
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
ISO  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
PBRRER 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**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Adjuvant</td>
<td>A pharmacological or immunological agent added to a vaccine to improve its immune response.</td>
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<tr>
<td>Adverse event following immunization (AEFI): general definition</td>
<td>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.</td>
</tr>
<tr>
<td>• AEFI by cause: coincidental events</td>
<td>An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.</td>
</tr>
<tr>
<td>• AEFI by cause: immunization anxiety-related reaction</td>
<td>An AEFI arising from anxiety about the immunization (see immunization stress related responses).</td>
</tr>
<tr>
<td>• AEFI by cause: immunization error-related reaction</td>
<td>An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, that, therefore, is preventable.</td>
</tr>
<tr>
<td>• AEFI by cause: vaccine product-related reaction</td>
<td>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).</td>
</tr>
<tr>
<td>• AEFI by cause: vaccine quality defect-related reaction</td>
<td>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.</td>
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<tr>
<td>Adverse event of special interest (AESI)</td>
<td>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.</td>
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<tr>
<td>Causal association</td>
<td>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.</td>
</tr>
<tr>
<td>Causality assessment</td>
<td>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.</td>
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<tr>
<td>Cluster</td>
<td>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.</td>
</tr>
<tr>
<td>Contraindication</td>
<td>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.</td>
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<tr>
<td>Immunity</td>
<td>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.</td>
</tr>
<tr>
<td>Immunization</td>
<td>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</td>
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<td>Term</td>
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<tr>
<td>Immunization safety</td>
<td>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.</td>
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<tr>
<td>Immunization safety surveillance</td>
<td>A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.</td>
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<tr>
<td>Immunization stress related responses (ISRR)</td>
<td>Stress response to immunization that may manifest just prior to, during, or after immunization.</td>
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<tr>
<td>Injection safety</td>
<td>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).</td>
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<tr>
<td>Mass vaccination campaign</td>
<td>Mass vaccination campaigns involve administration of vaccine doses to a large population over a short period of time.</td>
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<tr>
<td>Non-serious AEFI</td>
<td>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.</td>
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<tr>
<td>Risk management plan (RMP)</td>
<td>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.</td>
</tr>
<tr>
<td>Safe injection practice</td>
<td>Practices that ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.</td>
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<tr>
<td>Serious AEFI</td>
<td>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.</td>
</tr>
<tr>
<td>Severe vaccine reaction</td>
<td>Vaccine reactions can be mild, moderate or severe. Severe reactions may include both serious and non-serious reactions.</td>
</tr>
<tr>
<td>Signal (safety signal)</td>
<td>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.</td>
</tr>
<tr>
<td>Surveillance</td>
<td>The continual, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.</td>
</tr>
<tr>
<td>Trigger event</td>
<td>A medical incident following immunization that stimulates a response, usually a case investigation.</td>
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<tr>
<td>SAGE Values Framework</td>
<td>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</td>
</tr>
<tr>
<td>Vaccine</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Vaccine-associate enhanced disease (VAED)</strong></td>
<td>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.</td>
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<tr>
<td><strong>Vaccine pharmacovigilance</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Vaccination failure</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Vaccine reaction</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Vaccine safety</strong></td>
<td>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.</td>
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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. Fig 1 summarizes the four types of platform being explored.

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

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2. 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 later. 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, that could have specific risks related to the bacterial source.

2.2. Live-attenuated viral vaccines

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. 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

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genetic techniques. In the past, VSV and adenovirus have been used as vector for Ebola vaccines and in clinical trials with vaccines for Middle East respiratory syndrome (MERS) coronavirus, showing that such vaccines are well tolerated. Some viral-vector-based vaccines can replicate in the host cell (replicating viral-vector vaccines), such as the recently approved Ebola vaccine, 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, the pre-existence of anti-vector immunity, its wild-type behaviour and pathogenesis. 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.

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

### 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 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 virus shells that mimic the wild virus structure but are not infectious as they contain no genetic material. These VLPs can induce a strong immune response.

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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

AEFI could be related to 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. 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 of mRNA segment.

