

COVID-19 Vaccines: Safety Surveillance Manual

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

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Abbreviations

AACVS	African Advisory Committee on Vaccine Safety
ACE	Angiotensin-converting enzyme
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
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
GVAP	Global vaccine action plan
HCW	Health care worker
ICD	International classification of diseases
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
ISoP	International Society of Pharmacovigilance
ISRR	Immunization stress-related response
MAH	Marketing authorization holder
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
PBRER	Periodic benefit-risk evaluation report
PHEIC	Public health emergency of international concern
PLSS	Post-licensure safety studies
PSUR	Product 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 Ministry of Health)
VAED	Vaccine-associated enhanced disease
VLP	Virus-like particles
VPD	Vaccine preventable disease
WHO	World Health Organization

Glossary

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.
<ul style="list-style-type: none"> • AEFI by cause: coincidental events 	<ul style="list-style-type: none"> • An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
<ul style="list-style-type: none"> • AEFI by cause: immunization anxiety-related reaction 	<ul style="list-style-type: none"> • An AEFI arising from anxiety about the immunization (see immunization stress related responses).
<ul style="list-style-type: none"> • AEFI by cause: immunization error-related reaction 	<ul style="list-style-type: none"> • An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, that, therefore, is preventable.
<ul style="list-style-type: none"> • AEFI by cause: vaccine product-related reaction 	<ul style="list-style-type: none"> • 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).
<ul style="list-style-type: none"> • AEFI by cause: vaccine-quality defect-related reaction 	<ul style="list-style-type: none"> • 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 detecting, reporting, investigating, and responding to AEFI.
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)	A risk management plan is a document that describes the current knowledge about the safety and efficacy of a medicinal product. The RMP provides key information on plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine or vaccine. It also describes measures to be undertaken to prevent or minimise risks associated with the use of the product in patients.
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	Vaccine reactions can be mild, moderate or severe. Severe reactions may include both serious and non-serious reactions.
Signal (safety signal)	Information (from one or more sources) that suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verification.
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.

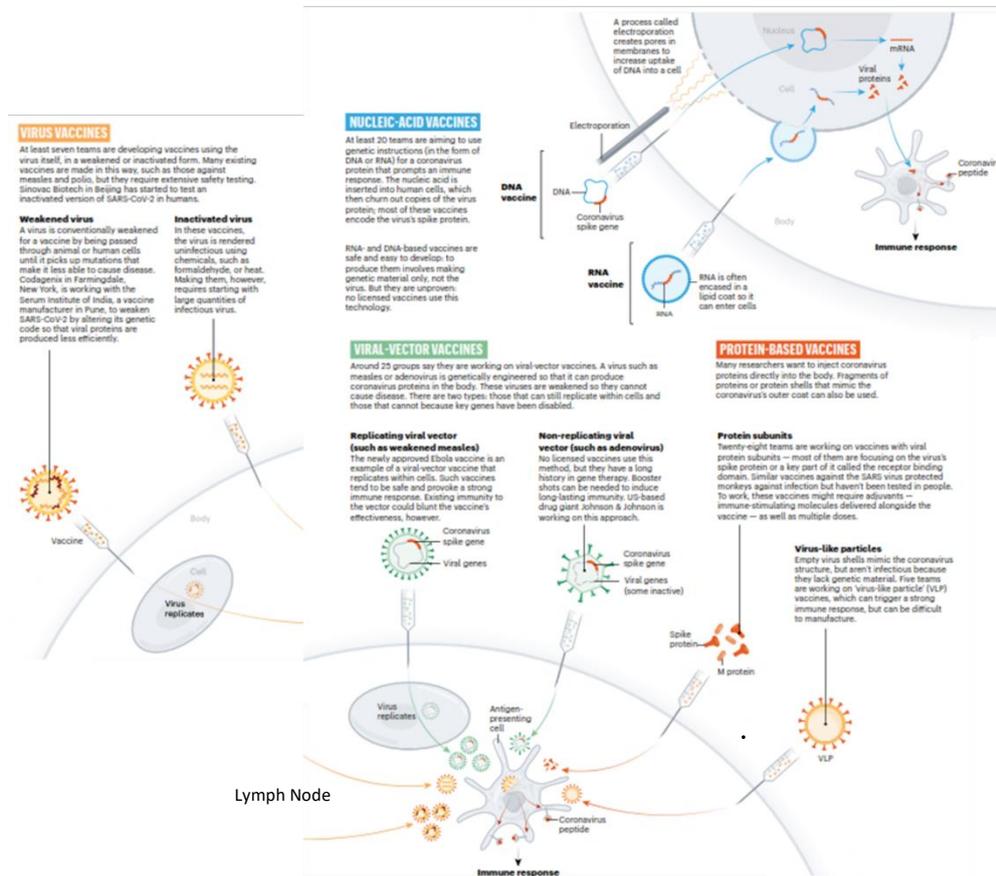
Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.
Vaccine pharmacovigilance	The science and 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.

