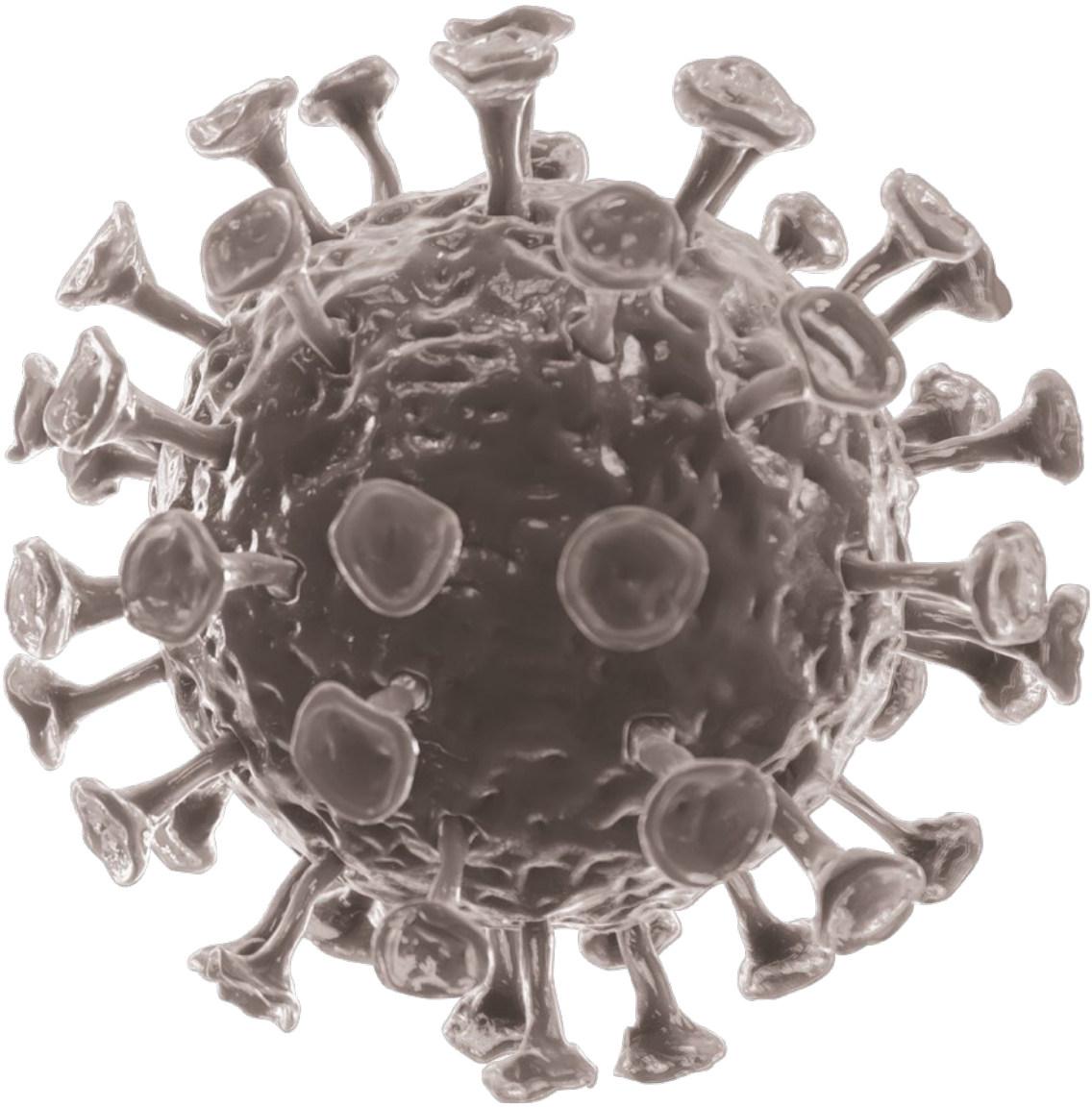
COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

