mRNA technology for improving global health

Potential and limitations of mRNA technology for vaccine research and development for infectious diseases and virus-induced cancers

A REPORT OF THE WHO SCIENCE COUNCIL

Draft for public consultation 2nd April 2023
1. **Contents**

2. Abbreviations 3

3. WHO Science Council 4

4. Acknowledgments 5

5. Executive summary 5

6. Introduction 7

7. mRNA technology and its applications for vaccine research and development 7

8. Key findings 10
   8.1. Contributions of previous R&D for mRNA vaccines to COVID-19 vaccines success 10
   8.2. Issues of equitable access arising from the use of the mRNA technology 11
   8.3. Scientific and technological advantages and limitations to the use of the mRNA platform for vaccines 12

9. Recommendations for advancing mRNA vaccine technology 14
   9.1. Assessing the value of mRNA technology in the context of a global vaccine strategy 15
      9.1.1. Identifying pathogens of interest 16
      9.1.2. Key indicators 17
      9.1.3. Positioning mRNA vaccines within the existing R&D and global health ecosystems 19
      9.1.4. Assessing Impact 20
   9.2. Biological and technological improvements 21
   9.3. End-to-end equitable development of the mRNA technology 22

10. Conclusion  Error! Bookmark not defined.

11. References 24

Annexe 1: Methodology, consultation, and participants 29

Annexe 2: Virus-induced cancers. 31

Annexe 3: Past and ongoing mRNA vaccine trials 32

Annexe 4: Pathogens priority lists 34

Annexe 5: Snapshot of vaccine R&D for priority diseases identified in the WHO R&D Blueprint 36
## 2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHF</td>
<td>Crimean-Congo haemorrhagic fever</td>
</tr>
<tr>
<td>CEPI</td>
<td>Coalition for Epidemic Preparedness Innovations</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CoP</td>
<td>Correlate of protection</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>EUL</td>
<td>WHO Emergency use listing</td>
</tr>
<tr>
<td>EVD</td>
<td>Ebola virus disease</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HAT</td>
<td>Human African trypanosomiasis</td>
</tr>
<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>hMPV/PIV3</td>
<td>Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3)</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomaviruses</td>
</tr>
<tr>
<td>IVT</td>
<td>In vitro transcription</td>
</tr>
<tr>
<td>LNP</td>
<td>Lipid nanoparticle</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Middle East respiratory syndrome coronavirus</td>
</tr>
<tr>
<td>MV</td>
<td>Measles virus</td>
</tr>
<tr>
<td>MVA</td>
<td>Modified vaccinia virus Ankara</td>
</tr>
<tr>
<td>MVD</td>
<td>Marburg virus disease</td>
</tr>
<tr>
<td>PPC</td>
<td>Preferred product characteristics</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SFTS</td>
<td>Severe fever with thrombocytopenia syndrome</td>
</tr>
<tr>
<td>TPP</td>
<td>Target product profile</td>
</tr>
<tr>
<td>UTR</td>
<td>Untranslated region</td>
</tr>
<tr>
<td>VLP</td>
<td>Virus-like particles</td>
</tr>
<tr>
<td>VSV</td>
<td>Vesicular stomatitis virus</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella zoster virus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
3. WHO Science Council

Harold Varmus, MD, Chair
Lewis Thomas University Professor of Medicine at the Meyer Cancer Center of Weill Cornell Medicine; Senior Associate Member, New York Genome Center, USA

Adeeba Kamarulzaman, MBBS, FRACP, Vice Chair
Professor of Medicine and Infectious Diseases, Universiti Malaya; Past-President, International AIDS Society, Malaysia

Salim Abdool Karim, MBChB, PhD
Director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA), South Africa

Edith Heard, PhD
Director General of the European Molecular Biology Laboratory (EMBL), Germany; Professor, Collège de France, France

Mary-Claire King, PhD
Professor of Genome Sciences and Medicine, University of Washington, USA

Denis Mukwege, MBBS
Gynaecologist, Founder, and Medical Director, Panzi Hospital, Democratic Republic of the Congo

Jean William Pape, MD
Director and Founder of Haitian Group for the Study of Kaposi’s Sarcoma and Opportunistic Infections (GHESKIO), Haiti

Firdausi Qadri, PhD
Senior Director of the Infectious Diseases Division at the International Centre for Diarrhoeal Disease Research, Bangladesh

Abla Mehio Sibai, PhD
Professor of Epidemiology and Dean, Faculty of Health Sciences, American University of Beirut, Lebanon.

Yongyuth Yuthavong, DPhil
Senior Specialist, National Centre for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA), Thailand

Cesar G. Victora, MD PhD
Emeritus Professor of Epidemiology at the Federal University of Pelotas, Brazil
4. Acknowledgments

*To be added*

5. Executive summary

The successful use of messenger RNA (mRNA) technology for the development of COVID-19 vaccines is fuelling interest in its potential to create new medicines to prevent, treat, or cure other health conditions. However, despite its benefits and promise, the technology has certain drawbacks that require further investigation to determine its value and power to have a positive impact on various health conditions on a global scale.

The World Health Organization (WHO) Science Council has taken an initial step towards assessing the potential of mRNA technology for improving global health by conducting an independent review of its role in the development of vaccines for the prevention of infectious diseases and virus-induced cancers. This report summarises our findings on the advantages and limitations of the technology and provides recommendations to focus research efforts and guide global research and development endeavours.

The Council acknowledges the potential of mRNA technology for vaccine research and development, and that future applications of mRNA technology for vaccines have the potential to improve the health and well-being of people worldwide. We also identify the obstacles to its use, especially in low- and middle-income countries (LMICs), which include biological and clinical feasibility, manufacturing capability and capacity, cold chain requirements, and intellectual property barriers, all of which can impede equitable access.

Our report to the Director-General makes 12 recommendations for WHO and for consideration by multiple sectors within its Member States. The recommendations are grouped under three themes:

1. Developing a framework to assess the value of mRNA technology for the development of vaccines against infectious diseases and virus-induced cancers.

   **Recommendation 1**

   WHO should emphasize the need to include thinking about mRNA technologies in strategies to control infectious diseases with vaccines, recognizing the need to make existing and new vaccines accessible to all.

   **Recommendation 2**

   WHO should use existing structures and committees leading the organisation’s vaccine strategy to conduct an annual assessment of vaccination strategies worldwide and provide regional advice on the use of a particular technology, including mRNA. This should regularly evaluate the benefits and limitations (scientific and social) of different technologies, including whether mRNA technology can be used for new tasks, for example therapeutics and pandemic preparedness and response.

   **Recommendation 3**

   WHO is encouraged to use its convening power and leadership role in global public health to develop a framework and identify indicators to assess the feasibility and value of developing and investing in mRNA vaccines for infectious diseases and virus-induced cancers.
**Recommendation 4**

WHO should actively engage in communication activities to disseminate, share, and promote the work done by the organization towards addressing infectious diseases and other diseases for which a vaccine is relevant.

**Recommendation 5**

WHO should use its convening power and leadership role in global public health to gather a broad and diverse range of experts in the field to facilitate the identification of pathogens of interest for the development of mRNA vaccines. WHO should encourage product developers to explore the potential of mRNA vaccines for pathogens associated with antimicrobial resistance, virus-induced cancers and to limit the impact of zoonotic disease spillover.

**Recommendation 6**

As part of its activities in the field of infectious diseases, WHO should use its convening power and leadership role in global public health to engage with all those involved in the response to epidemics, pandemics and high-burden diseases to ensure that mRNA vaccine R&D is integrated into the global R&D ecosystems and global health ecosystems.

**Recommendation 7**

WHO should use its reputability and trustworthiness to improve trust in research and science and address vaccine hesitancy to improve current and future vaccine uptake, with the goal of improving public health.

2. **Conducting more research to address the known and unknown limitations of mRNA technology.**

**Recommendation 8**

WHO should take a leading role in identifying biological and technological improvements specific to the mRNA technology (especially cold-chain requirements) and then specifically for pathogens of interest.

**Recommendation 9**

WHO should use its leadership role in global public health to advocate for and support ongoing investment and biomedical research to improve mRNA technology (especially thermostability) including the development of other mRNA platforms such as self-amplifying, trans-amplifying and circular mRNA.

3. **Ensuring end-to-end equitable development and access to mRNA technology.**

**Recommendation 10**

WHO should continue to work with Member States, product developers, funders, global health institutions, and civil society organizations to encourage investing in the end-to-end equitable development of the technology.

**Recommendation 11**

WHO should use its leadership role in global public health to advocate for and support socio-political and economic research to solve the problems of equity.

**Recommendation 12**

WHO is encouraged to review and build on the experience of the ACT-Accelerator partnership and expand its mission to the development of vaccines against other infectious diseases and to contribute to pandemic preparedness.
All recommendations are intended to support the sustainable development of and equitable access to vaccines developed using mRNA technology. We strongly encourage a critical approach and more basic and applied research to overcome the impediments of the technology and to fully realise its potential benefits.

In addition, the Council has determined that improving the conditions that restrict the manufacturing, distribution, and accessibility of vaccines in LMICs is crucial for the advancement of vaccines based on mRNA technology-based and to prevent exacerbating health disparities.

WHO has the capacity and expertise to communicate the benefits and limitations of mRNA technology and to engage broadly with all those involved in the development and use of the technology in Member States to ensure that the mRNA technology can collectively benefit the health of humankind.

