include:

- qualitative methods (interviews, focus groups, observations)
- tracking public opinion via surveys of representative samples
- insights from community and religious leaders and other influential people
- tracking calls to hotlines and other forms of public feedback
- monitoring traditional media
- digital and social media listening.

See **Appendix 5.5** for more detailed guidance.

Case study: Listening to community feedback—Guinea, 2014

In June-July 2014, the local population in a region of Guinea did not trust the international teams deployed to try to control the Ebola outbreak. This mistrust hindered containment efforts. The external agencies nominated community spokespeople, based on their assumed standing in the community. At the same time, a WHO anthropologist spent three days talking with the local people about who they would trust as spokespeople to raise their concerns. The spokespeople named by the local people were different from those nominated by the external parties. Once leaders respected by the community, such as those with traditional caring roles or religious duties, were given leadership roles, cooperation with outbreak measures increased notably. In other contexts, trusted spokespeople may include traditional practitioners, religious leaders, elders, and others.[38]

38 Wilkinson A, Parker M, Martineau F, Leach M. Engaging 'communities': anthropological insights from the West African Ebola epidemic. Philos Trans R Soc Lond B Biol Sci. 2017;372(1721):20160305. doi: 10.1098/rstb.2016.0305.

3.5 Communicate in ways that build understanding and trust

Communication that is transparent, timely, empathic and acknowledges uncertainty can help boost people's trust in health authorities, which in turn can positively influence people's willingness to be vaccinated.[39] These principles should be used to guide how, when, and with whom to communicate.

Communicate with openness and transparency: Be open and transparent about vaccine safety by providing access to all information, not withholding any, even when the facts are yet to be fully established.[29] There is no evidence to support the assumption that the public will panic if they have access to accurate information in a crisis.[40] Lack of honesty and withholding information can erode trust. Keep promises to share information and regularly update the public with new information. If specific information about vaccine safety is unavailable, communicators should say so and explain how they plan to get it. When it is not possible to share specific information about an on-going investigation, share information about the process and what is expected to take place. When details are scarce, communicating hope is appropriate.

Communicate with clarity: This includes demystifying vaccine safety for the public. For example, explaining how vaccines are tested and then monitored for safety. It is important to pay attention to health literacy when developing statements and materials.[41] This is particularly important when considering equity of access to information. Plain language communication includes being clear about what people need to do in relation to vaccine safety, getting to the point quickly, and understanding audience information needs.[42] Differing levels of numeracy should be accommodated when communicating probabilities, by communicating both qualitative (e.g., very low) and quantitative (e.g., 1 in every 100,000 people receiving the vaccine) estimates of risk.[43] See **Appendix 5.6** for further information.

Accept and acknowledge uncertainty: Convey uncertainty about vaccine safety, when it exists, in a way that avoids over- or under-confidence and will ensure informed decision making. Being over-confident, over-reassuring or minimising risks may reduce trust. On the other hand, evidence suggests that the communication of uncertainty about pandemic vaccines can reduce vaccine intentions.[44] Identify likely scenarios the public may need to consider

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39 Siegrist M, Zingg A. The role of public trust during pandemics: implications for crisis communication. Euro Psychol. 2014;19:23-32. doi: 10.1027/1016-9040/a000169.

40 Seeger MW. Best practices in crisis communication: an expert panel process. J Applied Comm Res. 2006;34(3):232–44. doi: 10.1080/00909880600769944.

41 McCaffery KJ, Dodd RH, Cvejic E, Ayre J, Batcup C, Isautier JMJ et al. Disparities in COVID-19 related knowledge, attitudes, beliefs and behaviours by health literacy. 2020. medRxiv 2020.06.03.20121814; doi: 10.1101/2020.06.03.20121814.

42 World Health Organization. Tactics to apply to make your communications understandable. 2020. Geneva: World Health Organization. https://www.who.int/about/communications/understandable/plain-language. Accessed 4 November 2020.

43 Trevena LJ, Zikmund-Fisher BJ, Edwards A, Gaissmaier W, Galesic M, Han PKJ, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. BMC Med Inform Decis Mak. 2013;13(Suppl 2):S7. doi: 10.1186/1472-6947-13-S2-S7.

44 Han PKJ, Zikmund-Fisher BJ, Duarte CW, Knaus M, Black A, Scherer AM, et al. Communication of scientific uncertainty about a novel pandemic health threat: ambiguity aversion and its mechanisms. J Health Commun. 2018;23(5):435-44. doi: 10.1080/10810730.2018.1461961.

and what decisions may need to be taken and when, and explain what is being done to reduce uncertainties.

Be responsive and timely with communications: If concerns about the safety of COVID-19 vaccines arise, do not wait to be certain before communicating. Anticipate concerns as much as possible and be forthcoming with information as it becomes available. Leaving an information vacuum will allow others with lower quality information or misinformation to fill it. Keep the public updated about actions being taken by governments, in the event of possible adverse events following immunization (AEFIs). If information is evolving, be transparent and say that. Partnering with the media can help to disseminate information quickly and get key messages to the public. Social media may offer a useful means of providing brief, frequent, and real-time updates, and can signal willingness to readily share information.

Act and speak with empathy: Speaking with empathy is not only important when addressing a press conference but also when participating in small meetings with community members or stakeholders. It may feel more comfortable to talk about vaccine safety by focusing on data and using impersonal and abstract language, but using personal language and showing concern helps to build trust. It is important to identify spokespeople whose manner and presence communicates both competence and empathy, not just with their words, but also with their non-verbal communication and their tone. Listen to, acknowledge, and respond to people's emotions about COVID-19 vaccines. Use genuine expressions of concern about issues and events related to vaccine safety.

Additional guidance on the principles of risk communication for a vaccine-related crisis can be found in the WHO publication Vaccine safety events: managing the communications response (p. 36). Information about other determinants of trust, such as competence, objectivity, fairness, consistency, sincerity, faith can be found in the WHO publication: Vaccination and trust (p. 25). Additional resources can be found in **Appendix 5.10**.

3.6 Construct messages about COVID-19 vaccine safety using an evidence-based approach

Insights from health communication research can make vaccine safety messages more effective and acceptable to audiences. For example, keeping messages clear, short and simple, focusing on the positive opportunities for COVID-19 vaccines to improve health, rather than focusing on the risks of disease. Scientific consensus around vaccine safety should be emphasized. Messages should be tailored to suit specific audiences, barriers and enablers, to ensure they are relevant and engaging. Data should be clearly presented with the addition of visuals to clarify text. The messages should include positive narratives to model vaccination behaviour. The messages should be around specific actions that people can do to reduce harms, e.g. talk to your doctor. Although messages should be tailored to specific audience needs, they must remain consistent. These messages will also be useful when developing resources for advocates and other communicators. See **Appendix 5.6** for more detailed guidance.

Case study: Communicate in ways that build trust during a vaccine safety scare—Australia, 2010

In April 2010, Australia suspended seasonal influenza vaccine for children under 5 years of age following reports of an increased rate of adverse events following immunization. An initial investigation found that the safety signal was related to one brand of influenza vaccine only, and thus paediatric vaccination with other brands restarted.[45] The scare affected confidence in paediatric influenza vaccination and vaccination rates dropped from 45.5% in 2009 to 7.9% in 2010 in one Australian state that had a funded programme.[46] The media provided extensive coverage of the actual vaccine suspension event and some follow up from health authorities to family doctors. Moreover, studies conducted both at the time and subsequently found that some parents and providers were uncertain about the ongoing safety of the vaccine due to a lack of information provided.[47,48]

Lessons learnt from this incident include:

- the need for public health authorities to be proactive during a vaccine safety incident and to engage with both, parents and providers;
- the need to give a name to the adverse event because not doing so can raise doubts;
- the need to provide information updates via trusted sources throughout the duration of a vaccine scare to avoid the development of information voids; and
- the need to acknowledge uncertainty and provide updates discussing what is known and unknown, using well-established risk and crisis communication principles.

Information should be disseminated via both traditional media sources and other trusted sources. This could be authoritative information from regulatory authorities or key heath experts provided via government health websites, childcare centres and schools.[47]

3.7 Pre-test messages with representatives of target audiences and adjust as needed

Public responses to COVID-19 vaccine safety messages may be unpredictable and not reflect previous experiences, so pre-testing messages is essential. In time- and resource-poor settings, testing with a small group is still useful. It is important to test the messages with people who

45 Horvath J. Review of the management of adverse events associated with Panvax and Fluvax. Canberra, ACT: Australian Government Department of Health and Ageing; 2011. Available from: https://www.health.gov.au/resources/publications/review-of-the-management-of-adverse-events-associated-with-panvax-and-fluvax. Accessed 24 October 2020.

46 Mak DB, Carcione D, Joyce S, Tomlin S, Effler PV. Paediatric influenza vaccination program suspension: effect on childhood vaccine uptake. Aust N Z J Public Health. 2012;36(5):494-5. doi: 10.1111/j.1753-6405.2012.00925.x.

47 King C, Leask J. The impact of a vaccine scare on parental views, trust and information needs: a qualitative study in Sydney, Australia. BMC Public Health. 2017;17(1):106. doi: 10.1186/s12889-017-4032-2.

48 Blyth CC, Richmond PC, Jacoby P, Thornton P, Regan A, Robins C, et al. The impact of pandemic A(H1N1)pdm09 influenza and vaccine-associated adverse events on parental attitudes and influenza vaccine uptake in young children. Vaccine. 2014;32(32):4075-81. doi: 10.1016/j.vaccine.2014.05.055.

are representative of the target audience to assess their impact, not with colleagues whose responses may not reflect those of the target audience.

Case study: Using positive narratives to model vaccinating behaviour—USA, 2009

In October 2009, the US implemented a vaccination programme against 'swine flu' caused by the H1N1 influenza virus. Due to an initial shortage, the vaccine was prioritized for risk groups, including young adults.[49] President Obama stated that he and his family would take the advice of health authorities as to when it would be appropriate for them to receive the vaccine.