2.5.1. mRNA vaccines

These vaccines are based on mRNA coding for the 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. mRNA has been proven to be 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.

2.5.2. DNA vaccines

The nucleic-acid segment is integrated in 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 cells’ DNA is a potential risk, none of the human or animal studies assessing these vaccines have shown integration.

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

All COVID-19 vaccines are novel vaccines that have never been used in humans on a large scale. All information that is currently available 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 (licensed) for use within their country or

region. The Summary of product characteristics of vaccines approved for use by WHO prequalification are accessible on the WHO platform for prequalified vaccines.

The number of individuals exposed during clinical trials is limited and the profile of the clinical trial participants does not represent the broader spectrum of individuals who will be the actual vaccine recipients when the vaccine is commercialized. As for other newly licensed vaccines, it is, therefore, unlikely that rare AEFIs, particularly those that are unique to specific populations, will be known when the COVID-19 vaccines are licenced. It is strongly recommended that high quality national or regional surveillance systems capable of identifying both known AEFIs seen in clinical trials and 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 maintains 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 19 October 2020, they have identified 15 clinical trials. Updated information can be consulted here.

4. Safety implications for implementing immunization programmes for priority target populations

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 billion people. In addition to safety monitoring 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.

4.1. Prioritising populations for COVID-19 vaccination

Initially when COVID-19 vaccination programmes will be 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. 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.

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.

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4.2. Potential safety implications related to prioritization

4.2.1. 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 and pregnant women. 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 AEFIs in all age groups, particularly adults are captured.

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 in older age groups where there many individuals will have medications for their 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.

4.2.2. Safety implications for immunization programmes

Immunization programmes must ensure the basic 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 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 time interval. In addition, immunization programmes need to ensure accurate recording of the brand name and batch/lot number of the COVID-19 vaccine given to each individual.
4.2.3. Safety implication for vaccine pharmacovigilance

- All COVID-19 vaccines used in countries should be licensed/authorized for use by the national regulatory authorities. Countries with inadequate regulatory capacity may use COVID-19 vaccines prequalified/authorized by WHO.
- National regulatory authorities should review the risk management plan (RMP) submitted by marketing authorization holders at the time of licensing and country surveillance systems should be prepared for detecting AEFIs. AESI surveillance for the list of events selected by countries (Module 6) should be conducted in accordance with standard guidelines.
- National AEFI committees for AEFI review and causality assessment may not exist in some countries and they may have limited experience in the evaluation of AEFIs in adults and individuals with underlying medical conditions.
- Larger volumes of AEFI reports 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.
- Data collation for AEFIs and transmission to the WHO global pharmacovigilance database, VigiBase\textsuperscript{23}, using standard procedures, should be done to ensure signals can be detected.

4.3. Immunization strategies during COVID-19 vaccine introduction

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

4.3.1. 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\textsuperscript{24}. 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 usage of the vaccines and infection prevention and control measures;
- personal protective equipment requirements for HCWs;
- size and characteristics of the target population;
- goal of immunization of priority target population;
- period of time for deployment and vaccination;
- standard operating procedures (SOPs) and training for the management of possible AEFI;
- additional human and financial resources needed;
- joint health information system for reporting vaccination coverage and AEFI reporting;
- rapid response teams for responding to vaccination emergencies, 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 steps for safe vaccine

\textsuperscript{23} VigiBase. \url{https://www.who-umc.org/vigibase/vigibase/}, accessed 19 October 2020.
administration and waste disposal should be implemented. Before vaccinating, HCWs should verify
the product on vaccine and diluent labels, check for vaccine contraindications, as indicated in the
product information leaflet. A clear communications strategy prior to vaccine introduction is also
critical (Module 9) to ensure the right safety messages are communicated prior to, during and after
vaccination and to maintain public trust in the immunization programme if any serious AEFIs occur.

Fig 3: Common safety challenges in mass immunization campaigns

4.3.2. 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 25. Specific COVID-19 vaccine AEFI surveillance as outlined in this
manual should be implemented in where COVID-19 immunization programmes are set-up. They also
should 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).