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



World Health Organization

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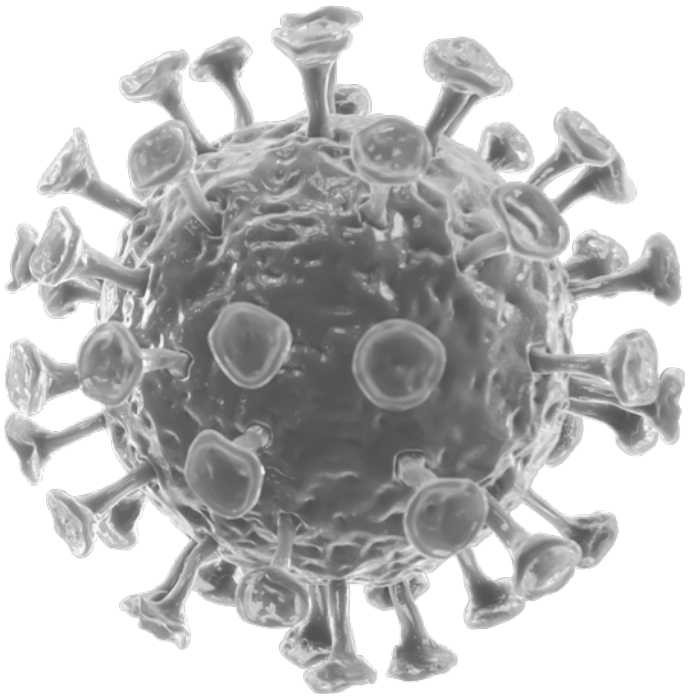