6. Introduction

The remarkable rapid development of COVID-19 vaccines based on mRNA technology has substantially changed the course of the pandemic, saving tens of millions of lives globally\(^1\). However, not everyone benefited from this success, and despite its benefits, some of the technology’s limitations accentuated social health inequalities while exposing the unequal power dynamics between wealthy nations and LMICs.

During an in-person meeting in July 2022 in Geneva, the WHO Science Council agreed to conduct an independent review of the uses and safety of mRNA technology, and its value and power to have a positive impact on various health conditions on a global scale.

The mRNA platform’s flexibility and versatility, which enables rapid product design and manufacturing, makes it a valuable tool for accelerating drug development, particularly for vaccines. Success with COVID-19 vaccines has re-ignited interest in developing vaccines for a range of conditions and pathogens with pandemic potential. In parallel, and mindful of production and supply constraints, WHO has established an mRNA technology transfer hub to increase mRNA vaccine production capacity in under-served regions, and thus promote regional health security.

Since it is vital to ensure that the platform’s development and use align with existing vaccine research and development strategies, and that its use is targeted towards the most pertinent applications, the WHO Science Council has taken an initial step towards assessing the potential of mRNA technology for improving global health by conducting an independent review of the technology’s potential for success and impact in preventing infectious diseases and virus-induced cancers.

With this report we present our key findings, highlighting both the advantages and limitations of mRNA technology, providing suggestions to focus research efforts, and making recommendations to guide global research and development endeavours. Our aim is to assist WHO in its efforts to promote the sustainable development and accessibility of the mRNA technology, so that mRNA-based applications can collectively benefit the health of humankind.

7. mRNA technology and its applications for vaccine research and development

Ribonucleic acid (RNA) was discovered in the early 1940’s. mRNA is one of many types of RNA involved in various cellular functions. mRNA are molecules that carry genetic information from DNA in the nucleus of cells to the sites of protein synthesis in the cytoplasm\(^2\).

Extensive research has been conducted to understand the function of mRNA and to find applications for research and health. mRNA was considered for potential new drugs more than 30 years ago and has a long
history of product development, including for vaccines\textsuperscript{3}. However, the poor stability of synthetic mRNA and the innate immune response it triggered once delivered into the body were major roadblocks to its use.

Further research in the mid-2000s led to the development of stable and less immunogenic mRNA molecules\textsuperscript{3–5}. Although most developmental work was done with cancer in mind, these breakthroughs opened the door to using mRNA in vaccine research and development (R&D)\textsuperscript{6–10}.

The mRNA platform has several potential R&D applications including the rapid design and production of vaccines for infectious diseases in humans and animals, the protection of crops against viruses\textsuperscript{11}, and therapeutic applications (cancers and regenerative therapies\textsuperscript{12}), all currently undergoing clinical testing.

mRNA has been an incredibly valuable tool for COVID-19 vaccine research and development with mRNA vaccines against SARS-CoV-2 developed and administered more rapidly than any other vaccines while demonstrating the safety and efficacy of the approach\textsuperscript{13}. Today, that success is driving an increased interest in mRNA technology to address a broad range of medical conditions.

mRNA vaccines are synthetic ribonucleic acid molecules encoding one or more immunogens of interest. Although different types of synthetic mRNA vaccines are in development, the most advanced form of mRNA vaccine is non-replicating linear mRNA (Box 1). Following the identification of a suitable target antigen, an mRNA molecule encoding the immunogen of interest is synthesised and formulated for injection. Once introduced in a person and translated in vivo using the cell machinery, the immunogen will trigger a specific immune response directed against a pathogen expressing the target antigen.

It took years of research to extensively optimize and stabilize the mRNA molecule, protect it from degradation, reduce its natural immunogenicity, and increase and prolong the expression of the immunogen of interest\textsuperscript{4,6,14,15} (Box 2).

Further, for efficient delivery, synthetic mRNA requires a packaging and delivery system that will protect it against degradation by nucleases, allowing efficient cellular uptake, intracellular release, and translation into proteins\textsuperscript{16}. Although various delivery systems are in development, the most clinically advanced consists of encapsulation of the mRNA in lipid nanoparticles (LNPs)\textsuperscript{17}.

**BOX 1: Different types of mRNA molecules**

- Synthetic mRNA usually contains five regions, from 5’ to 3’: 5’ cap, 5’ UTR, an open reading frame that encodes the immunogen, 3’ UTR, and a poly(A) tail. mRNA are categorized as non-replicating, self-amplifying (saRNA), trans-amplifying (taRNA) and circular (circRNA), based on their physical and genetic characteristics\textsuperscript{18}.

- Non-replicating mRNA encodes only the immunogen of interest. Self-amplifying mRNA, meanwhile, also encodes an mRNA replicase (mainly from an alphavirus), allowing the intracellular replication of the mRNA and enabling higher and longer expression of the immunogen. Very low doses of saRNA can produce a large amount of immunogen\textsuperscript{19}.

- Alternatively, saRNA can be delivered as two mRNAs (taRNA), one encoding the replicase and the other the immunogen of interest, thereby reducing the size of the construct.

- Circular mRNAs are produced by back folding the 5’ and 3’ ends, protecting the construct from exonuclease activity, extending its stability and longevity, and stimulating the production of the immunogen of interest. CircRNAs do not need capping of the 5’ and polyadenylation of the 3’ ends, and circularization also reduces the innate immunogenicity of the mRNA.

**BOX 2: mRNA modifications**, adapted from Pardi et al., 2018\textsuperscript{6}
Several modifications of the mRNA molecule contribute to its critical quality attributes which dictate its performance to efficiently and safely express immunogens of interest.

- Synthetic cap analogues and capping enzymes stabilize mRNA and increase protein translation via binding to eukaryotic translation initiation factor 4E (eIF4E).
- Regulatory elements in the 5'-UTR and the 3'-UTR stabilize mRNA and increase protein translation.
- Poly(A) tail stabilizes mRNA and increases protein translation.
- Modified nucleosides, in particular replacement of uridine with N1-methylpseudouridine (m1Ψ) decrease innate immune activation and increase translation.
- Separation and/or purification techniques: RNase III treatment and fast protein liquid chromatography (FPLC) purification decrease immune activation and increase translation.
- Sequence and/or codon optimization increases translation.
- Modulation of target cells: co-delivery of translation initiation factors and other methods alters translation and immunogenicity.

The use of mRNA technology to develop vaccines predates the COVID-19 pandemic but saw rapid developments following the success of mRNA-based COVID-19 vaccines. Research and development of mRNA vaccines is driven by academic institutions and governmental and non-governmental organizations, in collaboration with pharmaceutical companies. The value and potential of mRNA vaccines for infectious diseases and virus-induced cancers have previously been reviewed.

So far, only two vaccines based on mRNA technology have received emergency use authorisation by WHO for a single disease, namely COVID-19. Currently, research focuses on linear non-replicating mRNA and primarily targets infectious diseases and virus-induced cancers caused by relatively simple pathogens, making it easier to design effective immunogens (Table 1 and Annex 3). A few clinical studies are also investigating self-amplifying RNA (saRNA). The results of ongoing clinical studies, expected in the coming years, will provide important information for the future development and use of the mRNA platform for vaccines R&D.

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ebola fever</td>
<td>• Chikungunya</td>
<td>• Human</td>
<td>• SARS-CoV-2</td>
</tr>
<tr>
<td>• Lassa fever</td>
<td>• HIV</td>
<td>papillomaviruses</td>
<td></td>
</tr>
<tr>
<td>• Marburg virus disease</td>
<td>• hMPV/PIV3</td>
<td>• Zika</td>
<td></td>
</tr>
<tr>
<td>• MERS-CoV</td>
<td>• Malaria</td>
<td>• Varicella Zoster Virus</td>
<td></td>
</tr>
<tr>
<td>• Yellow fever</td>
<td>• Nipah</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rabies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tuberculosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Most advanced clinical development stage of mRNA vaccines in development for the prevention of infectious diseases and virus-induced cancers.

**Focus: WHO mRNA vaccine technology transfer programme**

The COVID-19 crisis has emphasized the importance of equitable access to life-saving technologies. This has highlighted the unequal power dynamics between wealthy nations and LMICs, as well as the significant role that vaccines can play in enhancing global health security.

By early 2021, production and supply constraints, vaccine hoarding by wealthy countries, and companies prioritizing sales to governments that could pay the highest price had made it clear that LMICs would be pushed to the end of the queue for receiving COVID-19 vaccines.

---

1 [https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub](https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub)
While WHO continuously advocated for equitable sharing of vaccines through the COVAX Facility, and for sharing of technology through bilateral and multilateral agreements (for example through the COVID-19 Technology Access Pool), the initiative of establishing an mRNA technology transfer hub surfaced as a valid strategy to increase mRNA vaccine production capacity in under-served regions, and thus promote regional health security.

Announced on 21 June 2021, the objective of the technology transfer hub is to build capacity in LMICs to produce mRNA vaccines through a centre of excellence and training (the mRNA vaccine technology hub). The hub is located at Afrigen, Cape Town, South Africa, and will work with a network of technology recipients (spokes) in LMICs. The Hub at Afrigen will share technology and technical know-how with local producers. WHO and partners will bring training and financial support to build the necessary human capital for production know-how, quality control and product regulation, and will assist where needed with the necessary licenses.

The Hub and partners aim to create a global common good for the benefit of all by providing a range of services along the entire vaccine value chain. Recipients will be able to contribute to the global effort to increase local vaccine production capacity and may sign agreements with producers or develop vaccines locally.