The President's daughters, Malia and Sasha, received the vaccine in October 2009 when it became available for school-aged children. The President and First Lady, Michelle Obama, received the vaccine in December 2009, when additional supplies became available and it was recommended more broadly for all adults. President Obama spoke in the media about his confidence in the safety of the vaccine and endorsed its use in both, children and adults.[50]

A study of trust in government and H1N1 vaccination intent found that discussion by President Obama of his daughters' H1N1 vaccination had a positive impact on vaccination decision making and uptake that was independent of political party association. This was seen to largely transcend politics and to be an example of a father trusting in the vaccine for his children.[51] A subsequent photo of President Obama with rolled up sleeve about to receive the H1N1 vaccine provided an additional powerful positive role model image.[50]

3.8 Work closely with the media

In many cases, the traditional media (television, radio, and print) will act as an important intermediary between health authorities and the public.[52] Briefing journalists regularly, and supporting their information needs around vaccine safety issues and concepts, may help reduce sensationalist reporting. Establishing relationships with journalists and engaging with them regularly is important. It is recommended to develop mutually beneficial relationships with the media by being easily accessible and responding promptly to requests for information. Become a go-to source for vaccine safety information by providing clear and concise media

49 Centers for Disease Control and Prevention. 2009 H1N1 Flu Vaccine. 2010.Available from: https://www.cdc.gov/h1n1flu/vaccination/. Accessed 24 October 2020.

50 Lee, J. 2009. The President and First Lady get vaccinated. The White House blog. Available from: https://obamawhitehouse.archives.gov/blog/2009/12/21/president-and-first-lady-get-vaccinated. Accessed 24 October 2020.

51 Quinn SC, Parmer J, Freimuth VS, Hilyard KM, Musa D, Kim KH. Exploring communication, trust in government, and vaccination intention later in the 2009 H1N1 pandemic: results of a national survey. Biosecur Bioterror. 2013;11(2):96-106. doi: 10.1089/bsp. 2012.0048.

52 Habersaat KB, Betsch C, Danchin M, Sunstein CR, Böhm R, Falk A. et al. Ten considerations for effectively managing the COVID-19 transition. Nat Hum Behav. 2020;4(7):677-87. doi: 10.1038/s41562-020-0906-x.

releases and background information and offering names of third parties for journalists to speak to about vaccine safety issues. See **Appendix 5.7** for more detailed guidance.

3.9 Build a social media presence

Social media offers significant potential for communicating about COVID-19 vaccine safety directly to the public. It is a convenient way to communicate regularly and give real-time updates. Some audiences may be using social media as a primary means of learning and communicating about COVID-19 vaccines. Anti-vaccine activists are certainly using social media to spread negative messaging about vaccines.

When communicating on social media, it is recommended to listen to what key audiences are saying and use this information to inform communications. Choose one or two platforms to communicate on; do not spread efforts too thinly across many platforms. Commit to two-way communication, including interacting, replying and conversing. Be active and interact regularly to build an online community. Use an authentic, personal approach and create safe spaces to encourage audiences to ask questions without fear of aggressive or hostile encounters. Regular interaction on social media requires substantial input, so allocate resources specifically for social media in the communications plan.

Using personal stories and other messages that elicit emotion can be useful for addressing emotional issues such as fear about vaccine safety. Personal stories can be part of an authentic, personal approach to communicating via social media.

See **Appendix 5.8** for more detailed guidance.

Case study: Using an authentic, personal approach via social media—Denmark, 2017

In 2013, the Danish media began to publish stories about young Danish women who experienced stress-related adverse events following HPV immunization. A television documentary, broadcast in 2015, brought attention to the experiences of girls with disabling symptoms. These stories were widely discussed in the media and concerns about vaccine safety were shared on social media. This negative attention was associated with a significant reduction in HPV vaccination uptake, although subsequent studies showed no association between the girls' events and HPV vaccination.[53]

Danish health authorities responded with a national campaign in 2017, '*Stop HPV – Stop Cervical Cancer*', to rebuild trust and increase uptake. Based on formative research identifying mothers as key vaccination decision makers and Facebook as an important information source for this priority group, they developed a social media strategy to engage mothers who were hesitant about vaccinating their daughters. The campaign, which was primarily focused on a dedicated Facebook page, refocused attention on cervical cancer prevention by communicating evidence supporting HPV vaccine safety and personal stories of women with cervical cancer. HPV vaccine ambassadors helped spread these positive messages. Both uptake and Danish parent's trust in HPV vaccination increased. The campaign's wide reach and positive engagement with audiences may have contributed to these results. The campaign's success was in part attributed to the use of personal stories, which audiences engaged with more readily than factual posts, and which encouraged more positive dialogue.[54,55]

3.10 Careful management of negative messages

While listening to and communicating with the public it is likely that negative messages about COVID-19 vaccine safety will be encountered. Negative messages include rumours, distorted, false or misleading opinions, misinformation and expressions of anti-vaccine sentiment. Not all negative messages warrant a response. Firstly, a vocal minority may generate a large proportion of the negative messages, which can then be amplified by social media algorithms and media attention. Responding to them could unintentionally add to this amplification and expose new people to them. Secondly, people may express fear and anxiety about vaccine safety, which is normal given the uncertainty around COVID-19 vaccines and their safety, particularly considering the accelerated development timeline. It is important not to assume these negative sentiments is simply misinformation, or other types of negative messages

53 Suppli CH, Hansen ND, Rasmussen M, Valentiner-Branth P, Krause TG, Malbak K. Decline in HPV-vaccination uptake in Denmark - the association between HPV-related media coverage and HPV-vaccination. BMC Public Health. 2018;18(1):1360. doi: 10.1186/s12889-018-6268-x.

54 Pedersen EA, Loft LH, Jacobsen SU, Søborg B, Bigaard J. Strategic health communication on social media: insights from a Danish social media campaign to address HPV vaccination hesitancy. Vaccine. 2020;38(31):4909-15. doi: 10.1016/j.vaccine.2020.05.061.

55 Loft LH, Pedersen EA, Jacobsen SU, Søborg B, Bigaard J. Using Facebook to increase coverage of HPV vaccination among Danish girls: an assessment of a Danish social media campaign. Vaccine. 2020;38(31):4901-8. doi: 10.1016/j.vaccine.2020.04.032.

coming from anti-vaccine and other activists. It is recommended to respond with compassion by acknowledging people's concerns and providing information.

Listening will help to analyse the situation, determine whether it is appropriate to respond or not, and allow close monitoring of the popularity of the negative messages which can be used to inform a reactive strategy. Only respond to negative messages that have spread beyond the source community and are getting considerable reach and engagement from target audiences.

Responses should be directed to the audience when responding to negative messages. Do not argue with or try to convince the person spreading the negative message. Emphasize facts and content that trigger positive emotions, such as the health benefits of vaccines. Expose flawed arguments, explain why any misinformation is incorrect and, if possible, provide alternative explanations. The Vaccine Safety Net website provides criteria for good information practices that can be used to guarantee that website provides reliable, timely, accurate and evidence-based information on vaccine safety. Disseminating reliable information to and training relevant stakeholders, such as journalists, health authority staff, health care workers and factcheckers are key strategies for communicating. See **Appendix 5.8** for more detailed guidance.

Pre-prepared messages in the form of Frequently Asked Questions (FAQs) can be useful when responding. Listening is important to help identify appropriate and relevant questions. For example, videos containing misinformation or conspiracies may indicate people's questions (but not necessarily attitudes) and can be used in developing FAQs. Note that FAQs developed without good understanding of community knowledge and attitudes may not address people's real questions. See **Appendix 5.9** for more detailed guidance.

3.11 Criteria for prioritizing responses to vaccine safety issues

It is inevitable that anti-vaccine activists and some professionals will make negative claims about the safety of COVID-19 vaccines. While early and responsive communication is important, it is not possible or appropriate to respond to every new claim, particularly if there are many. Communicators must consider resources and opportunity costs in responding. Therefore, the level and scale of response should depend on the potential impact of the claim. Events that meet at least one of the following criteria will require a response. Further guidance can be found on page 17 of WHO's Vaccine Safety Events: managing the communications response.

The AEFI is genuine. The primary role is to protect the health of the public. Responsiveness and expressions of empathy are essential. Misdiagnosing people's safety concerns as mere 'anti-vaccination' can lead to harms at population and clinical levels if the AEFI is not taken seriously and investigated.

The event or story is gaining attention. Via evidence from social listening or opinion monitoring, it is obvious that the event is gaining attention, particularly in the population groups prioritized for COVID-19 vaccination. The attention is the amount of exposure that the negative sentiment is getting, not the volume. Hence, some individuals, with only a few followers, may share a

large volume of messages but the amount of exposure will be low. Conversely, messages shared by influential individuals with many followers results in high levels of exposure by virtue of the number of their followers.

The alleged adverse event is unsubstantiated but publicised by a symptom/syndrome group. Safety concerns that reduced HPV coverage in Ireland and Denmark and those that changed HPV vaccine policy recommendations in Japan shared a common phenomenon: a group of individual parents were drawn together by a shared belief that the vaccine had caused their child's syndrome, condition or symptom cluster.

A respected opinion leader who is trusted in the community is advancing a view. A unique feature of vaccine safety scares is a medically-trained person publicly advancing a theory. They may influence HCWs and their confidence in recommending vaccination, and thus have an impact on the wider community.

The confidence of HCWs is likely to be affected. Vaccine safety concerns that amplify HCWs' existing hesitancy or trigger new concerns require rapid responses. Confident, committed HCWs are vital for the success of vaccination programmes. In the case of COVID-19 vaccines, HCWs are both recipients and recommenders of the vaccine.

The issue or event touches on moral foundations that are highly correlated with vaccine acceptance. Claims that touch on moral foundations associated with vaccine rejection may be more salient. Those found to have the strongest correlation with vaccine rejection include claims about the vaccine ingredients (purity/degradation) or where there is some level of coercion in vaccine programmes, either real or perceived (liberty).[56,57]

56 Amin AB, Bednarczyk RA, Ray CE, Melchiori KJ, Graham J, Huntsinger JR, et al. Association of moral values with vaccine hesitancy. Nat Hum Behav. 2017;1(12):873-80. doi: 10.1038/s41562-017-0256-5.

57 Rossen I, Hurlstone MJ, Dunlop PD, Lawrence C. Accepters, fence sitters, or rejecters: moral profiles of vaccination attitudes. Soc Sci Med. 2019;224:23-7. doi: 10.1016/j.socscimed.2019.01.038.