World Health Organization

Covid-19 vaccines: safety surveillance manual

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Contents

Key points

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

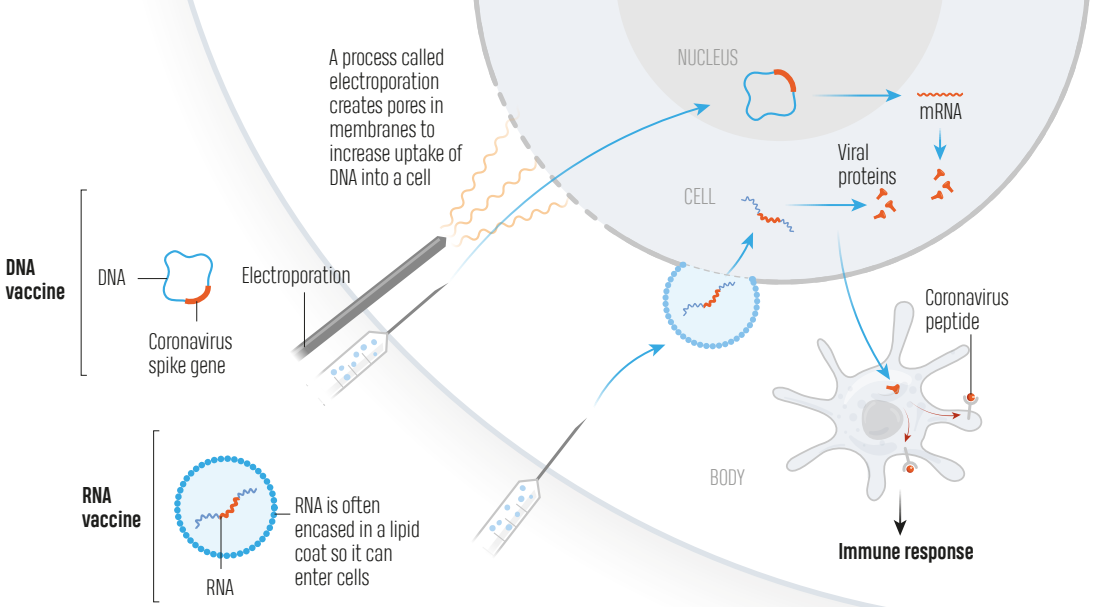
01 Introduction

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

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

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

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



VIRUS VACCINES

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

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

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

NUCLEIC-ACID VACCINES

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

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

VIRAL-VECTOR VACCINES

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

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

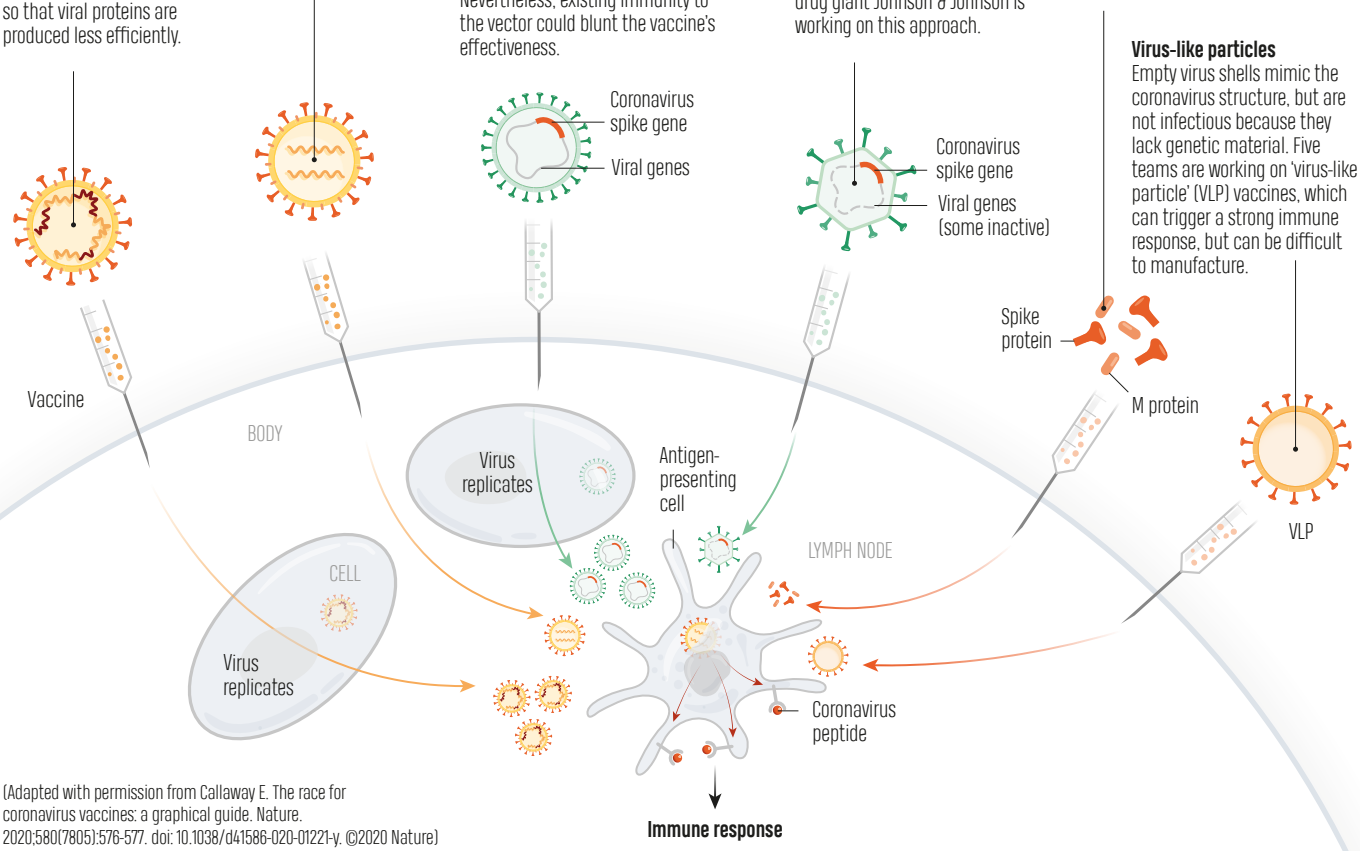
Non-replicating viral vector (such as adenovirus)
No licensed vaccines use this method, but they have a long history in gene therapy. Booster shots can be needed to induce long-lasting immunity. US-based drug giant Johnson & Johnson is working on this approach.

PROTEIN-BASED VACCINES

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

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

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



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

02 General safety considerations for viral vaccines

2.1 Inactivated viral vaccines

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

2.2 Live-attenuated viral vaccines

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

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

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

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

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

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

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

2.3 Viral vector-based vaccines

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

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

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

2.4 Protein-based vaccines

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

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

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

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

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

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

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

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

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

2.5 Nucleic acid vaccines

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

2.5.1 mRNA vaccines

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

2.5.2 DNA vaccines

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

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

15 Kim D, Robertson JS, Excler JL, Condit RC, Fast PE, Gurwith M, et al. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines. Vaccine. 2020 Jul 22;38(34):5556-5561. doi: 10.1016/j.vaccine.2020.06.017.