8. Key findings

The success of mRNA vaccines for infectious diseases is largely based on our experience with COVID-19 vaccines, the only safe and efficacious preventive mRNA vaccine developed and approved for human use to date. Previous R&D work with mRNA was primarily focused on therapeutic uses which have different requirements and applications\(^{12,24}\). This is a significant limitation to our knowledge of the potential of mRNA vaccines for other infectious diseases and virus-induced cancers.

In this part of our report, we summarize findings and observations based on a desk and literature review of existing, in-development, and forward-looking applications of mRNA-based vaccines for infectious diseases and virus-induced cancers. We also draw on two public consultations conducted to gather feedback on the advantages and limitations of mRNA technology and determine how it could most benefit the development of vaccines for infectious diseases and virus-induced cancers (Annex 1).

The findings are grouped under three key themes:

- **Contributions of previous R&D for mRNA vaccines to COVID-19 vaccines success.**
- **Issues of equitable access arising from the use of the mRNA technology.**
- **Scientific and technological advantages and limitations to the use of the mRNA platform for vaccines.**

\[8.1. \text{Contributions of previous R&D for mRNA vaccines to COVID-19 vaccines success}\]

The Moderna and Pfizer-BioNTech COVID-19 vaccines provided the first demonstration that a safe and effective vaccine based on mRNA technology could be developed. The development of these vaccines was a complex and challenging process, and a host of factors contributed to their rapid development\(^{4,25}\): decades of research in virology, immunology, structural biology, and several other scientific and biomedical fields; meaningful community engagement (central to successful clinical testing); and combination of existing research, collaborations, supported by unprecedented funding and a global focus on finding a solution to a global health threat\(^{3,26}\).

- **Existing mRNA vaccine R&D:** the development of mRNA vaccines builds on at least four distinct lines of research in the fields of molecular biology, lipid chemistry, microbiology, and immunology, which made critical contributions to their development\(^4\). In the case of COVID-19, research for similar viruses, such as SARS and MERS\(^{27}\), but also HIV\(^{28}\) and work to develop cancer vaccines\(^{29,30}\) supported the rapid and efficient development of effective vaccines.
• **Research skills and infrastructure**: Vaccine researchers quickly pivoted to use their expertise gained during the development of other vaccines, and existing clinical research infrastructure, to support the rapid development of COVID-19 mRNA vaccines for cancer vaccines.31.

• **Collaboration**: The scale and impact of the COVID-19 pandemic triggered an unparalleled global response that required the collaboration of scientists, researchers, public health organizations and pharmaceutical companies worldwide.

• **Funding**: COVID-19 vaccine R&D was funded to unprecedented levels. For example, Operation Warp Speed led to over $18 billion of US public funds being invested in six vaccine candidates over two years, equivalent to more than 20 years of investment in HIV vaccine research.13.

• **Global focus**: The COVID-19 pandemic affected people worldwide, which led to a global focus on finding a solution to a global health threat. Beyond R&D, this global focus allowed for better collaboration, data sharing and a faster regulatory review and approval process.

However, several other COVID-19 vaccines were quickly developed using different platforms, emphasising the continued importance of traditional vaccine strategies, especially for infectious disease response.

Importantly, there was a strong scientific rationale based on existing data and knowledge that a COVID-19 vaccine was feasible. Notably, it was long known that antibodies binding to the epitopes of the avian coronavirus infectious bronchitis virus (IBV) spike protein could neutralise the virus and more recently that an mRNA vaccine is translated into an immunogenic protein that can elicit functional antibodies.39.

It is tempting to believe that future vaccines based on mRNA technology will be produced with similar ease and timeframe. However, the technology may not readily or rapidly produce vaccines for viruses that pose greater biological and clinical challenges and research may not be backed by the same degree of global commitment and attention. In addition, existing mRNA technology still faces several challenges and limitations discussed in more detail in this report that must be considered before using the platform more widely for vaccine R&D.

### 8.2. Issues of equitable access arising from the use of the mRNA technology

The remarkable accomplishment of developing COVID-19 vaccines at a fast pace illustrates the significant potential of human innovation, strong medical research capabilities, and private industry infrastructure, when backed by considerable public investment, spanning from basic research to substantial funding along the entire R&D and production process.

However, the benefits from this success were not distributed equally, highlighting and sometimes worsening social inequalities. Although 69.7% of the world population has received at least one dose of a COVID-19 vaccine since the WHO declared SARS-CoV-2 a pandemic on 11 March 2020, only 27.9% of people in low-income countries have received at least one dose three years later.40.

The COVID-19 pandemic has occurred against a backdrop of existing social and economic health inequality which led to a significant unequal burden of the disease in relation to race, ethnicity, and socioeconomic status. These inequalities were influenced and further exacerbated by legal, economic, social and demographic factors specific to the COVID-19 pandemic that also disrupted the process of fair vaccination and contributed to unequal access to vaccines, preventions and treatments when available. 41,42.

While mechanisms were put in place to ensure fair and equitable access through the ACT-Accelerator partnership launched by WHO and partners, the effort fell short of meeting its goals. As WHO Director-General Dr Tedros Adhanom Ghebreyesus said in April 2021, “There remains a shocking and expanding disparity in the global distribution of vaccines.”43
Several barriers to COVID-19 health products, including vaccines, have been identified in LMICs and include market forces, unavailability, inaccessibility, and unaffordability of the products, incongruent donors’ agenda and funding, and unreliable health and supply systems.44

The challenge of delivering vaccines on an unprecedented scale and as quickly as possible affected all type of vaccines. However, in the case of mRNA vaccines, intellectual property barriers and ultra-cold chain requirements were two important drivers of inequitable access and cost.

The mRNA platform is entangled in a web of intellectual property claims and patents that create legal barriers limiting equitable access and fair allocation and potentially impede future research and development. It is estimated that there are more than 80 patents surrounding mRNA COVID-19 vaccines covering all aspects of mRNA technology, from design to encapsulation and manufacturing methods and techniques.45

In addition, mRNA vaccines require ultra-cold storage and transportation temperatures, which can range from -20°C to -80°C, depending on the vaccine. These requirements made it more difficult for LMICs to access and distribute mRNA vaccines in several ways:

- Limited storage and transportation infrastructure: Many countries lack the necessary storage and transportation infrastructure to maintain ultra-low temperatures. There are a limited number of locations where the vaccines can be stored which in turn limit the distribution of the vaccines, especially in remote or rural areas. Further, ultra-low storage temperature and transportation require expensive equipment.
- Limited shelf life: Once thawed, mRNA vaccines have a short shelf life which can result in wastage if doses are not used within a certain time frame.

This has resulted in a situation where wealthier countries with better storage and transportation infrastructure were better able to purchase and distribute the vaccines, while LMICs struggled to access them.

8.3. Scientific and technological advantages and limitations to the use of the mRNA platform for vaccines

The use of nucleic acids to produce immunogen within the human body is a strategy distinct from conventional vaccine approaches that rely on directly administering antigens to elicit immune responses. Although several vaccines based on nucleic acids, namely DNA, have been developed, mRNA vaccines can present a number of advantages over recombinant and DNA vaccines and when compared to killed, live attenuated, and pathogen subunits.6,21

While mRNA technology offers notable benefits from an R&D perspective, current scientific and technological constraints can limit the development of vaccines.21,48–50. These may impede the full realisation of the benefits of the mRNA technology. Work is ongoing to address some of these challenges and we encourage more research to realise the full benefits of the mRNA platform for vaccines.

In this section we summarize some of the promising features and known limitations of mRNA vaccines (summarized in Box 3).

**Design and immunogenicity**

mRNA technology enables encoding multiple immunogens in one or more mRNA to target variants of a pathogen or multiple pathogens, all in a single formulation. The coding sequence can be modified rapidly to produce different immunogens in response to the emergence of variants. However, unlike killed or live attenuated pathogens used in many common vaccines, an mRNA vaccine requires the identification and
genetic characterization of the target pathogen to identify a suitable antigen and design an appropriate immunogen. This may be easier in some cases (virus envelop) than others (bacteria, fungi and protozoans) and can delay vaccine development.

mRNA vaccines can be delivered intramuscularly, subcutaneously or intradermally using conventional needle and syringe. Preclinical testing of intranasal delivery is under investigation. The mechanisms that induce immune responses associated with immunogenicity and reactogenicity remain largely unknown and may impact the safety of mRNA vaccines. mRNA vaccines have been shown to be highly translatable and studies with COVID-19 mRNA vaccines have provided evidence that mRNA vaccines trigger a strong innate and adaptive immune response and promote durable immunological memory. In addition mRNA have an inherent adjuvant effect. mRNA formulation plays a role in modulating efficacy; while some formulations can boost the immune response, others can be detrimental and have clinical side effects, as well as leading to reduced expression of the immunogen of interest.

The experience with COVID-19 vaccines has raised the question of the durability of protection conferred by mRNA vaccines. Waning immunity, the decline in antibody levels over time, occurs here over a period of several months after vaccination. This reduces vaccine efficacy against symptomatic infection, but protection against severe disease is not as reduced. However, mRNA vaccines for COVID-19 confer longer protection as compared to conventional vaccines against the disease.

The use of mRNA COVID-19 vaccines has also raised concerns about their effectiveness against variants after immunization, as well as breakthrough infections. Studies have shown reduced protection against COVID-19 variants in the absence of a booster immunization. Although COVID-19 mRNA vaccines have been approved for use in children aged six months to four years, applications for other pathogens will require assessing their efficacy in specific populations, including immunodepressed or immunocompromised people, children, the elderly, pregnant women and the malnourished.

