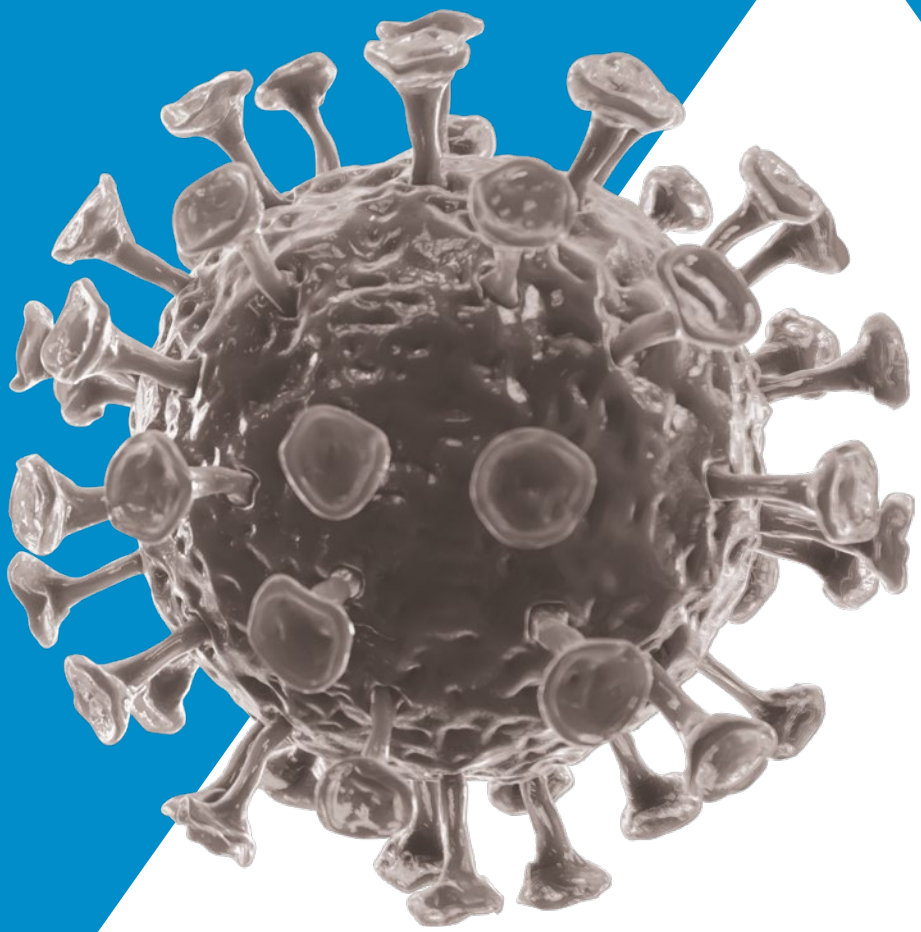
COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL



INTRODUCTION

World Health Organization

COVID-19 VACCINES:

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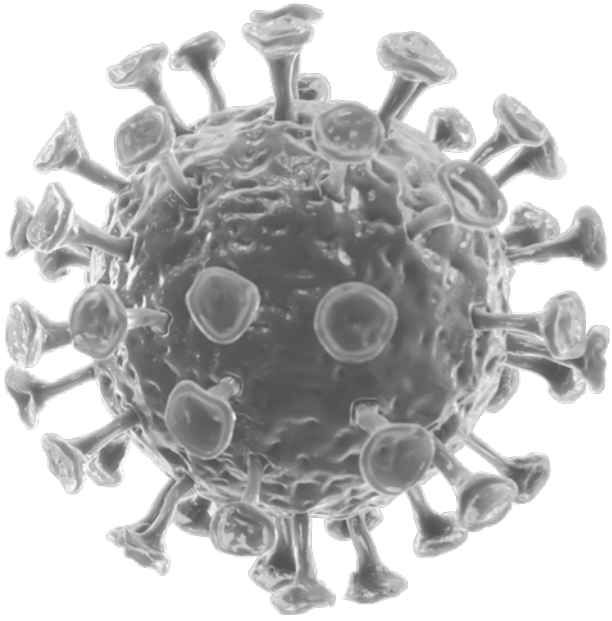

World Health Organization

Covid-19 vaccines: safety surveillance manual

ISBN 978-92-4-001828-0 (electronic version)
ISBN 978-92-4-001829-7 (print version)