1. Introduction

With the early availability of the full genome sequence of SARS-CoV-2, 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 19 October 2020, 248 candidate vaccines are in different stages of development: 199 in preclinical studies; 39 in phase I/II clinical studies; and 10 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.

Fig 1: Landscape of platforms used for COVID-19 vaccines (copyright permission granted)



¹ T. Thanh LE, 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.

2. General safety considerations for viral vaccines

2.1. Inactivated viral vaccines²

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 later.³ Although, VAED has not been seen with 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 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^{5,6}

There are no weakened or live-attenuated COVID-19 candidate vaccines in clinical evaluation, but as of 19 October 2020, four vaccine candidates generated by a genetic process called codon deoptimization, are 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 usually more than one mutation is introduced and, therefore, the risk is considerably minimized.

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. Such 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

² Sanders B, Koldijk M, Schuitemaker H. Inactivated viral vaccines. *Vaccine analysis: strategies, principles, and control*. 2014 Nov 28;45–80. doi: 10.1007/978-3-662-45024-6_2. PMID: PMC7189890.

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 Sep 30;94(20):10833-7. doi: 10.1073/pnas.94.20.10833.

⁵ Minor PD. Live attenuated vaccines: Historical successes and current challenges. *Virology*. 2015 May;479-480:379-92. doi: 10.1016/j.virol.2015.03.032. Epub 2015 Apr 8. PMID: 25864107.

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* in press (<https://www.sciencedirect.com/science/article/pii/S0264410X20312020/pdf?md5=d78b917775ba4bd3697545c1d6f438d2&pid=1-s2.0-S0264410X20312020-main.pdf>)

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.

37 genetic techniques. In the past, VSV and adenovirus have been used as vector for Ebola vaccines⁸ and
38 in clinical trials with vaccines for Middle East respiratory syndrome (MERS) coronavirus, showing that
39 such vaccines are well tolerated.⁹ Some viral-vector-based vaccines can replicate in the host cell
40 (replicating viral-vector vaccines), such as the recently approved Ebola vaccine¹⁰, and some vectors do
41 not replicate in the host cells (non-replicating viral vector vaccines), depending on the modifications
42 introduced into the vector genome.

43 Understanding the potential risks related to such vaccines requires knowledge of their main
44 components, the biology of the source virus, the pre-existence of anti-vector immunity, its wild-type
45 behaviour and pathogenesis. Also, the behaviour of the genetically modified version (the vector) and
46 the immunogenicity and pathogenesis of the specific vaccine should all be taken into consideration¹¹.

47 A theoretical risk of mutagenesis due to DNA integration into the host genome exists¹², as well as a
48 potentially very low risk of return to virulence of the vector. In addition, there is a risk of loss of the
49 genetic material codifying for the antigen during the manufacturing process which would result in
50 vaccine failure¹³.

51 **2.4. Protein-based vaccines**

52 Viral antigenic proteins, produced using recombinant techniques, can be used to generate a response
53 similar to that generated with the wild-type virus. These proteins may need to be combined with
54 adjuvants to generate an acceptable immune response. The surface spike protein from the SARS-CoV-
55 2 virus is the main target for this approach. Candidate vaccines have different molecular structures for
56 the antigenic protein, use different adjuvants and are produced using different processes to enhance
57 their efficacy. Some of these proteins may be assembled into a virus-like particles (VLP), which are
58 empty virus shells that mimic the wild virus structure but are not infectious as they contain no genetic
59 material.^{11,14} These VLPs can induce a strong immune response.