Safety
mRNA vaccines are non-infectious as they encode only a very small portion of a pathogen. They do not integrate in the genome of the vaccinee and they are degraded through normal cellular processes. In addition, acquired immune response against mRNA vaccine is limited and they have a good safety profile. However, anaphylactic reactions potentially attributable to pre-existing antibodies against the PEGylated lipid used in LNPs have raised safety concerns. The effect is dose-dependent and may impede vaccine efficacy.

Manufacturing
mRNA manufacturing is simpler, with fewer steps in a cell-free environment, at relatively lower cost and in smaller manufacturing facilities. The process can be standardized and scaled up with relatively large quantities produced in small bioreactors, enabling rapid production and adaptation. For example, a facility with a single 5 L bioreactor can produce an estimated 1 billion vaccine doses per year at a drug product cost below USD 1 per dose.

However, mRNA vaccine manufacture requires skills and know-how that are not yet widely available, leading to the geographic concentration of manufacturing and distribution sites that contributed to limiting equitable access. Further downstream processing improvements are needed to address scalability and cost of production. Cost and availability of raw materials, for example enzymes and other reagents needed to synthesise mRNA, can limit production at scale.

Mass production, storage and distribution of COVID-19 vaccines have highlighted the challenges of manufacturing a range of vaccines, including mRNA vaccines that require ultra-low temperatures for storage and transport.
Altogether, mRNA technology has the potential to be a powerful tool and an accelerator for the development of complex vaccines, allowing for the rapid identification and screening of immunogens, refining or improving existing immunogens through iterative design and testing. It could also be used as a proof of concept to support the development of conventional vaccines, for example protein-based vaccines, and for conducting preclinical testing/screening as part of immunogen design.

However, current limitations suggest that replicating the achievements of COVID-19 vaccines using mRNA technology to develop vaccines for other pathogens may not be a simple task and that further basic research and various improvements are necessary as part of vaccine R&D.

**BOX 3: The power and limitations of mRNA technology**

- Speed and ease of design and redesign
- Speed and ease of manufacturing
- Biological and clinical safety
- Inherent adjuvant effect
- Cellular and humoral immune response
- Requires a known immunogen
- Durability and breadth of the immune response
- Formulation and potential side effects
- Manufacturing capacity and cost
- Cold chain requirements

9. Recommendations for advancing mRNA vaccine technology

Vaccines play an important role in the prevention, control, and elimination of infectious diseases. The successful development of COVID-19 vaccines has re-ignited interest in developing vaccines for a range of conditions and for pathogens with pandemic potential for which several clinical studies are ongoing (Annexe 3). As such, mRNA vaccines should be considered as an additional approach to existing vaccine development strategies. As with any other vaccine platform, the development of a vaccine needs to be assessed against unmet public health needs, existing prevention and treatment, and other public health interventions aiming at reducing the burden of infectious diseases and virus-induced cancers.

In the case of mRNA technology, three important questions must be answered:

- What pathogens should be considered for the development of an mRNA vaccine?
- What are the advantages of developing an mRNA vaccine over other vaccine strategies?
- What is the added value of an mRNA vaccine for the prevention, control and elimination of infectious diseases and virus-induced cancer?

Here we make a series of recommendations to WHO and constituencies within its Member States – governments, academia, industry, health advocacy groups, professional societies, and others – for assessing and advancing mRNA technology. We address these recommendations to WHO, vaccine developers and to countries at all levels of economic development so that the benefits of mRNA technology may be experienced globally.

Our recommendations are based on public reports, the experiences of our members and consultants and an expert workshop held in January 2023. Discussion and feedback gathered during these events highlighted: the potential of mRNA technology for research and public health; the intrinsic limitations of mRNA technology; the recognition of the value of mRNA technology for pandemic preparedness and response; and manufacturing, legal and social issues arising with the use of the technology.

Our recommendations are focused on the potential of mRNA technology to contribute to the development of vaccines against infectious diseases and virus-induced cancers. Funding for vaccine R&D, capability and capacity building for manufacturing and its operationalization, intellectual property management, and cost effectiveness are critical but distinct matters that this report highlights but does not aim to explore or address in detail.
We make recommendations that emphasise the need to:

- Develop a framework to assess the value of mRNA technology for the development of vaccines against infectious diseases and virus-induced cancers.
- Conduct more research to address the known and unknown limitations of mRNA technology.
- Ensure end-to-end equitable development and access to mRNA technology.

9.1. Assessing the value of mRNA technology in the context of a global vaccine strategy

The mRNA platform’s flexibility and versatility, which enables rapid product design and manufacturing, makes it a valuable tool for accelerating vaccine development. Although this report focuses on preventive vaccines, it is worth considering its use for therapeutic vaccines (Box 4). However, there is a need to ensure that the development and use of the platform is aligned with existing vaccine R&D strategies and that it is applied to the most relevant infectious diseases and virus-induced cancers.

For WHO, this means participating in and/or leading the evaluation of the added value of an mRNA vaccine within existing treatment and prevention and its competitive advantage over existing vaccines.

R1 – WHO should **emphasize the need to include thinking about mRNA technologies in strategies to control infectious diseases with vaccines**, recognizing the need to make existing and new vaccines accessible to all.

R2 – WHO should use existing structures and committees leading the organisation’s vaccine strategy **to conduct an annual assessment of vaccination strategies worldwide and provide regional advice** on the use of a particular technology, including mRNA. This should regularly evaluate the benefits and limitations (scientific and social) of different technologies, including whether mRNA technology can be used for new tasks, for example therapeutics and pandemic preparedness and response.

Considering the large number of pathogens for which an mRNA vaccine could be considered, and other vaccines platforms available, mechanisms and a framework are needed to assess the value of the mRNA technology for a particular pathogen and to position mRNA vaccine R&D in the context of a global vaccine strategy.

Such a framework should combine diverse criteria, qualitative and quantitative evidence, along with the experience and expertise of stakeholders and should address challenges related to the mRNA technology, the pathogens of interest, and the purpose of using the technology (for example, prevention, control, elimination, and pandemic preparedness and response). The framework should also enable regular reviews based on new evidence.

R3 – WHO is encouraged to use its convening power and leadership role in global public health to **develop a framework and identify indicators** to assess the feasibility and value of developing and investing in mRNA vaccines for infectious diseases and virus-induced cancers.

**BOX 4: Therapeutic application of mRNA vaccines for virus-induced cancers**

Although vaccines have traditionally been developed to protect people from acquiring a virus or getting sick, in some cases a therapeutic vaccine may complement an existing preventative strategy or treatment.

Human papillomavirus (HPV) infection, which is recognized as the main cause of cervical cancer and other malignant cancers, provides an example of the potential use of mRNA technology for therapeutic purposes. Although several effective preventive vaccines are available, HPV infections have not yet been fully brought under control, especially in resource-limited settings. Further, existing therapeutic strategies for some HPV-related cancers may be excessively harsh, leading to lifelong complications and a diminished quality of life for people.
Different types of HPV therapeutics vaccines are in development, but despite preclinical success, they have failed to deliver in clinical studies\(^69,70\). There is currently one preclinical study of an mRNA therapeutics vaccine that highlighted the potential of an mRNA vaccine for the treatment of HPV-driven cancers\(^71\).

There is value in exploring the potential of mRNA technology for the development of therapeutic vaccines when they can add to existing prevention and therapy.

9.1.1. Identifying pathogens of interest

Several disease-causing pathogens and infectious diseases could be considered for the development of an mRNA vaccine (Annexe 4). To support the needed prioritization effort, various approaches have been used and led to the development of pathogen and disease priority lists.

The majority of emerging infectious diseases in the past decades have been caused by zoonotic viruses and bacteria that spillover from animals to humans\(^72,73\). Among them, coronaviruses, haemorrhagic fever viruses, arboviruses, and influenza A viruses have caused significant epidemics globally. Animal to human zoonotic disease transmission can be prevented, in some cases, by the vaccination of animals and/or humans and there is value in developing vaccines for both when there is a known or potential spillover risk\(^74\). The development of a vaccine against West Nile virus provides an example of vaccine co-development. Other examples, including rabies, Rift Valley fever, and Hendra virus illustrate the potential of preventing zoonotic and emerging diseases by integrating veterinary and human medicine in a One Health approach\(^75\).

R4 - WHO should **actively engage in communication activities to disseminate, share, and promote** the work done by the organization towards addressing infectious diseases and other diseases for which a vaccine is relevant.

R5 - WHO should **use its convening power and leadership role in global public health to gather a broad and diverse range of experts in the field to facilitate the identification of pathogens of interest for the development of mRNA vaccines**. WHO should encourage product developers to explore the potential of mRNA vaccines for pathogens associated with antimicrobial resistance, virus-induced cancers and to limit the impact of zoonotic disease spillover.

To support the prioritization of pathogens of interest, our report identifies key questions that product developers should consider prior to initiating R&D (Box 5) and key indicators for assessing the value of mRNA technology for vaccines.

**BOX 6: Key questions for mRNA vaccines developers**

**How does an mRNA vaccine fit into existing prevention strategies?**

- Is the disease preventable?
- What are the current national and global responses to the disease (prevention and treatment)?
- What is the epidemic risk of the disease?
- Is a vaccine recommended for the disease (WHO R&D Blueprint, WHO neglected diseases)?
- Are there vaccines already in development or available (mRNA and others)?
- What is the advantage of an mRNA vaccine over other vaccines?
- What is the aim of the vaccination: prevention of transmission, infection, serious disease, death?
- Will a vaccine be cost effective?