04 Hypothetical scenarios

This section describes some hypothetical scenarios involving vaccine safety at different stages of COVID-19 vaccine development and provides practical advice on how to respond.

The pre-licensure phase, when phase I, II and III vaccine clinical trials are being conducted, is characterised by:

— early communication about COVID-19 vaccine safety
— demonstration of trustworthiness of vaccine safety and efficacy information collected during clinical trials and the decision-making processes
— collection of data on knowledge, concerns and information needs.

Hypothetical scenario 1: Early concerns among influential experts

An influential doctor with high-media reach shares concerns about alleged 'shortcuts' on safety for the COVID-19 vaccines, the number of adverse events of special interest (AESI) being monitored, and the *'too many uncertainties'* about the vaccine's safety. The general population hear these concerns in the media. Some of them share their views that COVID-19 is 'the same as the flu anyway' (see example).

Example response

Communicators should engage early with professional leaders, ideally prior to such events. Proactively communicate about the unique vaccine safety considerations for COVID-19 vaccines. Respond promptly with sufficient detail and do not be dismissive about concerns. Correct the false belief that shortcuts are being taken for the COVID-19 vaccine safety by providing information about how it is being assessed in phase I, II and III vaccine trials (see **Appendix 5.9** for responses to FAQ about safety and vaccine trials).

Directly and specifically address the differences between AESIs and adverse events following immunization (AEFIs), using the level of detail appropriate for the audience (See **Appendix 5.9** for responses to FAQ about AESIs). Associate discussions of vaccine safety with existing ideas people have about common medicines that may have common side effects and rare adverse effects.

Communicate about the clinical trial outcomes that are known, using appropriate, accessible formats. Engage with local expert advocates to broaden the coalition of voices addressing concerns. Communicate:

— what AESIs are and why they are listed and being monitored (see **Appendix 5.9**),
— the role of phase II and II trials the evaluation of vaccine safety (see **Appendix 5.9**),
— what is known about safety, named AEFIs and their rates from COVID-19 vaccine trials so far
— what we know now, where uncertainty remains and what is being done to fill information gaps,
— plans for ongoing monitoring of AESIs and plans for detecting and managing safety signals,
— the potential benefits from a COVID-19 vaccine.

In some settings it may be reasonable to identify positive religious and community leaders as communication partners. Talk to them early about the upcoming vaccine programme. Ask them to be ready to be called if there are concerns about the vaccine to answer questions.

The pre-licensure phase, when phase I, II and III vaccine clinical trials are being conducted, is characterised by:

— early communication about COVID-19 vaccine safety
— demonstration of trustworthiness of vaccine safety and efficacy information collected during clinical trials and the decision-making processes
— collection of data on knowledge, concerns and information needs.

Hypothetical scenario 2: Rumours

A video about adverse events allegedly reported during phase II COVID-19 vaccine trials is shared via a local, known anti-vaccination Facebook group with 80,000 followers. Mainstream media organizations want to report the story.

Example response

Use the criteria in this manual to prioritise the level of response. Investigate the reach of the rumour. It may be possible to give trusted journalist(s) background information about the rumour and the potential harm in reporting it. If the rumour has been shared widely beyond original communities, address concerns on website or social media platform to enable advocates to respond. If the rumour has not been shared widely, not formally responding could be considered since responding may draw more attention to the topic. Avoid strategies that encourage polarization, such as entering into debates with those with strong beliefs. Debunk information with well-referenced facts. See **Appendix 5.2** for detailed guidance on managing negative messages.

Hypothetical scenario 3: Vaccine components

A group publicly expresses concern that a COVID-19 vaccine is made with new technology that modifies genes.

Example response

This issue will be specific to mRNA and DNA vaccine platforms. Governments should work with experts to rapidly produce information that answers FAQs about these vaccine platforms before the launch phase. Information should be specific to the vaccine(s) the country plans to introduce. See **Appendix 5.9** for responses for FAQs about new vaccine platform technologies.

Draft information about technically complex matters should be pre-tested on target audiences. Health literacy assessment tools like PEMAT can be used.

Governments should proactively provide information about the vaccine platforms and how different vaccines are produced.

Hypothetical scenario 4: Social media bombardment or attack

The Facebook page of a hospital recruiting for a candidate COVID-19 vaccine trial is attacked by anti-vaccine activists. The most frequent comments are: "*COVID-19 is mutating", "the vaccine will not work"; "we don't know anything about COVID-19 so how can we make an effective vaccine"; "recruit politicians for vaccine trials and then we will trust you"; "let us live our lives, we don't need vaccines (young people, not parents)"; "we will never accept mandatory immunization*".

The pre-licensure phase, when phase I, II and III vaccine clinical trials are being conducted, is characterised by:

— early communication about COVID-19 vaccine safety
— demonstration of trustworthiness of vaccine safety and efficacy information collected during clinical trials and the decision-making processes
— collection of data on knowledge, concerns and information needs.

Example response

Manage the immediate attack by banning offending individuals from the Facebook page and deleting false and offensive comments. Do not engage directly with the activists. Seek support from partners. See the Anti-Anti-Vaxx Toolkit for specific guidance on managing an activist Facebook attack.

Use listening techniques to determine whether these questions and concerns are more widespread and reflect target audiences' concerns. If so, communicate with broader audiences using other means. It is important not to argue with the people spreading the negative messages.

Counter any widespread negative messages by providing clear and simple explanations and exposing flawed arguments by providing evidence-based information. Emphasize the scientific consensus on COVID-19 vaccine safety. Provide opportunities for people to ask questions. Foster the audiences' trust by addressing concerns promptly, being transparent, and not over-reassuring. See **Appendix 5.8** for more guidance on managing negative messages.

Launch phase—After licensure, vaccination programmes for those eligible for vaccination will be implemented. This phase is characterised by:

— providing information on the safety profiles and risk-benefit balances of the different vaccine platforms (and individual products)
— ongoing monitoring of local knowledge, attitudes, concerns and information needs among the public and health care workers.

Hypothetical scenario 5: Cluster of immunization stress-related responses

A COVID-19 vaccine that caused moderate pain at the injection site in 10% of vaccine recipients in phase III trials is given in a mass vaccination campaign. At one clinic, there were long queues waiting to be vaccinated on a particular afternoon, a group of vaccine recipients complained of headaches and dizziness after the vaccine was given, and some fainted. The issue was reported widely in the media that evening.

Example response

Anxiety associated with shared beliefs about the cause of symptoms can spread easily and quickly, especially via the media or social media. This 'contagion' of fear can interfere with immunization programmes.

Spokespeople should acknowledge the symptoms and the distress experienced by the vaccine recipients and state that the causes are being investigated. They should identify the process for investigation and what others should do in the meantime. They should be available to update journalists on the incident.

Public sentiment should be monitored using listening techniques (see **Appendix 5.5**). Local leaders and health care workers should be engaged to reassure the community. Health care workers should be provided with messages and communication materials that explain acute stress responses (including syncope or fainting) (see **Appendix 5.6**). Work with the media to disseminate information (see **Appendix 5.7**). Engage audiences on social media, and counter negative messages as appropriate (see **Appendix 5.8** and **Appendix 5.9**). Communicate and address concerns promptly and transparently.

Prior to launching an immunization programme, develop a plan to respond to stress response clusters, including pre-testing messages in potential priority groups, nominating spokespeople and points of contact for the media, and training spokespeople and health care workers in communication. See **Appendix 5.3** for developing a communications plan. See also Section 5 and 7 of WHO's Immunization stress-related responses manual.

Hypothetical scenario 6: A community with questions

An influential community leader is urging people not to be vaccinated, saying that the vaccine is not safe, "*it is a conspiracy and it is being given to people in lower-income countries to control fertility*".

Example response

The National Immunization Programme manager can provide information about vaccine safety and the importance of vaccination to community leaders before the launch. Vaccine safety communication resources tailored to the local needs and culture can be proposed, with support from the Vaccine Safety Net or the Vaccine Safety Communication e-library. If vaccination resistance develops during the launch, work with positive influencers to engage with the resisting religious and community leaders. For example, it will be helpful to provide a simple one-page guideline on vaccine safety for these leaders, and to share information about how other leaders have previously dealt with such issues.

Vaccine roll-out—This is when the vaccine program is becoming established and larger number of the population receive it. This phase is characterised by:

— Staged communication as more evidence becomes available
— Communication of situational AEFI signal versus perceived but unsupported AEFI
— Communication integrated in AEFI management

Hypothetical scenario 7: Safety signal

An AEFI signal for one COVID-19 vaccine is being investigated. Regardless of the outcome, it has the potential to undermine confidence in other COVID-19 vaccines although no AEFI signal has been detected for the other vaccines.

Example response

Implement a vaccine safety communication plan (see **Appendix 5.3**). Use the criteria described in this module to prioritise the level and scale of response. Assess community sentiment and concerns using listening techniques (see **Appendix 5.5**). Prepare and pre-test messages, if possible, prior to vaccination campaign in anticipation of this issue. Tailor these messages to questions and concerns of different audiences, as needed.

Messages about vaccine safety should come from knowledgeable people (such as the National AEFI Committee spokesperson) with good communication skills. They should convey clear information about differences between the COVID-19 vaccines and focus on the benefits of COVID-19 vaccination. Messages should be short and simple, emphasizing evidence-based information and scientific consensus on COVID-19 vaccine safety. Confirm that messages are consistency with vaccine safety partners (see **Appendix 5.6**).

If the AEFI safety signal receives widespread media or public attention, communicate promptly and transparently. Brief journalists. Communicate and interact with audiences on social media. Provide health care workers with communication materials to respond to people's concerns. Continue to update audiences on the progress of the investigation and recommend what actions individuals should take in relation to the incident (e.g., continue to be vaccinated, continue to be vaccinated with other available vaccine(s)).

Hypothetical scenario 8: False rumour

A rumour is circulating that a COVID-19 vaccine has caused a spike in the incidence of a specific autoimmune disorder common in one of the groups of adults with comorbidities that is a COVID-19 vaccination priority target group. Investigations have shown the link is not plausible and no safety signal has been detected in AEFI monitoring. Some health care workers and a prominent immunologist are giving support to the rumour. A significant number of health care workers are refusing vaccination, stating their concerns about 'reactions'.