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 Jul 1;20(7):816–26.

¹⁰ New vaccine for prevention of Ebola virus disease recommended for approval in the European Union European Medicines Agency [Internet]. Available from: <https://www.ema.europa.eu/en/news/new-vaccine-prevention-ebola-virus-disease-recommended-approval-european-union>, accessed 18 October 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;38(36):6410-6419. 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 [Internet]. 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 Jul 19;15(7):e1006857. doi: 10.1371/journal.pcbi.1006857.

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. Epub 2019 Jun 17.

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

64 **2.5. Nucleic acid vaccines**

65 AEFI could be related to nucleotide sequence of the antigenic gene, the surrounding sequences or
66 promoters, the source of the plasmid and the nature of the microorganism and its origin.¹⁵The main
67 theoretical risks are immune-mediated events, local and systemic reactions due to pro-inflammatory
68 properties of the plasmids carrying the DNA sequence or of mRNA segment.¹⁶

69 **2.5.1. mRNA vaccines**

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

77 **2.5.2. DNA vaccines**

78 The nucleic-acid segment is integrated in a bacterial plasmid carrier that contains the encoding
79 segment for the antigen, plus a promoter and other residual segments from the virus or bacteria of
80 origin. Although the integration of the DNA into the host cells' DNA is a potential risk, none of the
81 human or animal studies assessing these vaccines have shown integration.^{19,20}

82 **3. Characteristics and safety profile of COVID-19 vaccine** 83 **candidates**

84 All COVID-19 vaccines are novel vaccines that have never been used in humans on a large scale. All
85 information that is currently available has been provided by the vaccine manufacturers during
86 clinical trials. Dossiers containing safety data that are submitted to national regulatory authorities
87 should be carefully assessed before the vaccine is approved (licensed) for use within their country or

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. Epub 2016 Oct 5.

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. Epub 2014 Feb 19.

¹⁸ Liu MA. A comparison of plasmid DNA and mRNA as vaccine technologies. *Vaccines (Basel)*. 2019 Apr 24;7(2):37. doi: 10.3390/vaccines7020037.

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 Jun 28;91(2):610-9.

88 region. The Summary of product characteristics of vaccines approved for use by WHO
89 prequalification are accessible on the [WHO platform for prequalified vaccines](#).

90 The number of individuals exposed during clinical trials is limited and the profile of the clinical trial
91 participants does not represent the broader spectrum of individuals who will be the actual vaccine
92 recipients when the vaccine is commercialized. As for other newly licensed vaccines, it is, therefore,
93 unlikely that rare AEFIs, particularly those that are unique to specific populations, will be known
94 when the COVID-19 vaccines are licenced. It is strongly recommended that high quality national or
95 regional surveillance systems capable of identifying both known AEFIs seen in clinical trials and
96 potential rare adverse events are implemented to ensure that any safety issues are detected in a
97 timely fashion.

98 Since 24 August 2020, the London School of Hygiene and Tropical Medicine maintains [a living review](#)
99 that summarises the available clinical trial data on different COVID-19 vaccine candidates. For this
100 they perform a weekly search of medRxiv and PubMed to identify publications reporting outcome
101 data from human clinical trials of COVID-19 vaccine candidates from which they extract
102 immunogenicity and safety data. As of 19 October 2020, they have identified 15 clinical trials.
103 Updated information can be consulted here.

104 **4. Safety implications for implementing immunization** 105 **programmes for priority target populations**

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

112 **4.1. Prioritising populations for COVID-19 vaccination**

113 Initially when COVID-19 vaccination programmes will be initiated there will be limited supplies of the
114 COVID-19 vaccines. Hence, a strategy to prioritize the allocation of available COVID-19 vaccines
115 between countries and between populations will be needed. WHO's Strategic Advisory Group of
116 Experts (SAGE), has developed guidance for the allocation of COVID-19 vaccines between countries,
117 and for the prioritization of groups. to be vaccinated within countries, while supply is limited²¹. In
118 addition, a 'roadmap' that proposes public health strategies and target priority groups in different
119 epidemiological settings and for different levels of vaccine availability has been developed by WHO's
120 SAGE to support countries in their planning for prioritizing use of COVID-19 vaccines²².