**Is an mRNA vaccine feasible?**

- Is the genome of the pathogen available?
- What is the degree of genetic diversity of the pathogen?
• Are there known immunogens?
• Is the immune response characterized?
• Are there animal models?
• Are there known correlates of protection? Validated clinical endpoints?
• Are there existing data that suggest a vaccine is feasible?
• Will an adjuvant be needed?
• Can clinical testing be conducted (especially if outbreaks are episodic or localized)?
• What are the target populations?
• Are PPC and TTP available?

What are the expectations for an effective mRNA vaccine?
• What efficacy would be required?
• What regimen would be acceptable?
• Would an mRNA vaccine need to be multivalent?
• Would an mRNA vaccine need to be combined with one or more vaccines?
• Is durability a prerequisite? For example, are breadth and speed of manufacturing more important, especially for seasonal epidemics?

9.1.2. Key indicators

The identification of relevant indicators for assessing the value of mRNA technology for infectious diseases and virus-induced cancers is an important step toward designing an assessment framework. These will need to be consistent or complementary with ongoing work in this area and should reflect burden of disease, globally and regionally; biological and product development feasibility; and consider implementation and access. In the case of mRNA vaccines, three high-level indicators should play an important role in evaluating the potential value of mRNA technology:

• Burden of disease
• Vaccine feasibility
• Vaccine characteristics

Further, Product Preferred Characteristics (PPC) and Target Product Profile (TPP) developed by WHO to support vaccine development should also be considered.

Burden of disease

Burden of disease, which measures the impact of living with illness and injury and dying prematurely, is an important indicator when considering the application of mRNA technology. It is often measured using Quality-Adjusted Life-Years (QALY) and Disability-Adjusted Life-Years (DALY) but other methods and indicators can be used such as prevalence, incidence, mortality, morbidity, and financial cost of a disease.26

Many infectious diseases remain localised geographically or limited to specific populations. When assessing the value of mRNA technology against burden of disease, it will be important to determine the most relevant indicators in relation to affected populations and to consider regional versus global burden of diseases.

mRNA vaccine R&D may help draw attention to and increase research activities for neglected diseases with high regional DALYs. Therefore, pathogens should be assessed independently, and burden of burden of disease considered in the local context.

Vaccine Feasibility
Developing a vaccine is a significant, costly, long-term endeavour, and it is critical that WHO contributes to prioritizing research activities and investments. The ease of designing and testing a vaccine is often determined by the type and complexity of the target pathogen. Protozoans, as complex organisms, present the biggest challenges. Understanding the feasibility of a vaccine is a key step in an end-to-end R&D effort (Box 6).

**BOX 6: What makes developing a vaccine difficult?**

- Target antigens not known
- Pathogen complexity, diversity, variability
- Unknown correlate of protection
- Lack of relevant animal models
- Lack of optimized clinical immunologic assays
- Vaccine-associated enhanced disease (VAED) and immunopathogenesis
- Clinical testing difficult due to sporadic outbreaks, geographies, lack of infrastructure
- Complex immunization regimens needed
- Limited protection (low efficacy or short-term protection)

Two aspects of vaccine feasibility have been previously recognized:77:

- **Biological feasibility:** This considers progression of clinical development, existence of immunity from natural exposure, current understanding of mechanisms of immunity, known correlate of protection, and likelihood of a vaccine protecting against the most pathogenic strains.
- **Clinical feasibility:** This considers the existence of established animal and in-vitro models to facilitate vaccine development, the ease of clinical development and setting up of a late-stage clinical trial, and the availability of human challenge models if these are likely to be required.

Table 2 describes a potential approach to evaluate vaccine feasibility. While these criteria are not tailored to mRNA vaccines, mRNA vaccines may present greater challenges compared to traditional vaccinology approaches that do not require the identification of individual immunogens. For example, toxoid, whole inactivated, or attenuated vaccines which form the basis of vaccines against several infectious diseases.

<table>
<thead>
<tr>
<th>Feasible</th>
<th>Possible</th>
<th>Difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more immunogens have been identified or can be identified.</td>
<td>One or more immunogens can be identified.</td>
<td>No immunogens have been identified.</td>
</tr>
<tr>
<td>Animal models are available, enabling rapid pre-clinical testing.</td>
<td>Animal models can inform preclinical testing.</td>
<td>There are no animal models.</td>
</tr>
<tr>
<td>Clinical data support the efficacy of a vaccine.</td>
<td>Some clinical data support the development of a vaccine (in animal models, for example).</td>
<td>Clinical testing is difficult.</td>
</tr>
<tr>
<td>Target populations have been identified.</td>
<td>Target populations have been identified.</td>
<td></td>
</tr>
<tr>
<td>Clinical testing can be conducted using existing infrastructure.</td>
<td>Clinical testing is feasible although could be limited by the nature or localization of the disease.</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2: Evaluating vaccine feasibility using a composite set of criteria*

**Vaccine characteristics (efficacy, durability, breadth, and regimen)**
The experience with COVID-19 vaccines has highlighted the challenges of developing vaccines that provide durable protection against ancestral viruses but also against emerging variants. The efficacy of the different COVID-19 vaccines varies according to the platform used\textsuperscript{56,57}. Although mRNA COVID-19 vaccines have been shown to be the most efficacious and provided durable protection against severe disease, booster immunisations are required to counter waning immunity. Therefore, durability and breadth of the immune response against other pathogens will need to be assessed in addition to efficacy.

The immunization regimen may also differ in relation to the platform used. The need for multivalent vaccine and booster immunisations is an important aspect of a vaccine regimen and it is important to assess platforms against immunological requirements.

When considering vaccine efficacy, it will also be important to determine the purpose of developing a vaccine. Required efficacy may differ whether a vaccine is used to control an epidemic, to contribute to eliminating an endemic disease, to prevent infection, severe disease, hospitalisation and death, or as part of epidemic preparedness and response.

Table 3 summarises key criteria for assessing vaccine efficacy, durability, breadth, and regimen. Although not specific to mRNA vaccines, the experience with COVID-19 vaccines underlines the need to assess the performance of mRNA vaccines on their own merit and against other vaccine platforms.

<table>
<thead>
<tr>
<th>Optimal</th>
<th>Acceptable</th>
<th>Not suitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly efficacious against existing pathogen strains and emerging variants</td>
<td>Moderately efficacious against existing pathogen strains or emerging variants</td>
<td>Limited efficacy against pathogen strains or emerging variants</td>
</tr>
<tr>
<td>A multivalent vaccine is required.</td>
<td>A heterologous prime-boost vaccine regimen may be required.</td>
<td>A complex immunization regimen or repeated immunizations and boosters are required.</td>
</tr>
<tr>
<td>A vaccine could be rolled out broadly as part of an existing immunization agenda.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Evaluating vaccine efficacy and regimen using a composite set of criteria

9.1.3. Positioning mRNA vaccines within the existing R&D and global health ecosystems

It is essential that all those involved in product development bear in mind that the development of an mRNA vaccine is one aspect of the global response to infectious diseases, alongside other existing prevention strategies and treatments. It is necessary to integrate the efforts of all individuals, governments and organizations involved on a global scale.

Table 44 illustrates how to assess the potential of mRNA vaccines to add value within existing R&D and global health ecosystems. Although not specific to mRNA vaccines, it emphasises the need to carefully consider the position of an mRNA vaccine within existing R&D and global health ecosystems.
Few effective vaccines available.  
Complex or limited manufacturing, costly vaccine.  
Active vaccine R&D.  
needed to control the epidemic.  
Transmission/acquisition dynamics are not well described.  
Effective vaccines available.

<table>
<thead>
<tr>
<th>Few effective vaccines available.</th>
<th>needed to control the epidemic.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex or limited manufacturing, costly vaccine.</td>
<td>Transmission/acquisition dynamics are not well described.</td>
</tr>
<tr>
<td>Active vaccine R&amp;D.</td>
<td>Effective vaccines available.</td>
</tr>
</tbody>
</table>

Table 4: Potential for mRNA vaccines R&D to add value within existing R&D and global health ecosystems.

When an mRNA vaccine is deemed to be advantageous, strong advocacy campaigns will be required to support its development (for example through the mRNA vaccine technology transfer programme) especially in LMICs, because of significant investment costs and complexities.

The mRNA technology used to respond to the COVID-19 pandemic has established the credibility of the approach. WHO should encourage vaccine developers to consider the use of the mRNA technology as part of pandemic preparedness and response as this is an opportunity to support technology transfer, including know-how and training to LMICs.

However, the application of mRNA technology to pandemic preparedness and response should not unduly take precedence over, or be a substitute for, other pandemic preparedness responses and it will be paramount to ensure that vaccines will be accessible to all those who need them. Further, investment in the technology should consider its use between pandemics.

R6 - As part of its activities in the field of infectious diseases, WHO should use its convening power and leadership role in global public health to engage with all those involved in the response to epidemics, pandemics and high-burden diseases to ensure that mRNA vaccine R&D is integrated into the global R&D ecosystems and global health ecosystems.

9.1.4. Assessing Impact

The impact of a vaccine will need to be measured against existing prevention, treatment, and other public health interventions. The use of mRNA technology should be aligned with national and global health agendas, as well as those of non-governmental organizations and the pharmaceutical industry, while identifying gaps in these agendas.

Table 5S provides an overview of criteria to assess the potential impact of an mRNA vaccine. Although not tailored specifically to mRNA vaccines these are reminders that a vaccine needs to be developed with the end game in mind. This is vital in fast-changing prevention and treatment landscapes.