Example response

Respond rapidly with sufficiently detailed, frank information to address the claims. This can be done by a professional with sound and relevant knowledge in immunology or vaccine safety and could be in the form of an online statement that can be shared by relevant professional networks.

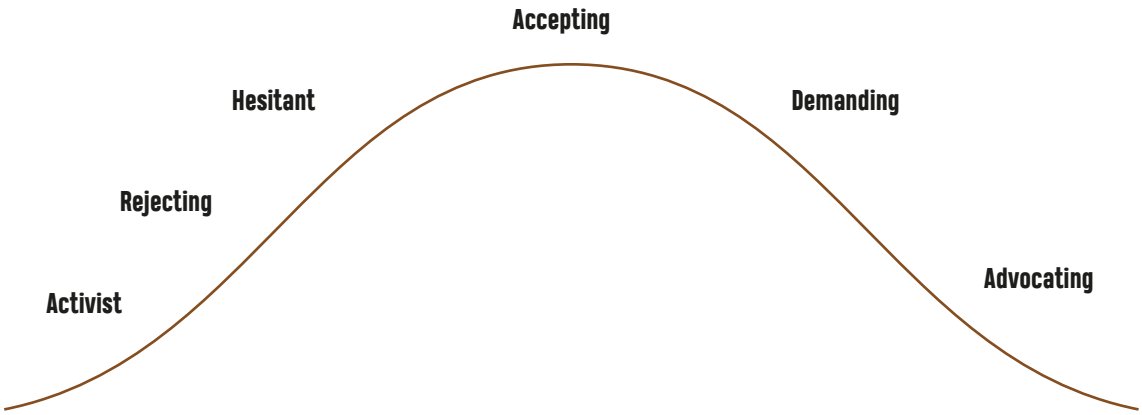
Assess whether more proactive modes of response are needed via listening for sentiment and spread of rumour among health care workers (see **Appendix 5.5**). Develop and, if possible, pre-test messages tailored to the concerns and information needs. Messages should explain why the rumour is incorrect, what is known about the vaccine's safety in that group and expose flawed arguments. Recruit respected opinion leaders, advocates and other influencers within health communities and professional societies to disseminate information to disprove the rumour. Initiate dialogue with health care workers to allow them to ask questions and have their concerns addressed.

05 Appendices and additional resources

Appendix 5.1: Spectrum of vaccination intentions for COVID-19 vaccines

The spectrum of vaccination intentions to receive a COVID-19 vaccine, adapted from other work, for example, WHO spectrum of positions on childhood vaccination, is represented below.[58] This takes into account results from recent studies on COVID-19 vaccine intentions, issues known to be unique to new vaccine programmes, and experiences with past pandemic and epidemic vaccines (e.g., H1N1 and polio). This figure serves as a diagrammatic rather than proportional representation of motivational states, which will be highly dependent on context.

Spectrum of intentions related to COVID-19 vaccines.



58 World Health Organization. Report of the SAGE Working Group on vaccine hesitancy. 01 October 2014. Available from: https://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf. Accessed 4 December 2020.

Further resources

Name of resource	Language	Source	About
CERC: Psychology of a Crisis	English	Centers for Disease Control and Prevention (CDC)	How people take in, process, and act on information in a crisis
WHO Euro vaccination and trust	English, Russian	WHO Regional Office for Europe	p. 9 How people make decisions about vaccination
The Science of Science Communication	English	The Cultural Cognition Project at Yale Law School	How people process information about science
Vaccine safety and confidence	English	Excellence in Pediatrics Institute (EIPI) Vaccine Virtual Days	Assessing vaccine safety and confidence in the COVID-19 era (access available on request)
Immunization stress related responses	English	WHO Health Product Policy and Standards	Guidance for prevention, identification and response to stress-related responses following immunization

Appendix 5.2: Managing negative messages (misinformation and anti-vaccine activists)

Responding to negative messaging will be a key communications activity[59], that requires a considered approach. Here are some steps to take and things to consider when encountering negative messaging. Listening will help analyse the situation, determine whether it is appropriate to respond or not and closely monitoring the popularity of negative messaging will help to inform a timely reactive strategy.

- **Prepare a response**, regardless of plans to respond publicly. Use the principles of constructing evidence-informed messages, and work with stakeholders to ensure consistency.
- **Try to understand context of negative messages.** Sometimes, by the time the negative message has reached you, it has been decontextualized, i.e. key details about where and why it was spread and by whom and why are missing. Attempt to track down details that help clarify the content of the message, as well as why it may have spread, such as where the article clip or featured image came from.
- **Try to work out how far negative messages have already spread**, and the nature of that spread. Where did the negative message appear? Was it in a known anti-vaccine or fringe group on social media, or in an environment with a larger and more general audience? Has the media reported on it? Only respond to negative messaging that has spread beyond the source community.

59 Habersaat K, Betsch C, Danchin M, Sunstein CR, Böhm R, Falk A, et al. Ten considerations for effectively managing the COVID-19 transition. Nature Human Behav. 2020;4(7):677-687. doi: 10.1038/s41562-020-0906-x.

- For negative messaging on social media, **consider the number of negative posts *as well as* the reach of and engagement with these posts**. People may be posting large volumes of negative messages on social media but have hardly any followers and thus have minimal influence. Try and work out how many people are being reached by and are engaging with (and therefore spreading) the message, and whether this has changed over time. If an individual or page is posting messages of interest, look at their number of followers to assess their influence, as well as the number of people engaging with or sharing this message.
- **Are target audiences engaging with and discussing the message?** What is the content and tone of their engagement? Just because a target audience is engaging does not mean they support the negative messaging. The target audience may be responding to and countering negative messaging on their own, which can be an effective strategy.
- **Is the audience asking questions or expressing concerns** in response to the negative messaging? This is where providing answers and assurance may be especially valuable.

Negative messaging that has spread beyond the source community and is being engaged with and discussed in non-fringe environments may warrant response. Here are some recommendations for responding to negative messaging:

- **Remember the audience is the people who are listening**, *not* the person or organization spreading the negative message. This is equally true when pitted against an anti-vaccine activist in a TV broadcast, responding to a critical remark from the crowd in a town hall meeting, or responding to a post on social media. Craft your response for the audience, not to argue with or convince the person spreading the negative message.
- **Emphasize factual information** when refuting negative messages. Too much focus on the misinformation may strengthen the falsehood in people's minds.
- **Create content that triggers positive emotions**, such as the health benefits of vaccines. This type of content is important to counteract negative messaging on vaccines based on emotional values and will complement information based on data and evidence.
- **Emphasize scientific consensus,** such as "90% of clinicians agree that this vaccine is safe"
- **Warn the audience** by explicitly signposting repeated misinformation, e.g., "There are many myths about COVID-19 vaccine safety. This myth, for example, is about…"
- **Explain why the misinformation is incorrect** and if possible, provide an alternative explanation. This is more effective than simply saying something is incorrect. Provide links to reputable sources where appropriate.

- **Expose any flawed arguments** by pointing out the techniques the person spreading the negative message is using, such as selective use of evidence, using fake experts, referring to conspiracy theories, false logic.
- **Avoid hostile interactions** with anti-vaccine activists. If you engage in arguments, you may be signalling to your audience that there is disagreement around what you are saying.
- **Do not refer to activists using imprecise collective nouns**, i.e. the anti-vaccine community or anti-COVID-19 vaccine groups. This can imply they are larger and more organised than they really are, may confer them more perceived power and influence, and get them more followers. If necessary, refer to activists as individuals, e.g., Joe Bloggs has posted this falsehood about…

Further resources

Name of resource	Language	Source	About
The Debunking Handbook 2020	English	PDF available	Guidance for debunking misinformation
How to respond to vocal vaccine deniers in public	English	WHO Regional Office for Europe	Algorithm for responding to anti-vaccine activists
Anti-anti-Vaxx Toolkit: A Strategy Guide to Prepare For, Defend Against, and Clean Up After a Facebook Anti-Vaxx Attack	English	Kids Plus	Guidance on preparing for anti-vaccine activist attacks on social media
Vaccine safety events: managing the communications response	English, Russian	WHO Regional Office for Europe	Chapter 11 (p. 43) – Dealing with rumours
Coronavirus disease (COVID-19) advice for the public: myth busters	English	WHO	Information for the public on various myths associated with COVID-19
Social Media Response Assessment and Management Guide	English	American Academy of Pediatrics	Guidance on whether and how to respond on social media, as well as resources for multiple platforms

Appendix 5.3: Development of a COVID-19 vaccine safety communication plan

A vaccine safety communication plan does not eliminate risk, but will help to prepare to communicate more effectively with the public, and collaborate with partners and the media in the face of risks. The plan may include the following activities:

- **Designate responsibilities**. These may lie within the coordination mechanism, i.e. vaccine communication group. Responsibilities may include scientific subject matter experts, media liaisons, spokespeople, and research or listening. Identify lines of responsibility, especially authority to sign-off/information clearances. This activity will also help to identify any training needs, e.g. media training, social media listening and analysis.

- **Nominate spokespeople.** A spokesperson should be someone trusted by the community. If health authorities are experiencing complex socio-political relationships with the public, it may be helpful to team up with an academic or scientific spokesperson outside the government to connect with the public and help rebuild trust. Members of National Immunization Technical Advisory Groups (NITAGs) may be able to act as sources of trusted expertise. Identify and meet any training needs for spokespeople in advance, e.g. media training.
- **Develop a decision tool to help determine your communications response to a vaccine-related event.** Responses must be context specific, based on your assessment of the potential impact of an event on confidence in vaccine safety. A decision tool will help you assess the type of event and its potential impact (low, medium, high), and choose the appropriate communications response. See further resources for examples.
- **Identify and secure resources required to perform the plan**. Resources are both human and financial, and might include a budget for research and listening, training, equipment, and spaces. List the number of people and skills needed. If possible, include a budget to employ people dedicated to managing specific channels, e.g. social media, and specific areas of work such as social data collection and social listening. If possible, secure resources in advance.
- **Define target audiences** and audience segments. Segments are those people who share similar knowledge and concerns, or are reached through similar channels. Use listening and social media analytics, including content analysis, to identify and understand audiences and assess your reach. Special outreach may be needed for groups who are at higher risk or are traditionally more difficult to reach.
- **Identify key influencers and ambassadors.** These may include digital or social media influencers, for example a blogger or Instagram profile with many followers, as well as community and religious leaders, high profile health experts, educators, and other people with a large audience. Influencers can help spread your messages. Health care workers will also be influential in the dissemination of vaccine safety information. They may need training and guidance on interpersonal communication to help them to be effective in passing on vaccine safety information (see further resources below).
- **Determine key communication channels**, e.g. the lead organization and stakeholder websites, social media platforms, media releases, local/national media, brochures or handouts, public forums, schools and other educational institutions. Key channels will be where target audiences are seeking health information or talking about vaccine safety. Include strategies to access any target groups who are not easily reached through these channels. Strategies may include access through immunisation providers and community health workers, social mobilizers, and civil society organizations.
- **Seek input from key stakeholders** when developing your vaccine safety communications plan, especially those representing audiences who have specific information needs or concerns, i.e. older people, health care workers.
- **Agree on procedures to coordinate information dissemination** with partners, including who releases what, when, and how. This may be led by government. Clarify approval processes, especially if information needs to be disseminated quickly in the event of a crisis.
- **Create contact lists** of key individuals in your organization, the media and strategic partners.