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

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

Design and Layout: Agence Gardeners

Contents

Acknowledgements ..... **iv**

Abbreviations and acronyms **1**

Glossary **3**

1. Background **7**

2. Lessons learnt from novel vaccine introduction during pandemic and epidemic emergencies **8**

3. Objectives of this manual **9**

4. Intended audience **10**

5. Organization of the manual **10**

6. Scope of the manual **10**

6.1 COVID-19 vaccines: description and general safety considerations for implementation 10

6.2 Stakeholders in COVID-19 vaccine safety surveillance 11

6.3 Establishing surveillance systems in countries using COVID-19 vaccines 11

6.4 Monitoring and responding to adverse events following immunization (AEFIs) 11

6.5 Monitoring and responding to adverse events of special interest (AESIs) 11

6.6 Safety data management systems, methods of post-introduction evaluation and assessing performance in countries using COVID-19 vaccines 12

6.7 Engaging with the pharmaceutical industry for COVID-19 vaccine safety surveillance 12

6.8 Regulatory reliance and work-sharing 12

6.9 COVID-19 vaccine safety communication 12

Acknowledgements

The Pharmacovigilance team in WHO wishes to acknowledge the following experts for their contributions to this manual:

Dure Samin **Akram**, Health Education Literacy Program and Nutrition Resource Center, Pakistan; Narendra Kumar **Arora**, The INCLEN Trust International, India; Aurel Constant **Allabi**, University of Abomey-Calavi, Benin; Steve **Anderson**, Food and Drug Administration (FDA), USA; Maima **Baysah**, Redemption Hospital, Liberia; Cornelia **Betsch**, University of Erfurt, Germany; Steve **Black**, Safety Platform for Emergency vACcines (SPEAC), USA; Noel **Brewer**, UNC Gillings School of Global Public Health, USA; Helen **Byomire Ndagije**, National Drug Authority, Uganda; Laura **Conklin**, Centers for Disease Control and Prevention (CDC), USA; Riadh **Daghfous**, National Pharmacovigilance Center (CNPV), Tunisia; Mimi Delese **Darko**, Food and Drugs Authority, Ghana; Jean-Michel **Dogné**, University of Namur, Belgium; Eve **Dubé**, Institut national de santé publique du Québec, Canada; Jane **Gidudu**, Centers for Disease Control and Prevention (CDC), USA; Gloria **Giraldo**, Public Health Agency of Canada, Canada; Michael **Gold**, University of Adelaide, Australia; Cecilia **Gonzalez**, Ministry of Health, Chili; Abdulrazaq G. **Habib**, Aminu Kano Teaching Hospital, Nigeria; Pradeep **Haldar**, Ministry of Health & Family Welfare, India; Rita **Helfand**, Centers for Disease Control and Prevention (CDC), USA; Kari **Johansen**, European Centre for Disease Prevention and Control (ECDC), Sweden; Ambujam **Kapoor**, Indian Council of Medical Research, India; Cindy **Ke Zhou**, Food and Drug Administration (FDA), USA; Li **Keli**, China Center for Disease Control and Prevention, China; Catherine **King**, University of Sydney, Australia; Sonali **Kochhar**, University of Washington, USA; Comfort **Kunak Ogar**, National Agency for Food and Drug Administration and Control, Nigeria; Xavier **Kurz**, European Medicines Agency (EMA), the Netherlands; Barbara **Law**, University of Manitoba, Canada; Julie **Leask**, University of Sydney, Australia; Kristine **Macartney**, University of Sydney, Australia; Afework Assefa **Mitiku**, Paediatrician, International Public Health consultant, Ethiopia; Chris **Morgan**, Monash University, Australia; Sten **Olsson**, Pharmacovigilance Consulting, Sweden; Saad **Omer**, Yale School of Medicine, USA; Maria **Paz Bertoglia Arredondo**, Chilean Epidemiology Society, Chile; Jia **Peiyuan**, Harbin Institute of Technology, China; Monica **Plöen**, Uppsala Monitoring Centre, Sweden; Deepak **Polpakara**, Immunization Technical Support Unit, India; Juan Roldan **Saelzer**, National Agency of Medicines, Chili; Rachida **Soulaymani**, Centre Anti Poison et de Pharmacovigilance WHO Collaborating Center, Morocco; Maryke **Steffens**, University of Sydney, Australia; Miriam **Sturkenboom**, University of Utrecht, the Netherlands; Ming **Su**, Public Health Agency of Canada, Canada; Amina **Tebaa**, Anti-Poison and Pharmacovigilance Centre WHO Collaborating Center, Morocco; Alberto **Tozzi**, Ospedale Pediatrico Bambino Gesù, Italy; Nguyen **Van Cuong**, former EPI Consultant, National Institute of Hygiene and Epidemiology, Viet Nam; Elisabeth **Wilhelm**, Centers for Disease Control and Prevention (CDC), USA; Corinne **Willame**, GSK vaccines, Belgium; Hui-Lee **Wong**, Food and Drug Administration (FSA), USA; Wang **Yali**, National Medical Products Administration, China.

The Pharmacovigilance team wishes to acknowledge all the WHO colleagues for their contributions to this manual.

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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