Remarkably, mRNA may also contribute to technological innovation and the refinement and enhancement of other vaccine strategies. The potential for success could also trigger interest in vaccine R&D at the discovery stage, for example to identify immunogens for further vaccine development. An mRNA vaccine could also make an important contribution to pandemic preparedness and response, and to meeting an unmet need.

<table>
<thead>
<tr>
<th>High Impact</th>
<th>Medium Impact</th>
<th>Low Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significantly lower the risk of acquisition, the severity of the disease or the DALYs.</td>
<td>Complement existing public health interventions. Contribute to disease control.</td>
<td>An vaccine would not significantly contribute to lower acquisition or severity of the disease but may add to</td>
</tr>
</tbody>
</table>
Amplifying RNA vaccine against SARS longevity, replicating mRNA, such as higher and longer expression of the immunogen, platform GEMOVAC formulation. Preclinical studies are ongoing to develop thermostable mRNA vaccines stable vaccine tech.

Epidemic Preparedness Innovations requirements to improve global access to vaccines and therapeutic use. Research is already ongoing to vaccine Other three of which are cancers identified. As mRNA vaccine technology was being developed for SARS protection at individual and population level scepticism about its efficacy contributed to a persistent vaccine hesitancy worldwide. Even though vaccine acceptance improved slightly during the course of the pandemic, alongside vaccine development and roll out, a lack of trust in COVID-19 vaccine safety and science and scepticism about its efficacy contributed to a persistent vaccine hesitancy worldwide, limiting effective protection at individual and population level.

R7 - WHO should use its reputability and trustworthiness to improve trust in research and science and address vaccine hesitancy to improve current and future vaccine uptake, with the goal of improving public health.

9.2. Biological and technological improvements

As mRNA vaccine technology was being developed for SARS-CoV-2, limitations and improvements were identified that are specific to this platform and for vaccines against infectious diseases and virus-induced cancers. Our report identifies several areas of research that would lead to improvements of the technology, three of which are of critical importance:

- Increasing the durability of the protection conferred by mRNA vaccines.
- Extending the breadth of the immune response to ensure protection against diverse pathogen strains and variants, particularly for viruses.
- Improving the cold-chain requirements to develop temperature-stable vaccines for use in LMICs.

Other areas of research are related to improving the effectiveness, safety and/or ease of use of a mRNA vaccine or to technological advancements to manufacture mRNA. These include:

- Improving safety by removing components known to cause side effects.
- Developing various vaccine administration routes.
- Modifying the mRNA molecule to reduce its innate immunogenicity and toxicity.
- Developing diverse vaccine formulations, including the use of adjuvants.
- Improving the production processes to support manufacturing at scale and commercialization.

Research is already ongoing to advance the mRNA technology in several of these areas for both preventive and therapeutic use. The need to improve thermostability and minimise the complex cold-chain requirements to improve global access to vaccines is recognised broadly. Notably, the Coalition for Epidemic Preparedness Innovations (CEPI) has launched a $17.5 million call for proposals to develop heat-stable vaccine technology for use against epidemic and pandemic threats.

Preclinical studies are ongoing to develop thermostable mRNA vaccines and two thermostable formulations have been licenced for emergency use, AWcorna in China, Mexico, Nepal and Indonesia, and GEMOVAC-19 in India. Further improvements may arise from the development of other types of mRNA platforms like self-amplifying, trans-amplifying and circular mRNA that have advantages over non-replicating mRNA, such as higher and longer expression of the immunogen, better stability, increased longevity, and reduced immunogenicity. For example, a preclinical study in mice showed that a self-amplifying RNA vaccine against SARS-CoV-2, stable at room temperature and formulated with a

Table 5: Impact assessment criteria for an vaccine.

As part of the impact assessment, it will be important to address the issue of vaccine hesitancy. The swift development of COVID-19 vaccines was accompanied by a significant level of vaccine hesitancy that contributed to inequitable access. As a new technology, mRNA vaccines frequently raised safety and efficacy concerns. Despite strong recommendations from public health organizations, including WHO, vaccine hesitancy was, and remains, an obstacle to the successful roll out and uptake of COVID-19 vaccines. Even though vaccine acceptance improved slightly during the course of the pandemic, along with vaccine development and roll out, a lack of trust in COVID-19 vaccine safety and science and scepticism about its efficacy contributed to a persistent vaccine hesitancy worldwide, limiting effective protection at individual and population level.

R7 - WHO should use its reputability and trustworthiness to improve trust in research and science and address vaccine hesitancy to improve current and future vaccine uptake, with the goal of improving public health.

9.2. Biological and technological improvements

As mRNA vaccine technology was being developed for SARS-CoV-2, limitations and improvements were identified that are specific to this platform and for vaccines against infectious diseases and virus-induced cancers. Our report identifies several areas of research that would lead to improvements of the technology, three of which are of critical importance:

- Increasing the durability of the protection conferred by mRNA vaccines.
- Extending the breadth of the immune response to ensure protection against diverse pathogen strains and variants, particularly for viruses.
- Improving the cold-chain requirements to develop temperature-stable vaccines for use in LMICs.

Other areas of research are related to improving the effectiveness, safety and/or ease of use of a mRNA vaccine or to technological advancements to manufacture mRNA. These include:

- Improving safety by removing components known to cause side effects.
- Developing various vaccine administration routes.
- Modifying the mRNA molecule to reduce its innate immunogenicity and toxicity.
- Developing diverse vaccine formulations, including the use of adjuvants.
- Improving the production processes to support manufacturing at scale and commercialization.

Research is already ongoing to advance the mRNA technology in several of these areas for both preventive and therapeutic use. The need to improve thermostability and minimise the complex cold-chain requirements to improve global access to vaccines is recognised broadly. Notably, the Coalition for Epidemic Preparedness Innovations (CEPI) has launched a $17.5 million call for proposals to develop heat-stable vaccine technology for use against epidemic and pandemic threats.

Preclinical studies are ongoing to develop thermostable mRNA vaccines and two thermostable formulations have been licenced for emergency use, AWcorna in China, Mexico, Nepal and Indonesia, and GEMOVAC-19 in India. Further improvements may arise from the development of other types of mRNA platforms like self-amplifying, trans-amplifying and circular mRNA that have advantages over non-replicating mRNA, such as higher and longer expression of the immunogen, better stability, increased longevity, and reduced immunogenicity. For example, a preclinical study in mice showed that a self-amplifying RNA vaccine against SARS-CoV-2, stable at room temperature and formulated with a
nanostructured lipid carrier, can induce strong humoral immunity against the Alpha, Beta, and Delta variants of concern. This work that combined the development of a different type of mRNA and formulation shows that the mRNA technology can be improved and potentially lead to a wider access to RNA vaccine for the current pandemic and the development of future mRNA vaccines.

R8 - WHO should take a leading role in identifying biological and technological improvements specific to the mRNA technology and then specifically for pathogens of interest.

R9 - WHO should use its leadership role in global public health to advocate for and support ongoing investment and biomedical research to improve mRNA technology (especially thermostability) including the development of other mRNA platforms such as self-amplifying, trans-amplifying and circular mRNA.

9.3. End-to-end equitable development of the mRNA technology

Experience with COVID-19 has shown that the development of a new technology can increase health inequality. Therefore, ensuring equitable access is paramount to the development and use of mRNA technology, and effort to ensure equitable access should take place alongside research and development.

This will require engaging with commercial and non-commercial organizations to address issues of intellectual property that prevent and slow down the development of and access to the technology. WHO should engage with organizations and individuals with the knowledge, resources, and influence to serve as advocates to make the development, use, benefits, and limitations of the mRNA technology more widely known and accessible. Altogether, they should encourage others to join advocacy campaigns as part of efforts to bring the benefits of the mRNA technology to everyone in an effective, ethical, and equitable manner.

The benefits and limitations of the mRNA technology should be communicated clearly and in a compelling fashion, providing balanced presentations that include accounts of difficulties and examples of specific successes, as well as information based on, and thus applicable to, local needs and priorities, especially in LMICs. Collaborations and partnerships are important for sharing technological and technical expertise that will facilitate the development, use of, and access to mRNA technology in WHO Member States. In advocating for the development and uses of mRNA technology, WHO should consider all stakeholders, including the lay public, governments, businesses, academia, and professional organizations. Public education and engagement can create an informed basis for trust, encouraging participation in research and public health initiatives.

The development and use of mRNA technology could build on the experience of the Access to COVID-19 Tools (ACT) Accelerator launched by WHO and partners in response to the COVID-19 pandemic with the aim of accelerating the development and production of, and equitable access to, COVID-19 diagnostics, therapeutics, and vaccines.

A rapid, forward-looking evaluation exercise of the partnership was carried out between 11 July and 10 October 2022. Its main objective was to learn from ACT-Accelerator experiences and identify key lessons learnt for future pandemic preparedness and response. WHO is encouraged to review the findings of the rapid evaluation and, through its convening power, facilitate the application of the lessons learned to the future development of mRNA vaccines.

R10 - WHO should continue to work with Member States, product developers, funders, global health institutions, and civil society organizations to encourage investing in the end-to-end equitable development of the technology.

R11 - WHO should use its leadership role in global public health to advocate for and support socio-political and economic research to solve the problems of equity.
R12 - WHO is encouraged to review and build on the experience of the ACT-Accelerator partnership and expand its mission to the development of vaccines against other infectious diseases and to contribute to pandemic preparedness.
10. References


63. EMA. Safety of COVID-19 vaccines. European Medicines Agency

64. Bigini, P. et al. The role and impact of polyethylene glycol on anaphylactic reactions to COVID-19 nano-

65. Sellaturay, P., Nasser, S., Islam, S., Gurugama, P. & Ewan, P. W. Polyethylene glycol (PEG) is a cause of
anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. Clinical & Experimental Allergy 51, 861–
863 (2021).