- **Create key messages and communication materials** to disseminate through the planned communication channels. These might be developed in anticipation of identified threats and include holding statements, i.e., a brief, simple statement that can acknowledge an event such as a safety signal, which will avoid a 'no comment' response, template media releases, Frequently Asked Questions (e.g., explaining vaccine safety concepts like AEFIs or AESIs), and talking points for spokespeople.
- **Determine training needs**, such as media and de-escalation training for spokespeople, who often can become the focus of public anger and concerns and must perform well under pressure to be effective. Health care workers will also be on the frontline of communicating about COVID-19 vaccine safety. Supporting them with resources and training on how to have conversations about vaccination can help to improve their confidence and effectiveness as communicators.
- **Develop strategies to monitor and evaluate communications**. These may include evaluating the effectiveness of communications, documenting challenges and lessons learned, identifying gaps in skills and resources, and identifying actions to improve communications in the future. Evaluate communications using various tools, including social media listening, media monitoring and monitoring at the community level via health care workers, community-based mobilizers or social mobilizers, seeking feedback from community and religious leaders and civil society organizations. Input from strategic partners will also be useful. Evaluation of communication activities including effectiveness of vaccine safety communication could be integrated into vaccine post-introduction evaluations. Your evaluations should inform ongoing communications responses.

The COVID-19 safety communication plan should not be overly long. This plan will need to be regularly revised, especially after any vaccine-related events; to incorporate lessons learned and to keep contact lists up to date.

Further resources

Name of resource	Language	Source	About
Guidance on developing communications plans			
Crisis Communication Plans Manual	English	CDC CERC	Guidance on developing and applying a crisis communications plan
Communication Plan checklist	English	CDC CERC	Checklist for creating a communication plan
Vaccine safety events: managing the communications response	English, Russian	WHO Regional Office for Europe	Guidance on developing a media communications plan (p. 18) Communications plan template (p. 51)
Decision tools for responding to vaccine-related events			
How to ensure a context-specific response	English, Russian	WHO Regional Office for Europe	An algorithm for analysing vaccine safety events and determining appropriate communications response

Name of resource	Language	Source	About
Vaccine Safety Events: managing the communications response	English, Russian	WHO Regional Office for Europe	Appropriate responses to low, medium and high-impact vaccine-related events (p. 49) Guide timeline for responses (p. 54)
Determining target audiences			
RCCE Action Plan Guidance. COVID-19 preparedness and response	English	WHO Global	Defining and prioritising your RCCE audiences and other stakeholders (p. 20)
Training for spokespeople and other ambassadors			
SKAI eLearning module	English	NCIRS	Training for health care workers on conversations about immunisation with patients
SKAI Resources for healthcare providers	English	NCIRS	Discussion guides and other resources to support health care workers' conversations about immunisation with patients
Tips for spokespersons	English, Russian	WHO Regional Office for Europe	Principles for successful communication during a crisis
Determining key communication channels			
Vaccine safety events: managing the communications response	English, Russian	WHO Regional Office for Europe	Guidance on choosing key communication channels (p. 25)
RCCE Action Plan Guidance. COVID-19 preparedness and response	English	WHO Global	Choosing channels (p. 21)
Evaluation			
New vaccine post-introduction evaluation (PIE) Tool	English, French	WHO Department of Immunization, Vaccines and Biologicals	Guidance on evaluation as part of PIE (p. 17)
Vaccine Safety Events: managing the communications response	English, Russian	WHO Regional Office for Europe	Guidance on communications evaluation (p. 59)
Preparedness checklists			
Checklist for preparedness	English, Russian	WHO Regional Office for Europe	A checklist to prepare for events that may erode trust in vaccines
New vaccine introduction: Checklist for planning communication and advocacy	English, Russian	WHO Regional Office for Europe	Checklist of communication and advocacy strategies for working with health care workers, influencers, the media and the public
Other			
Crisis communication templates and tools	English	CDC CERC	A range of templates and tools to prepare and communicate during a crisis

Appendix 5.4: Planning and preparing COVID-19 vaccine safety communication

Planning and preparing to communicate about COVID-19 vaccine safety should take place as early as possible, ideally well in advance of vaccines being deployed and should include:

- involving the communications team in vaccine safety work,
- establishing strategic partnerships,
- setting up communication pathways with the public,
- identifying potential threats to confidence in vaccine safety.

Developing a vaccine safety communications plan is covered in **Appendix 5.3**.

(i) Integrate communications team into vaccine safety work

As soon as the organization starts planning for and making decisions about vaccine safety work, the communications team[60] should be involved. This principle applies at all levels of organizations, from national to local area levels. Communications should not be brought in at the last minute, when leadership and technical experts are ready to implement decisions or in the event of a crisis. Vaccine safety risk communications considerations should be included in preparedness assessments and planning meetings before the introduction of COVID-19 vaccines.

This approach will support effective communication that will be considered, appropriate, and proactive, rather than reactive. As a result, decisions about vaccine safety will be more likely to take into account the needs and perceptions of key audiences. The communications team will also have a better understanding and ability to communicate about technical aspects of vaccine safety.

(ii) Establish strategic partnerships

Establishing strategic partnerships with other vaccine safety stakeholders will improve information sharing and coordination of vaccine safety information dissemination. Coordination will help reduce the possibility of disseminating contradictory messages and advice, which can create confusion and distrust.

In the context of COVID-19 vaccine safety, key stakeholders might include:

- national and regional health authorities and other government bodies;
- National Immunization Technical Advisory Groups (NITAGs);
- regulatory agencies;

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60 Various people may be responsible for communications in different countries, this may be the manager of the Expanded Programme on Immunization (EPI) or the National Immunization Programme (NIP), a designated team under the responsibility of the local COVID-19 response team, e.g., the emergency response controller, or public health lead, a communication expert from a United Nations or a funded technical support organization in partnership with the EPI/NIP manager.

- United Nation bodies and other international organizations;
- professional associations, for example representing health care workers or welfare associations working for elderly populations;
- private sector organizations with a role in immunization, e.g. workplace immunization, local branches of pharmaceutical companies, vaccine manufacturers;
- research scientists, and educational institutions at all levels;
- nongovernmental organizations (NGOs);
- religious organizations;
- community groups, e.g. representing key population groups such as culturally and linguistically diverse communities, and those committed to vaccine advocacy; and
- science journalists, the media, national science media centre if available.

Develop a network of stakeholders as early as possible. Partners may exist across disciplinary and geographical boundaries. It may be possible to leverage existing networks, such as regional surveillance networks, coordination mechanisms, and groups of key stakeholders. Consider seeking inclusion in the WHO Vaccine Safety Net. Linking with partners on social media may be a useful way to network and may also enhance your ability to reach wide audiences and increase your mutual credibility.

Activities between strategic partners will involve:

- agreeing on shared communications objective;
- developing processes for sharing and coordinating information dissemination, for example who releases what, when, and how;
- standardizing messages; and
- identifying and training spokespeople.

Governments, who lead AEFI communication at the country level, may be best positioned to coordinate vaccine safety communications between stakeholders and lead the response in the event of a crisis. Non-government voices, however, still have an important role in reassuring the public about the systems in place to investigate safety issues and respond appropriately.

Respected public health voices can also provide comments to the media and offer a supportive perspective. Certain partners, like community groups and health care workers, may act as advocates, mobilizers and peer educators for vaccine safety issues. Journalists and social media influencers can be potential partners in information dissemination as their reports can have an important impact on public trust. Partnerships with the media are discussed in more depth in **Appendix 5.7**.

Further resources

Name of resource	Language	Source	About
Stakeholder management	English, Russian	WHO Regional Office for Europe	List of key vaccine-related stakeholders, and principles for establishing and maintaining relations with them
Template terms of reference for a vaccine communication working group	English, Russian	WHO Regional Office for Europe	Advice on creating working groups with partners
Vaccine safety events: managing the communications response	English, Russian	WHO Regional Office for Europe	Guidance on building partnerships (p. 40)
Risk communication and community engagement (RCCE) action plan guidance. COVID-19 preparedness and response	English	WHO Global	Defining and prioritising RCCE audiences and other stakeholders (p. 20)

(iii) Setting up communication pathways with the public

The 'public' is anyone who has an interest in, or is affected by, decisions about COVID-19 vaccine safety, including health care workers. Engaging the public as legitimate partners can help to build trust and create a sense of shared responsibility for managing vaccine safety risks.

Public engagement means continuously listening to people's concerns about vaccine safety, and actively engaging people in dialogue; not just informing the public about vaccine safety, risks, and benefits.

Public engagement can be facilitated by:

- offering multiple ways for the public to ask questions or raise concerns directly, e.g., via public forums, website feedback forms, email, hotlines, online chat, or through social media;
- scheduling regular meetings with stakeholders, community and religious or cultural leaders, health care workers and others to provide a forum for discussing and addressing vaccine safety concerns; and
- partnering with community influencers and mobilisers to disseminate information.

These actions signal an acknowledgement of people's right to know about COVID-19 vaccine safety, vaccination risks and benefits, and acceptance of their concerns as legitimate.