121 Fig 2 shows that the potential priority target groups include adults such as frontline workers in
122 health care settings, other individuals who are likely to be exposed and spread virus, adults over 65
123 years old and adults under 65 years old who have underlying conditions that are at a higher risk of
124 mortality.

²¹ 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

²² https://www.who.int/immunization/sage/covid-19_documents/en/. Accessed 30 October 2020.

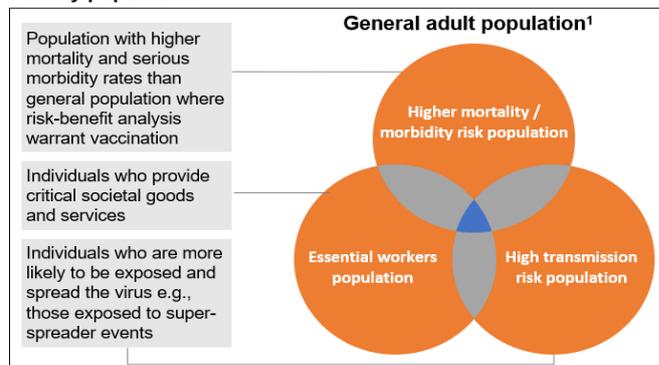
125

126 **Fig 2: Potential priority populations for COVID-19 vaccination**

WHY

Priority populations are defined by the rationale for their vaccinations i.e., why would you want to vaccinate this population?

Priority populations



Vaccines should also be prioritized / reserved for disease outbreaks

1. Non-adult populations require further consideration

WHO

Target groups are who you would want to vaccinate and are defined by a common characteristic (e.g., age, health status, occupation) which allows you to identify them

Examples of potential target groups
(ordering does not imply sequencing or prioritization)

- Elderly (>65 years)
- Workers in health and social care settings
- <65 with co-morbidities
- Other essential workers
- Adults in densely populated areas
- Rest of adult population

127

128 **4.2. Potential safety implications related to prioritization**

129 **4.2.1. Safety implications in priority target populations**

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

135 COVID-19 vaccine interactions with medications, other vaccines and other products used by
136 potential vaccine recipients are currently unknown. This may be a concern, particularly in older age
137 groups where there many individuals will have medications for their underlying conditions.

138 Health care workers (HCWs) will be among the priority target groups when vaccines become
139 available and this population includes many women, some of whom will be in the reproductive age
140 group. These women may be unaware of their pregnancy status when they receive the vaccine.

141 **4.2.2. Safety implications for immunization programmes**

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

147 Some vaccines schedules may require two or more doses per person at specified time intervals. As
148 there is currently no information on the interchangeability of the vaccines, subsequent doses of the
149 same vaccine should be delivered to the vaccine recipients at the correct time interval. In addition,
150 immunization programmes need to ensure accurate recording of the brand name and batch/lot
151 number of the COVID-19 vaccine given to each individual.

152 **4.2.3. Safety implication for vaccine pharmacovigilance**

- 153 • All COVID-19 vaccines used in countries should be licensed/authorized for use by the
154 national regulatory authorities. Countries with inadequate regulatory capacity may use
155 COVID-19 vaccines prequalified/authorized by WHO.
- 156 • National regulatory authorities should review the risk management plan (RMP) submitted by
157 marketing authorization holders at the time of licensing and country surveillance systems
158 should be prepared for detecting AEFIs. AESI surveillance for the list of events selected by
159 countries (Module 6) should be conducted in accordance with standard guidelines.
- 160 • National AEFI committees for AEFI review and causality assessment may not exist in some
161 countries and they may have limited experience in the evaluation of AEFIs in adults and
162 individuals with underlying medical conditions.
- 163 • Larger volumes of AEFI reports should be anticipated, as vaccines will be given to a larger
164 proportion of the population than those included in routine immunization programmes,
165 many of whom may have one or more co-morbidities.
- 166 • Data collation for AEFIs and transmission to the WHO global pharmacovigilance database,
167 VigiBase²³, using standard procedures, should be done to ensure signals can be detected.