66. Kozma, G. T., Shimizu, T., Ishida, T. & Szebeni, J. Anti-PEG antibodies: Properties, formation, testing and
role in adverse immune reactions to PEGylated nano-biopharmaceuticals. Adv Drug Deliv Rev 154–155,
163–175 (2020).

67. Kis, Z., Kontoravdi, C., Dey, A. K., Shattock, R. & Shah, N. Rapid development and deployment of high-

Pharmaceutical Policy and Practice 15, 16 (2022).

69. Mo, Y. et al. Prophylactic and Therapeutic HPV Vaccines: Current Scenario and Perspectives. Frontiers
in Cellular and Infection Microbiology 12, (2022).

(Kaunas) 58, 860 (2022).

71. Grunwitz, C. et al. HPV16 RNA-LPX vaccine mediates complete regression of aggressively growing HPV-
positive mouse tumors and establishes protective T cell memory. OncoImmunology 8, e1629259
(2019).

72. Weiss, R. A. & Sankaran, N. Emergence of epidemic diseases: zoonoses and other origins. Fac Rev 11, 2
(2022).

73. Judson, S. D. & Rabinowitz, P. M. Zoonoses and global epidemics. Current Opinion in Infectious Diseases
34, 385 (2021).

74. Carpenter, A. et al. Vaccine Preventable Zoonotic Diseases: Challenges and Opportunities for Public
Health Progress. Vaccines (Basel) 10, 993 (2022).

75. Monath, T. P. Vaccines against diseases transmitted from animals to humans: A one health paradigm.


77. Frost, I. et al. The role of bacterial vaccines in the fight against antimicrobial resistance: an analysis of
the preclinical and clinical development pipeline. The Lancet Microbe (2022) doi:10.1016/S2666-
5247(22)00303-2.


80. Betsch, C. et al. A call for immediate action to increase COVID-19 vaccination uptake to prepare for the

81. Lazarus, J. V. et al. Revisiting COVID-19 vaccine hesitancy around the world using data from 23

82. Olivera Mesa, D. et al. Modelling the impact of vaccine hesitancy in prolonging the need for Non-


Annexe 1: Methodology, consultation, and participants

Conflict of interest. Each Science Council member has completed a WHO declaration of interest form and his/her appointment by the WHO Director-General as a Council member has been subjected to evaluation for conflicts of interest by the WHO Secretariat.

Selection of topic. During an in-person meeting in July 2022 in Geneva, the WHO Science Council agreed to conduct an independent review of the uses of mRNA technology (and other nucleic-acid based approaches) and their potential to improve the global health R&D landscape. During the project kick-off meeting, a subgroup of the WHO Science Council, it was agreed that as a first step toward evaluating mRNA for improving global health, the WHO Science Council will review the potential for success and impact of new and emerging applications of the technology for the prevention of infectious diseases.

Desk review

To support the work of the WHO Science Council, WHO commissioned desk and literature review of existing, developing, and prospective applications of RNA-based vaccines.

Expert consultation

An expert consultation was conducted on 10 January 2023 bringing together diverse stakeholders to examine the most promising directions for RNA technology and identify potential concerns that could limit a scalable and equitable access.

Participants

<table>
<thead>
<tr>
<th>First name</th>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salim</td>
<td>Abdool Karim</td>
<td>Centre for the AIDS Programme of Research in South Africa (CAPRISA)</td>
</tr>
<tr>
<td>Brigitte</td>
<td>Autran</td>
<td>Comité de Veille et d’Anticipation des Risques Sanitaires (COVARS)</td>
</tr>
<tr>
<td>Hanan</td>
<td>Balkhy</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>R.</td>
<td>Bäuerle</td>
<td>Agency</td>
</tr>
<tr>
<td>Sophie</td>
<td>Biernaux</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>Karin</td>
<td>Bok</td>
<td>Vaccine Research Center (VRC) at the National Institutes of Health (NIH)</td>
</tr>
<tr>
<td>Véronique</td>
<td>Bruniquel</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>Cristina</td>
<td>Bruno</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>Mireille</td>
<td>Centlivre</td>
<td>Vaccine Research Institute (VRI)</td>
</tr>
<tr>
<td>Christopher</td>
<td>Chadwick</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>Kizzmekia</td>
<td>Corbett</td>
<td>Harvard T.H. Chan School of Public Health</td>
</tr>
<tr>
<td>Michel</td>
<td>De Wilde</td>
<td>MDW Consultant, LLC</td>
</tr>
<tr>
<td>Eric</td>
<td>D’Ortenzio</td>
<td>ANRS</td>
</tr>
<tr>
<td>Lea</td>
<td>Druet</td>
<td>Institut national de la santé et de la recherche médicale (INSERM)</td>
</tr>
<tr>
<td>Gilles</td>
<td>Forte</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>Birgitte</td>
<td>Giersing</td>
<td>World Health Organization (WHO)</td>
</tr>
<tr>
<td>Charles</td>
<td>Gore</td>
<td>Medicines Patent Pool (MPP)</td>
</tr>
<tr>
<td>Glenda</td>
<td>Gray</td>
<td>South African Medical Research Council (SAMRC)</td>
</tr>
<tr>
<td>Barton</td>
<td>Haynes</td>
<td>Duke University</td>
</tr>
<tr>
<td>Edith</td>
<td>Heard</td>
<td>European Molecular Biology Laboratory (EMBL)</td>
</tr>
<tr>
<td>Ike</td>
<td>James</td>
<td>Medicines Patent Pool (MPP)</td>
</tr>
<tr>
<td>Adeeaba</td>
<td>Kamarulzaman</td>
<td>University of Malaya</td>
</tr>
<tr>
<td>Wiweka</td>
<td>Kaszubska</td>
<td>Medicines for Malaria Venture (MMV)</td>
</tr>
<tr>
<td>Name</td>
<td>Organization</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Jerome Kim</td>
<td>International Vaccine Institute (IVI)</td>
<td></td>
</tr>
<tr>
<td>Odile Launay</td>
<td>Université de Paris</td>
<td></td>
</tr>
<tr>
<td>Jean-Daniel Lelievre</td>
<td>Institut national de la santé et de la recherche médicale (INSERM)</td>
<td></td>
</tr>
<tr>
<td>Yuhua Li</td>
<td>National Institute for Food and Drug Control</td>
<td></td>
</tr>
<tr>
<td>Morena Makhoana</td>
<td>Biovac</td>
<td></td>
</tr>
<tr>
<td>Ziad Memish</td>
<td>King Saud Medical City</td>
<td></td>
</tr>
<tr>
<td>Joerg Moehrle</td>
<td>Medicines for Malaria Venture</td>
<td></td>
</tr>
<tr>
<td>Monica Moschioni</td>
<td>Medicines Patent Pool (MPP)</td>
<td></td>
</tr>
<tr>
<td>Genevieve Nguyen</td>
<td>National Institute of Health and Medical Research</td>
<td></td>
</tr>
<tr>
<td>Martin Nicholson</td>
<td>World Health Organization (WHO)</td>
<td></td>
</tr>
<tr>
<td>Martina Ochs</td>
<td>Coalition for Epidemic Preparedness Innovations (CEPI)</td>
<td></td>
</tr>
<tr>
<td>Inmaculada Ortega Perez</td>
<td>ANRS</td>
<td>Maladies infectieuses émergentes</td>
</tr>
<tr>
<td>Jean Pape</td>
<td>Centres GESKIO</td>
<td></td>
</tr>
<tr>
<td>Ralf Piotrowski</td>
<td>Center for Pandemic Vaccines and Therapeutics (ZEPAI) / Paul-Ehrlich-Institute</td>
<td></td>
</tr>
<tr>
<td>Thidar Pyone</td>
<td>World Health Organization (WHO)</td>
<td></td>
</tr>
<tr>
<td>Firdausi Qadri</td>
<td>International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)</td>
<td></td>
</tr>
<tr>
<td>John Reeder</td>
<td>World Health Organization (WHO)</td>
<td></td>
</tr>
<tr>
<td>Helen Rees</td>
<td>Wits Reproductive Health and HIV Institute (Wits RHI)</td>
<td></td>
</tr>
<tr>
<td>Sebastian Rosigkeit</td>
<td>Paul-Ehrlich-Institute</td>
<td></td>
</tr>
<tr>
<td>Anna Laura Ross</td>
<td>World Health Organization (WHO)</td>
<td></td>
</tr>
<tr>
<td>Fatima Serhan</td>
<td>World Health Organization (WHO)</td>
<td></td>
</tr>
<tr>
<td>Robin Shattock</td>
<td>Imperial College London</td>
<td></td>
</tr>
<tr>
<td>Jennifer Short</td>
<td>Monash University</td>
<td></td>
</tr>
<tr>
<td>Abla Sibai</td>
<td>American University of Beirut (AUB)</td>
<td></td>
</tr>
<tr>
<td>Yves Souteyrand</td>
<td>ANRS</td>
<td>Maladies infectieuses émergentes</td>
</tr>
<tr>
<td>Erin Sparrow</td>
<td>World Health Organization (WHO)</td>
<td></td>
</tr>
<tr>
<td>Petro Terblanche</td>
<td>Afrigen Biologics</td>
<td></td>
</tr>
<tr>
<td>Nadia Tornieporth</td>
<td>Coalition for Epidemic Preparedness Innovations (CEPI)</td>
<td></td>
</tr>
<tr>
<td>Cesar Victoria</td>
<td>Federal University of Pelotas</td>
<td></td>
</tr>
<tr>
<td>Yazdan Yazdanpanah</td>
<td>ANRS</td>
<td>Maladies infectieuses émergentes</td>
</tr>
<tr>
<td>Yongyuth Yuthavong</td>
<td>National Science and Technology Development Agency</td>
<td></td>
</tr>
</tbody>
</table>

Public consultation process
Annexe 2: Virus-induced cancers.