(iv) Identifying potential threats to confidence in vaccine safety

Identifying potential threats to people's confidence in vaccine safety can guide how and with whom to communicate and also help to shape messages. In a COVID-19 vaccination safety context, anticipated threats, sometimes called 'vaccine-related events', may include:

- adverse events following immunization (AEFIs), either connected or perceived to be connected with vaccination, or adverse events of special interest (AESIs);
- new scientific data on COVID-19 vaccines benefits and risks;
- events such as a temporary suspension of a vaccine, vaccine recall, change in vaccine or introduction of a new vaccine;
- negative messaging, e.g. news and other media reports, misinformation, or the actions of anti-vaccine activists, including social media;
- community attitudes and beliefs, including any pre-existing vaccine hesitancy, may also threaten confidence in COVID-19 vaccine safety; and
- low acceptance of the COVID-19 vaccines that may affect confidence in other vaccines.

Track anticipated threats using a tool such as a 'risk register', which lists each threat and related information i.e., description of the threat, category (type of 'vaccine-related event' as above), probable settings and populations, likelihood and potential impact (e.g. low, medium, high), response strategies, and risk 'owner' or manager.

Threats posed by negative messaging, and community attitudes and beliefs will often be specific to contexts and locations. Research and listening methods can help to detect and understand issues related to vaccine safety.

Further resources

Name of resource	Language	Source	About
Vaccine Safety Events: managing the communications response	English, Russian	WHO Regional Office for Europe	Definition and explanation of vaccine-related events (p. 12)
TIP Tailoring Immunization Programmes	English, Russian	WHO Regional Office for Europe	Guidance for understanding barriers to vaccination
WHO tool for behavioural insights on COVID-19	English, Russian	WHO Regional Office for Europe	Rapid, flexible and cost-effective monitoring of public knowledge, risk perceptions, behaviours and trust to make their COVID-19-related response relevant and actionable, includes vaccination

Appendix 5.5: Guidance on social listening

An overabundance of information and misinformation about the COVID-19 pandemic, especially online, called an 'infodemic', can lead to a range of poor outcomes. The infodemic makes it difficult for individuals to know where to seek credible information. Concerns and negative messaging circulating online and on social media may affect public perceptions of COVID-19 vaccine safety and lead to behaviours that do not protect people's health.

Listening using multiple data sources is essential for formulating a tailored response. Listening can help to:

- identify audiences, including specific audience segments;
- understand what audiences are thinking, what information they need, and what actions they want to see happen;
- identify community influencers and trusted sources of information;
- adapt messages, prepare and disseminate targeted communications; and
- detect negative messaging.

Listening should be part of preparations to communicate about vaccine safety, as well as a continuous activity. People's concerns and information needs will change as the pandemic evolves and as vaccines are deployed in different populations and contexts. Inadequate listening activities can lead to incomplete understanding of audiences. Missed opportunities to respond may include issues such as emerging misinformation or public outrage over a perceived crisis before it becomes widespread.

Methods for listening

Methods for listening to the public include:

- media monitoring to understand how the media covers issues related to vaccine safety and what narratives seem to be listened to;
- formative research to gather insights directly from local populations. This is sometimes called a situational analysis; Tailoring Immunization Programmes describes the process in-depth. There are a variety of methods such as interviews, focus groups, and observations that can be used. Strategic partners, other vaccine safety stakeholders, community and religious leaders and other influential people may have access to a range of different audiences and can also help gather insights;
- tracking public opinion e.g., via surveys;
- speaking to community and religious leaders and other influential people;
- tracking calls to hotlines and other forms of public feedback to identify community questions and concerns around safety; and
- digital and social media listening. For an example, see the EPI WIN COVID-19 Infodemic Digital Intelligence reports. The Vaccine Safety Net has also initiated global digital and social media listening activities on vaccine safety.

If possible, monitor places where people actively search for information and converse about vaccine safety. This may be at public events such as seminars or town hall meetings, in the comments sections of news articles, in online discussion forums, or on social media. Digital and social media listening is covered in more detail below.

Listening can be a time-consuming and expensive activity. If possible, allocate specific resources to employ people with dedicated listening responsibilities in the communication plan. Share listening insights with strategic partners to amplify the collective listening capacity. Sharing

can also help to hear from a greater diversity of voices. Depending on available skills and resources, external help might be needed to gather these insights.

Listening online and on social media

Listening online and on social media can improve understanding of the online audience, identify influencers, adapt messages to formulate targeted communications, and detect negative messaging.

Depending on the social media platform, content and associated engagement may be public or private or a combination of both. For example, Twitter, Reddit, Instagram, YouTube and TikTok host predominantly public content (although some also allow private content), while Facebook has some public pages and groups. Commercial monitoring tools or services are useful for monitoring public content but may require substantial resources and specialized expertise to analyse. Monitoring services based on natural language processing will likely become increasingly popular. These services, including their algorithms and the transparency of the data they monitor, should be evaluated before use to ensure their outputs are correctly applied.

Here is some guidance for listening manually:

- **Generate a list of keywords and hashtags** relevant to COVID-19 vaccine safety. These may change frequently, so will have to be updated.
- **Find out when particular keywords appear online** on web pages, in news, blogs, etc. by setting up notifications via Google Alerts. You can set the parameters to receive alerts instantly, daily, or weekly.
- **Track trending Google searches of keywords** by country via Google Trends. Weekly or monthly notifications can be set up via 'Subscriptions'.
- **Search for keywords or hashtags on social media platforms** using platform search tools, e.g., via Twitter advanced search or Reddit search. Facebook search that can explore public posts in public groups or pages. Instagram search can be used to search for people or hashtags. Facebook, Instagram and YouTube are also searchable using Google.
- **Track multiple keywords or hashtags** using tools like social media aggregators, e.g. Tweetdeck for Twitter. This will help to automate the monitoring partially.
- **Use free tools to search and analyse listening data. For example,** Onemilliontweetmap provides a real-time geographic map of geolocated tweets with specific search terms or hashtags. Media Cloud provides analysis of digital news media, including some social media shares. WhatsApp monitor supports searching WhatsApp public groups in Brazil, India and Indonesia.
- **Generate a list of key individuals, groups, or websites** that may be useful to track. This might include influential individuals, community groups or other groups representing target audiences. For listening to negative messaging, develop and track a list of individuals, groups or websites that generate or share misinformation or negative sentiment about COVID-19 vaccine safety.

- **See how often links have been shared** on Facebook, Instagram, Twitter and Reddit using Chrome browser plugin CrowdTangle Link Checker. This tool also shows associated posts (limited to public pages or accounts) and engagement data.
- It is important to **determine how many people are being reached by and are engaging with messages of interest**. Counting the number of messages posted on a particular topic gives a false impression of message influence. People may post a large volume of messages on social media but have hardly any followers, and therefore little influence. If an individual or page is posting messages of interest, look at the number of followers and the number of people engaging with or sharing the message to assess their influence.

Note that the information gathered can be useful for understanding what people are saying about vaccine safety on social media, but may or may not correspond with vaccination sentiment in broader populations or groups, especially those who do not have digital access. To broader the information gathered other means of listening, such as monitoring mainstream media and community conversations should be used.

Further resources

While many of these resources were designed for journalists, they contain relevant information anyone listening on social media, including health authorities and other people working in vaccine safety.

Name of resource	Language	Source	About
RCCE Action Plan Guidance. COVID-19 preparedness and response	English	WHO Global	Tools for formative research: — COVID-19 Rapid Qualitative Assessment Tool (p. 8) — COVID-19 Rapid Quantitative Assessment Tool (p. 14)
How to monitor public opinion	English, Russian	WHO Regional Office for Europe	Tools to monitor public opinion on vaccination
CERC Messages and Audiences	English	CDC CERC	Guidance on gathering audience insights (p. 9)
Essential Guide to Newsgathering and Monitoring on the Social Web	English	First Draft	Monitoring best practices across major platforms and online services
How to begin to monitor social media for misinformation	English	First Draft	Strategies to monitor Reddit, 4chan, Twitter and Facebook (Part one)
Monitoring social media for misinformation, part two	English	First Draft	Free tools to monitor social media (Crowdtangle, 4chan, Tweetdeck) (Part two)
How to investigate health misinformation (and anything else) using Twitter's API	English	First Draft	Guide to collecting data from Twitter

Name of resource	Language	Source	About
Speed up your social newsgathering with these Twitter search shortcuts	English	First Draft	Guide to monitor tweets (including using Tweetdeck) using search operators
Closed Groups, Messaging Apps & Online Ads	English	First Draft	Monitor groups and closed messaging apps
RCCE Action Plan Guidance. COVID-19 preparedness and response	English	WHO Global	Guidance on learning about audiences (p. 25)
The 101 of disinformation detection	English	Institute for Strategic Dialogue	Toolkit for detecting disinformation online via listening

Appendix 5.6: Development of evidence-based messages

It will be necessary to develop messages about COVID-19 vaccine safety for a variety of uses, such as media releases, talking points for spokespeople, or posts for social media. The type of COVID-19 vaccine safety information that the public may seek, or you may wish to communicate could include: vaccine risks and benefits, information about vaccine safety regulatory processes and surveillance systems, and vaccine safety concepts such as AEFIs and AESIs. Through listening, it is possible to identify commonly asked questions that can be addressed.

Here are some tips from health communication research to help make these messages more effective and acceptable to your audiences.

- **Keep messages clear, simple and short**. Avoid using vaccine safety jargon or technical terms like 'AEFIs' or even 'adverse events'. These terms are not part of most people's everyday language.
- **Convey balanced, evidence-based information** that communicates potential risks to a level of detail appropriate for the audience.
- **Explain the costs and benefits of vaccination, but focus on the positive** opportunities for COVID-19 vaccines to improve health ('gain frames') rather than on the risk of disease ('loss frames'). Example: vaccinate against COVID-19 and protect our community's health.
- **Balance messages about vaccine safety with more general COVID-19 vaccine information**. This may help to avoid over- emphasizing vaccine safety issues and unintentionally triggering concerns in people seeking other types of information.
- **Emphasize scientific consensus,** e.g., "90% of clinicians agree that this vaccine is safe" and develop straightforward consistent terms to use when presenting the limits of scientific confidence.
- **Provide people with specific actions they can do to reduce harms.** In uncertain situations, such messages can give people a sense of control e.g., "Get vaccinated", "Talk to your doctor about COVID-19 vaccines" or "Ring this number to find out more".