168 **4.3. Immunization strategies during COVID-19 vaccine introduction**

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

173 **4.3.1. Safety considerations for COVID-19 vaccine administration in mass immunization
174 campaigns**

175 WHO has published guidance document for the assessment of vaccine safety in the setting of mass
176 immunization campaigns²⁴. When COVID-19 vaccines will be used, the following additional key safety
177 aspects for mass vaccination immunization campaigns need to be considered:

- 178 • training for the usage of the vaccines and infection prevention and control measures;
- 179 • personal protective equipment requirements for HCWs;
- 180 • size and characteristics of the target population;
- 181 • goal of immunization of priority target population;
- 182 • period of time for deployment and vaccination;
- 183 • standard operating procedures (SOPs) and training for the management of possible AEFI;
- 184 • additional human and financial resources needed;
- 185 • joint health information system for reporting vaccination coverage and AEFI reporting;
- 186 • rapid response teams for responding to vaccination emergencies, conducting AEFI
187 investigations and crisis management.

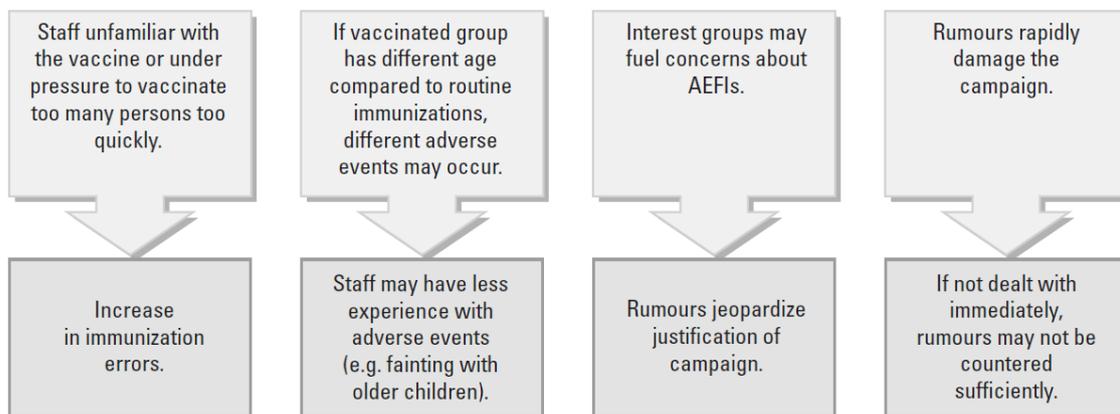
188 The common safety challenges during mass immunization campaigns and consequences if they are
189 not addressed are summarized in Fig 3. To prevent immunization error-related reactions in mass
190 immunization campaigns, specific training of HCWs is needed and steps for safe vaccine

²³ VigiBase. <https://www.who-umc.org/vigibase/vigibase/>, accessed 19 October 2020.

²⁴ 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.

191 administration and waste disposal should be implemented. Before vaccinating, HCWs should verify
192 the product on vaccine and diluent labels, check for vaccine contraindications, as indicated in the
193 product information leaflet. A clear communications strategy prior to vaccine introduction is also
194 critical (Module 9) to ensure the right safety messages are communicated prior to, during and after
195 vaccination and to maintain public trust in the immunization programme if any serious AEFIs occur.

196 Fig 3: Common safety challenges in mass immunization campaigns



197

198 4.3.2. Safety considerations for all immunization programmes

199 The global manual on surveillance of adverse events following immunization provides generic
200 guidance for vaccine safety surveillance for countries, which can be adapted to the local context in
201 Member States and WHO regions²⁵. Specific COVID-19 vaccine AEFI surveillance as outlined in this
202 manual should be implemented in where COVID-19 immunization programmes are set-up. They also
203 should be implemented, regardless of the specific immunization programmes and strategies used,
204 which could include routine immunization strategies and practices, house to house programmes and
205 outreach strategies for hard-to-reach areas, catch-up vaccination programmes, institution-based
206 immunization (e.g., workplaces and care-homes) and mobile strategies (e.g., in the event of
207 humanitarian emergencies) in all settings, including the private sector. This will require preparedness
208 and basic training of staff to strengthen the local capacity to follow national guidelines or protocols
209 for AEFI surveillance (detection, reporting, investigation, causality assessment and coordinated
210 response).

211

²⁵ World Health Organization. (2014). Global manual on surveillance of adverse events following immunization. Available from: https://www.who.int/vaccine_safety/publications/aeft_surveillance/en/, accessed 19 October 2020