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

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

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

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

2.6 Characteristics and safety profile of COVID-19 vaccine candidates

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

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

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

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

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

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

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

03 Safety implications for implementing immunization programmes

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

3.1 Prioritising populations for COVID-19 vaccination

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

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

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

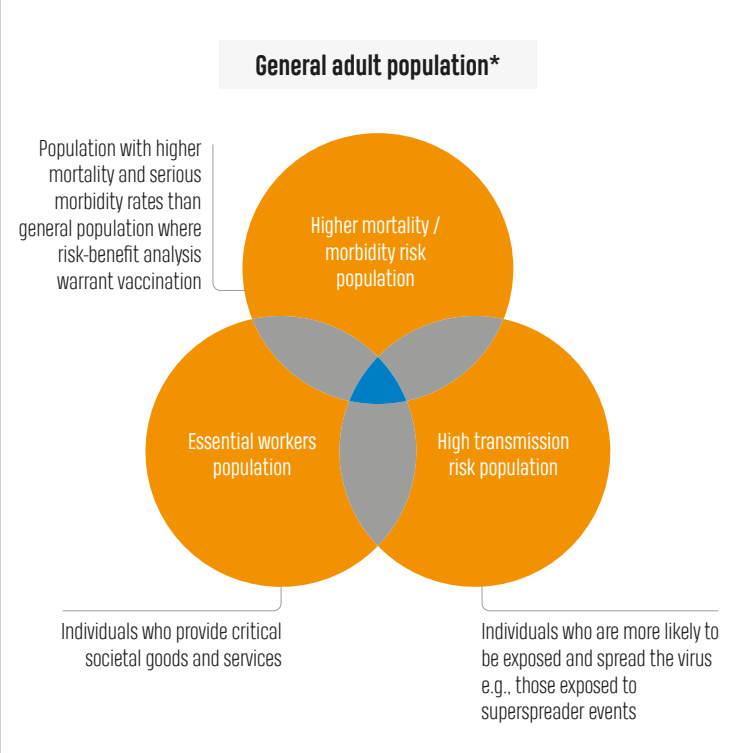
23 Strategic Advisory Group of Experts on Immunization (SAGE). COVID-19 materials. Available from: https://www.who.int/immunization/sage/covid-19_documents/en/. Accessed 30 October 2020.

Fig 2: Potential priority populations for COVID-19 vaccination

WHY

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

Priority populations



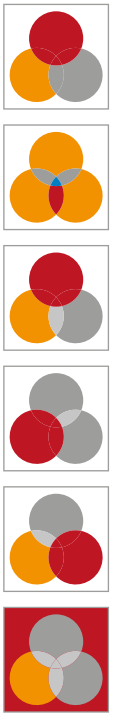
Vaccines should also be prioritized / reserved for disease outbreaks

** 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)



3.2 Potential safety implications related to prioritization

3.2.1 Safety implications in priority target populations

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

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

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

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

3.2.2 Safety implications for immunization programmes

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

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

3.2.3 Safety implication for vaccine pharmacovigilance

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

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

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

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

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

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

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

3.3 Immunization strategies during COVID-19 vaccine introduction

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

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

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

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

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

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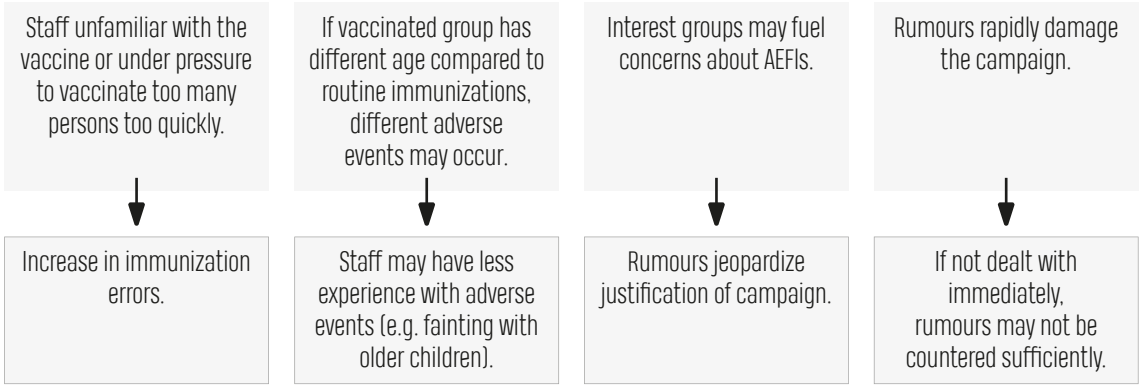
25 VigiBase. https://www.who-umc.org/vigibase/vigibase/. Accessed 19 October 2020.

26 World Health Organization (2002). Safety of mass immunization campaigns. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/67726. Accessed 16 October 2020.

27 World Health Organization (2004). Management of wastes from immunisation campaign activities, Practical guidelines for planners and managers. Available at: https://www.who.int/water_sanitation_health/publications/hcwm/en/. Accessed 12 November 2020.

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

Fig 3: Common safety challenges in mass immunization campaigns



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

3.3.2 Safety considerations for all immunization programmes

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

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

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

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