- **Shape messages to suit specific audiences**. This means considering cultural differences, literacy levels, or the specific communication needs of particular groups. Audiences on digital and social media may be particularly fragmented and require messages tailored specifically to their needs.
- **Present data clearly** to support audience comprehension.[61] For example, use frequencies, 1 out of 100, rather than percentages, 1% or abstract terms, such as 'common'. Use the same denominator when comparing risks. Use absolute, not relative risks.
- **Use illustrations and visuals.** Visuals can clarify text and data, but they should be closely related to what is said in the text, to be effective. Using visuals on their own can make messages accessible by overcoming language, cultural and literacy barriers.[62] See this example about COVID-19 from Stanford Medicine.
- **Use personal stories about vaccination and other messages that elicit emotion.** Negative narratives about vaccine safety can have a powerful influence on how people perceive vaccine risk. Positive, emotive narratives can help model vaccination behaviour and are often more memorable than factual information.[63] Narratives are effective for addressing emotional issues and overcoming resistance.[64] See this example of President Obama receiving his H1N1 vaccine in 2009. Social media users may want to share their own positive stories of vaccination via your pages or posts; allowing them to do this also demonstrates trust in your online community.
- **Pre-test your messages** with representatives of target audiences and adjust as needed. How the public responds to COVID-19 vaccine safety messaging may be unpredictable and not reflect previous experiences.
- **Consistency of messages is important**. Use and reuse the same messages in all channels and platforms without changes to avoid confusion.

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61 Trevena LJ, Zikmund-Fisher BJ, Edwards A, Gaissmaier W, Galesic M, Han PK, et al. Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers. BMC Med Inform Decis Mak 2013;13 Suppl 2(Suppl 2):S7. doi: 10.1186/1472-6947-13-S2-S7.

62 Adam M, Barnighausen T, McMahon SA. Design for extreme scalability: A wordless, globally scalable COVID-19 prevention animation for rapid public health communication. J Global Health. 2020;10(1):010343. doi: 10.7189/jogh.10.010343.

63 World Health Organization. Vaccination and trust. 2017. Available from https://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2017/vaccination-and-trust-2017. Accessed 18 November 2020.

64 Cawkwell PB, Oshinsky D. Storytelling in the context of vaccine refusal: a strategy to improve communication and immunisation. Med Humanit. 2016;42(1):31-35. doi: 10.1136/medhum-2015-010761.

Further resources

Name of resource	Language	Source	About
Guidance on developing messages			
Vaccination and Trust: How concerns arise and the role of communication in mitigating crises	English, Russian	WHO Regional Office for Europe	Guidance on creating effective vaccine messaging (p. 30)
Vaccine Safety Events: managing the communications response	English, Russian	WHO Regional Office for Europe	Guidance on developing vaccine message content (p. 20)
CERC Messages and Audiences	English	CDC CERC	Guidance on developing messages (p. 6)
International Patient Decision Aid Standards (IPDAS) criteria	English	IPDAS Collaboration	Criteria for assessing the quality of patient decision aids
Tools for developing messages			
How to prepare a message map	English, Russian	WHO Regional Office for Europe	Tool to develop and pre-test messages
Message Development for Communication Worksheet	English	CDC CERC	Worksheet to develop six basic emergency message components
Everyday Words for Public Health Communication	English	CDC	Index of plain language alternatives for public health jargon
Pre-prepared messages on vaccine safety			
Vaccine safety messages	English, Russian	WHO Regional Office for Europe	Pre-prepared messages on vaccine safety and AEFIs
Societal benefits of immunization	English, Russian	WHO Regional Office for Europe	Information on wider social benefits of vaccination, for use in messaging, talking points
List of Vaccine Safety Net websites	Various	Global Vaccine Safety Initiative, WHO	List of websites that provide credible vaccine safety information
RCCE Action Plan Guidance. COVID-19 preparedness and response	English	WHO Global	List of COVID-19 information sources for generating content (p. 23)
Country & Technical Guidance - Coronavirus disease (COVID-19)	Various	WHO Global	Technical guidance on COVID-19
Presenting data			
Key principles for presenting data	English, Russian	WHO Regional Office for Europe	Principles for presenting numbers about vaccination to the public
Communicating Risks and Benefits: An Evidence-Based User's guide	English	FDA	Presenting quantitative data (p. 53)
Reporting the findings: Absolute vs relative risk	English	Health News Review	Using absolute versus relative risk

Appendix 5.7: Responding to the needs of the media

In many cases the traditional media (television, radio, and print) will act as an important intermediary between the communicating organization and the public.[65] For certain communities, radio may be particularly useful given its reach and availability. Several specific actions can develop mutually beneficial relationships with the media.

- **Establish relationships with journalists**. Initiate these connections early and engage regularly. Many journalists use social media to source stories and contacts so you may be able to initiate a relationship through platforms such as Twitter.
- **Be easily accessible and available** for interviews, including after hours. Ensure journalists can readily contact you.[66]
- **Respond promptly** to requests for information. The media needs to turn information around quickly, often within a few hours.
- **Provide clear and concise media releases** that explain complex information in straight forward language. Avoid jargon or technical terms. Media releases should lead with the most important information, and include who, what, where and when.
- **Provide background material** if the issue to discuss is complex, for example explaining AEFIs versus AESIs, rapid authorization, emergency and compassionate use. Background knowledge may improve reporting.
- **Work with the media to decrease sensationalism**. Brief journalists regularly and provide support for understanding vaccine safety issues and concepts. Relationships with specialist health reporters can be especially useful as they often have skills to understand and translate technical concepts into lay language.
- **Identify potential spokespeople** from your organization as early as possible, preferably as part of your communications plan, and organize media training to help them prepare to interact with the media.
- **Become a *'go-to'* source** for vaccine safety information. Offer names of third parties for journalists to speak to about vaccine safety issues.
- **Be guided by values and actions that foster public trust** when talking with the media (see above). Be honest and open with information. Do not minimise risks or make over-reassuring statements about COVID-19 vaccine safety. If you do not know the answer to a question, acknowledge the uncertainty and say what you are doing to find the answer. Do not refuse to answer or say 'no comment'.

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65 Habersaat KB, Betsch C, Danchin M, et al. Ten considerations for effectively managing the COVID-19 transition. Nat Hum Behav. 2020 Jul;4(7):677-687. doi: 10.1038/s41562-020-0906-x.

66 Leask J, Hooker C, King C. Media coverage of health issues and how to work more effectively with journalists: a qualitative study. BMC Public Health. 2010;10:535. doi: 10.1186/1471-2458-10-535.

Further resources

Name of resource	Language	Source	About
Setting the media agenda	English, Russian	WHO Regional Office for Europe	Guidance on working with the media on vaccination issues
Guide to being a media officer	English	Stempra	Practical advice on: — developing media releases (p. 14) — pitching to journalists (p. 19) — targeting journalists (p. 23) — press briefings (p. 25) — using spokespeople (p. 27)
Top tips for media work: a guide for scientists	English	Science Media Centre	Practical advice on preparing to interact with the media
Vaccine safety events: managing the communications response	English, Russian	WHO Regional Office for Europe	Guidance on: — interacting with the media (p. 29) — writing media releases (p. 52) — typical media questions (p. 62) — responding to typical journalist tactics (p. 64)
How to prepare a press release	English, Russian	WHO Regional Office for Europe	Key elements of a press release
How to prepare a message map	English, Russian	WHO Regional Office for Europe	Tool to develop messages and help prepare spokespeople for interviews
The questions journalists always ask in a crisis	English, Russian	WHO Regional Office for Europe	Sample questions asked by journalists in a crisis
Tips for spokespersons	English, Russian	WHO Regional Office for Europe	Principles for successful communication during a crisis, useful for spokesperson training and to prepare for an interview or press conference

Appendix 5.8: Communication on social media

Social media has significant potential for communication about COVID-19 vaccine safety directly to the public.[67] Some audience may be using social media as a primary means of learning and communicating about COVID-19 vaccines. Anti-vaccine activists are certainly using social media to spread negative messaging about vaccines. Social media offers a convenient way to communicate regularly and give real-time updates. Here are some tips.

- **Listen to what key audiences are saying** through social media listening and use this information when developing your communications.

67 Veil SR, Buehner T, Palenchar MJ. A work-in-process literature review: incorporating social media in risk and crisis communication. J Conting Crisis Man. 2011;19(2):110–22. doi 10.1111/j.1468-5973.2011.00639.x.

- **Decide what content may be attracting attention on social media**. Identify the most popular topics online and their associated keywords. Listening is also useful for identifying any gaps in messages.
- **Decide on the platform/s**. This decision will depend on where they key audiences are. Note that spreading efforts too thinly across many platforms may be ineffective. Top ranking social media platforms globally include Facebook, YouTube, Instagram, TikTok (Douyin), Weibo, Reddit, SnapChat, Twitter, Pinterest and Kuaishou. Consider those most likely to be used by the groups you want to target.
- **Decide on the format.** Although text is almost always appropriate, the use of multimedia, including podcasts, which are increasingly popular, may enhance the virality of messages.
- **Consider the available audience**. Certain groups defined by age, culture, language and gender may be more likely to use certain platform or not at all. Choose language and content that matches the platform and speaks to audiences using the platform.
- **Commit to two-way communication**, including interacting, replying and conversing. This is a rich opportunity to develop relationships and trust with audiences. Posting and responding to audience comments shows you are listening and actively responding to people's needs and concerns. However, it is not necessary to respond to every comment or to unfounded criticisms.
- **Be active and interact regularly** to build your community of followers and your credibility, such as hosting livestreams, live Q&As or Ask Me Anything (AMA) threads. Chatbots designed for interactions on COVID-19 could supplement, but not replace, your communication activities. Examples include WHO's Facebook Messenger COVID-19 Chatbot (a version of its WHO Health Alert platform) and Healthbuddy.
- **Monitor the impact of your messages.** Simple metrics and more sophisticated tools for getting analytics may be useful to continuously monitor the number of individuals and their interactions (number of visits and time spent in reading). Monitoring may be helpful to refine original messages and improve understanding what works best.
- **Create safe spaces** for audiences to ask questions and to encourage dialogue, such as offering more private ways to seek advice. Encourage individuals to post questions publicly to benefit others who may have similar concerns. Respond promptly and protect the space by removing aggressive or hostile posts. Make community management expectations clear from the outset and choose moderators who commit to maintaining a civil discussion.
- **Remember that many individuals may be cautious about making themselves publicly visible** on social media. They may be 'silent', i.e. observing but not openly commenting, liking or sharing posts.[68] Design messaging with this audience in mind, not just as a response to the most vocal and active users on social media.
- **Use an authentic, personal approach** rather than impersonal statements. If possible, post as an individual with a first name rather than as an anonymous organization. Social media users expect human conversations with real people, so offer a way for them to connect to with a real person, whether through the chat function on a social media platform or connecting them to a hotline.

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68 Steffens, M. S., Dunn, A. G., Wiley, K. E., Leask, J. How organisations promoting vaccination respond to misinformation on social media: a qualitative investigation. BMC Public Health. 2019;19(1),1348. doi: 10.1186/s12889-019-7659-3.

- **Amplify reach** to wide and diverse audiences using two-way communication. An active community of followers can also help disseminate your posts. Paid posts or campaigns can also be useful.
- **Identify influential and credible users** who can help spread your messages. These might be for example health care workers[69] or others with widely followed Facebook pages or Instagram accounts that already act as trustworthy and influential sources of information.
- **Interact with partners** to share information and increase your mutual credibility. Creating a collective presence on social media will amplify balanced, pro-vaccine voices and can act as a counterbalance to anti-vaccine voices.
- **Allocate resources** specifically for social media in your communications plan. Listening and regular interaction on social media requires substantial input. Dedicated social media staff will be useful for this.
- **Make a policy of avoiding hostile interactions** to preclude being drawn into protracted dialogue with anti-vaccine activists.
- **Use a considered approach** when responding to negative messaging.

Note that social media will not reach everyone, such as unnetworked people in vulnerable or poor communities, particularly in developing countries. The traditional media, alongside interpersonal communication, can be better used to reach such communities.

Further resources

Name of resource	Language	Source	About
Guide to being a media officer	English	Stempra	Developing social media campaigns (p. 35)
Setting the media agenda	English, Russian	WHO Regional Office for Europe	Guidance on setting the vaccination social media agenda
CERC social media and mobile media devices	English	CDC CERC	Guidance on using social media in a crisis
Social media fact sheet	English	Pew Research Center	Social media patterns and trends (US data)
The 2020 social media demographics guide	English	Khoros	Social media demographic information
More than half of the people on earth now use social media	English	DataReportal	Information on global social media use and top-ranking social media platforms
Digital 2020	English	DataReportal	Global digital trends
140+ Social media statistics that matter to marketers in 2020	English	HootSuite	Sociodemographic data on users of various social media platforms

69 Eghtesadi M, Florea A. Facebook, Instagram, Reddit and TikTok: a proposal for health authorities to integrate popular social media platforms in contingency planning amid a global pandemic outbreak. Canadian J Public Health. 2020;111(3):389-391. doi: 10.1186/s12889-019-7659-3.

Appendix 5.9: Frequently Asked Questions

Note that these questions and answers will require pre-testing with target audiences, and revision as new information becomes available.

1. How are we ensuring that the COVID-19 vaccines are safe?

Even though researchers are developing COVID-19 vaccines quickly, they are checking their safety very carefully. Safety checks are done in the laboratory, in clinical trials, and when vaccines are used in the population.

Clinical trials assess vaccines in people to see if they work to prevent COVID-19 and are safe. Clinical trials have three parts, called phases. In phase 1, the vaccine is given to a small number of people. In phase 2, the vaccine is given to hundreds of people. Finally, in phase 3, the vaccine is given to many thousands of people. Researchers are able to observe potential reactions by including lots of people in clinical trials.

If the clinical trials show the vaccine is safe, the government regulatory agency checks the safety information. They also check the way vaccines were developed in the laboratory. The government regulator is independent, which means they are separate from the researchers who develop the vaccine, and from the manufacturers who make the vaccine.

If the government regulator agrees the vaccine is safe, the manufacturer can start supplying doses of the vaccine for those who need it. The government and manufacturers continue to monitor the safety of the vaccine when people are being vaccinated in the community.

All these steps have been and will be followed for the development of COVID-19 vaccines to make sure they are safe. It might look like shortcuts are being taken, but this is not so, these steps are just happening faster than usual. People are joining the clinical trials more quickly than usual and funding and approval steps have been fast-tracked. Also, researchers; manufacturers and government regulators are working together to check vaccine safety information from clinical trials more rapidly than usual.

2. How are we going to monitor for COVID-19 vaccine safety when they are given to the community?

After the clinical trials are finished, governments, manufacturers and researchers will keep looking for rare or unexpected reactions to COVID-19 vaccines. One way of doing this is to make a list of uncommon health problems that could occur in those that are vaccinated. These problems might happen to someone by chance, or they might be caused by the vaccine. These are called 'adverse events of special interest' (AESIs). These might include things like allergic reactions (anaphylaxis) or other health conditions that may not have an obvious cause. These health issues might be so rare that researchers can only see if they occur in vaccinated people by looking at very high numbers of people.

If researchers find any possible rare reactions, they do specific studies to find out if the vaccine is causing them. If the studies show the vaccine is causing rare reactions, the government

regulator will act. They look at benefits of the vaccine, as well as the risks, to make their decision. The decision could include changing advice about how we use the vaccine, or in certain cases, even stopping vaccinations.

3. Will it be worth having a COVID-19 vaccine?

COVID-19 can be an extremely serious disease. A vaccine will reduce the risk that you get the disease or pass the infection on to others.

Many people with COVID-19 have a fever, dry cough and feel tired, but some people have trouble breathing and need to go to hospital. Some people die from the disease. Older people and people with health problems like high blood pressure or diabetes are more likely to become seriously sick, but anyone can get very sick from COVID-19. Some people have symptoms that last for many months. The virus can damage your lungs, heart, and brain.

Anyone of any age can be infected and spread the virus to others, even if they do not show signs of disease. Vaccinations help stop the spread of the virus, especially those more vulnerable to severe disease or dying.

4. I've heard that there are some vaccines using new technologies. How can we know these are safe?

All new vaccine technologies are being put through stringent testing and quality checks to make sure they are safe. This is the same for all COVID-19 vaccines, no matter what technology they use.

RNA vaccines are a new vaccine technology. We have successfully used RNA to target cancer cells, but using it to protect against infectious diseases like COVID-19 is new. RNA vaccines have a different way of working than traditional vaccines. Traditional vaccines imitate a viral or bacterial infection to train your immune system to rapidly respond if you come into contact with them. RNA vaccines contain instructions (or a code) that direct your body to make the disease antigen itself. Your immune system then responds to that antigen by making protective antibodies against the disease.

RNA vaccines do not introduce any actual parts of the virus into your body. RNA vaccines only deliver instructions that allow your body to make a protective response. These vaccines are sometimes called mRNA or messenger RNA vaccines. This name reflects the RNA vaccine's role in delivering instructions or a 'message', rather than the actual disease antigen.

5. Can a COVID-19 vaccine give me COVID-19?

Almost none of COVID-19 vaccines in development are 'live' vaccines. This means they do not include any weakened form of the SARS-COV-2 virus that causes COVID-19. This means you cannot get COVID-19 from the vaccine.

COVID-19 vaccines teach your immune system to recognise the SARS-COV-2 virus and make protective antibodies against it. If you are exposed to the SARS-COV-2 virus after getting a vaccine, you will already have protective antibodies in your body to fight the virus.

A small number of COVID-19 vaccines in development use live virus, but this live virus has been weakened (attenuated). This means the live virus in the vaccine is strong enough to teach your immune system to make protective antibodies, but too weak to give you the actual disease. We already use live virus vaccines to protect against measles, mumps, rubella and chickenpox.

All COVID-19 vaccines will undergo stringent clinical trials, testing and quality checks before health authorities approve them for use.

Appendix 5.10: General resources

Name of resource	Language	Source	About
The Vaccine safety communication eLibrary	Various	WHO	Open-source library of tools and resources for vaccine safety communication
Vaccine safety communication: Guide for immunization programme managers and national regulatory authorities	English	WHO Western Pacific Region	Guide for immunization programme Managers and national regulatory authorities
Vaccine safety basics learning manual	English	WHO	Manual to accompany eLearning course on vaccine safety basics. Guidance on communicating vaccine safety is covered in Module 6 (Communication, p. 145)
CIOMS Guide to vaccine safety communication	English	Council for International Organizations of Medical Sciences (CIOMS)	Recommendations for vaccine safety communication with a specific focus on regulatory bodies and authorities
Communicating risks and benefits: an evidence-based user's guide.	English	United States Food and Drug Administration, US Dept of Health and Human Services	Scientific base for effective communication
Vaccine safety communication library	English, Russian	WHO Regional Office for Europe	A library of guidance for national health authorities and others who communicate about vaccine safety
CERC Templates and tools	English	CDC CERC	Crisis and Emergency Risk Communication tools to help agencies prepare and communicate before, during, and after an emergency

Name of resource	Language	Source	About
COVID-19. Guidelines for communicating about coronavirus disease 2019	English	Pan American Health Organization & WHO Regional Office for the Americas	Guidance, principles and templates for risk communication in relation to COVID-19
The COVID-19 risk communication package for healthcare facilities	English	WHO Regional Office for the Western Pacific	Risk communication information, procedures, and tools for health care workers and healthcare facility management
RCCE action plan guidance. COVID-19 preparedness and response	English	WHO Global	Action plan for effectively with the public, engaging with communities, local partners and other stakeholders
COVID-19 Vaccine Questions and Answers for Healthcare Providers	Various	CANVAX	Answers to questions pertaining to COVID-19 vaccine safety prior to, and during the vaccines roll out to 1) facilitate scientific discussion between stakeholders, including front line health workers with potential vaccine recipients and 2) increase comprehension and transparency of information to facilitate acceptance and uptake of the vaccines
CERC in an infectious disease outbreak.	English	US-CDC	Discussion of principles of communication in an infectious disease outbreak

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

World Health Organization

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