Several viruses have been linked with a higher risk of developing cancers or identified as causal agents of cancers. Approximately 10% of cancer cases worldwide are thought to be caused by viruses^{89,90}. Table 2 describes the seven most common viruses associated with cancers, available prevention against viral infection and existing cancer treatment.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Cancer</th>
<th>Risk</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human papillomaviruses (for example HPV16 and 18)</td>
<td>Cervix, penis, anus, vagina, vulva, mouth, throat</td>
<td>High</td>
<td>Vaccine</td>
<td>No</td>
</tr>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Nasopharynx, Burkitt lymphoma, Hodgkin lymphoma, stomach cancer</td>
<td>Low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Hepatocellular carcinoma, non-Hodgkin lymphoma</td>
<td>High</td>
<td>Risk reduction strategy</td>
<td>Antiviral, interferon</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Hepatocellular carcinoma, non-Hodgkin lymphoma</td>
<td>High</td>
<td>Risk reduction strategy</td>
<td>Yes</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Increased risk of getting several types of cancer, including Kaposi sarcoma, cervical cancer, certain kinds of non-Hodgkin lymphoma, anal cancer, Hodgkin disease, lung cancer, cancers of the mouth and throat, some types of skin cancer, liver cancer</td>
<td>Low to medium Reduced in individuals on effective treatment</td>
<td>Risk reduction strategy Antivirals</td>
<td>Antivirals</td>
</tr>
<tr>
<td>Human herpes virus 8 (HHV-8)</td>
<td>Kaposi sarcoma, primary effusion lymphoma, Castleman disease</td>
<td>Low in healthy individuals</td>
<td>Risk reduction strategy</td>
<td>Topical, surgery, radiotherapy, chemotherapy, immunotherapy</td>
</tr>
<tr>
<td>Human T-lymphotrophic virus-1 (HTLV-1)</td>
<td>Lymphocytic leukaemia, non-Hodgkin lymphoma</td>
<td>Low in Europe and North America to 25% in Japan</td>
<td>Risk reduction strategy</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Merkel cell polyomavirus (MCV)</td>
<td>Merkel cell carcinoma</td>
<td>Low</td>
<td>Limit exposure to UV rays</td>
<td>Surgery, radiotherapy, chemotherapy, immunotherapy</td>
</tr>
</tbody>
</table>

Table 2: Viruses that are associated with cancer. Note: HIV infection predisposes to cancer but does not seem to induce cancer directly.
Annexe 3: Past and ongoing mRNA vaccine trials

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Type</th>
<th>Developers</th>
<th>Development stage</th>
<th>Candidate mRNA</th>
<th>Trial registration</th>
<th>Completion date</th>
<th>Other vaccines in development - most advanced development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya Virus</td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 1</td>
<td>VAL-181388 mRNA-1944</td>
<td>NCT03325075⁹¹</td>
<td>1 November 2019 7 June 2021</td>
<td>Phase 2: Recombinant (MV, ChAdOx), inactivated (BBV87) Phase 3: Live attenuated (VLA1553), VLP (PXV0317)</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 3</td>
<td>mRNA-1647</td>
<td>NCT05085366</td>
<td>29 July 2025</td>
<td>Phase 2: Protein, peptides, recombinant (MVA, ALVAC) Phase 3: DNA</td>
</tr>
<tr>
<td>Ebola</td>
<td>Virus</td>
<td>Moderna</td>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
<td>Ervebo (Food and Drug Administration, FDA, approved, WHO Pre-Qualification) Zabdeno-and-Mvabea (EMA approved)</td>
</tr>
<tr>
<td>HIV</td>
<td>Virus</td>
<td>Moderna/IAVI</td>
<td>Phase 1</td>
<td>mRNA-1644 mRNA-1644v2-Core</td>
<td>NCT05414786 NCT05001373</td>
<td>30 June 2023 11 April 2023</td>
<td>Phase 3: Recombinant (Ad26, MVA), DNA, protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NIAID</td>
<td>Phase 1</td>
<td>BG505 MD39.3, BG505 MD39.3 gp151</td>
<td>NCT05217641</td>
<td>13 October 2023</td>
<td></td>
</tr>
<tr>
<td>hMPV/PIV3</td>
<td></td>
<td>Moderna</td>
<td>Phase 1</td>
<td>mRNA-1653</td>
<td>NCT03392389⁹²</td>
<td>29 July 2019 31 March 2023</td>
<td></td>
</tr>
<tr>
<td>Human papillomaviruses</td>
<td>Virus</td>
<td>pHion</td>
<td>Preclinical</td>
<td>Therapeutic vaccine</td>
<td></td>
<td></td>
<td>Gardasil (MSD) and Cervarix (GSK)</td>
</tr>
<tr>
<td>(HPV)</td>
<td></td>
<td>BioNTech SE</td>
<td>Phase 2</td>
<td>BNT113 BNT163</td>
<td>NCT04534205⁹³ NCT05432583</td>
<td>May 2028 June 2025</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CureVac</td>
<td>Phase 1</td>
<td>qIRV (22/23)</td>
<td>NCT05596734</td>
<td>4 June 2024</td>
<td>Several vaccines approved in 2022</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CureVac/GSK</td>
<td>Phase 1</td>
<td>CVSQIV</td>
<td>NCT05252338</td>
<td>November 2022</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderna</td>
<td>Phase 1</td>
<td>VAL-506440 mRNA-1010</td>
<td>NCT03076385⁹⁴ NCT03345043 NCT05566639</td>
<td>October 2018 13 August 2018 31 March 2024</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pfizer</td>
<td>Phase 1/2</td>
<td>mIRV, bIRV, qIRV saRNA</td>
<td>NCT05052697 NCT05540522 NCT05227001</td>
<td>25 July 2023 1 August 2023 1 August 2023</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Viral</td>
<td>Phase</td>
<td>Candidate</td>
<td>Study ID</td>
<td>Start Date</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Lassa</td>
<td>Virus</td>
<td>Preclinical</td>
<td>mRNA vaccine</td>
<td>NCT05624606, NCT05553301, NCT05650554, NCT05426174</td>
<td>30 January 2024, 19 January 2024, 14 February 2024, 30 November 2023</td>
<td>Preclinical: Recombinant, DNA, replicon particles, other vectors Phase 1: recombinant (VSV, MV)</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>Protozoan</td>
<td>Phase 1</td>
<td>BNT165b1</td>
<td>NCT05581641</td>
<td>September 2024</td>
<td>RTS, S/AS01B WHO recommended Phase: 1/2b R21/Matrix-M</td>
<td></td>
</tr>
<tr>
<td>Marburg virus disease</td>
<td>Virus</td>
<td>Preclinical</td>
<td>CEPI Imperial College London</td>
<td></td>
<td></td>
<td>Phase 1: DNA, recombinant (ChAd3, MVA)</td>
<td></td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Virus</td>
<td>Discovery</td>
<td></td>
<td></td>
<td></td>
<td>Phase 1: Recombinant (ChAdOx1 MVA, Ad5), DNA</td>
<td></td>
</tr>
<tr>
<td>Nipah</td>
<td>Virus</td>
<td>Phase 1</td>
<td>mRNA-1215</td>
<td>NCT05398796</td>
<td>24 June 2024</td>
<td>Phase 1: Recombinant (VSV), protein</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td>Virus</td>
<td>Phase 1</td>
<td>CV7202</td>
<td>NCT03713086</td>
<td>23 November 2021</td>
<td>27 Licensed vaccines. Several candidates in development</td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Virus</td>
<td>Phase 3</td>
<td>mRNA-1345</td>
<td>NCT05330975</td>
<td>10 May 2023</td>
<td>Passive immunization: Beyfortus (AstraZeneca/Sanofi), Synagis (Biovitrum)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 1</td>
<td>CL-0059 or CL-0137</td>
<td>NCT05639894</td>
<td>2 April 2025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Virus</td>
<td>Phase 4</td>
<td></td>
<td></td>
<td></td>
<td>11 vaccines have received WHO emergency use listing (EUL)</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Bacteria</td>
<td>Phase 1</td>
<td>BNT164a1, BNT164b1</td>
<td>NCT05537038, NCT05547464</td>
<td>December 2025, April 2025</td>
<td>BCG, 16 candidates under active clinical development</td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Virus</td>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
<td>Stamaril (Sanofi Pasteur)</td>
<td></td>
</tr>
<tr>
<td>Varicella Zoster Virus</td>
<td>Virus</td>
<td>Phase 2</td>
<td>V2V modRNA</td>
<td>NCT05703607</td>
<td>July 9, 2025</td>
<td>Several licensed vaccines</td>
<td></td>
</tr>
<tr>
<td>Zika</td>
<td>Virus</td>
<td>Phase 1</td>
<td>mRNA-1325</td>
<td>NCT04064905, NCT03014089, NCT04917861</td>
<td>22 March 2021, July 2019, 26 April 2024</td>
<td>Phase 1: Live attenuated, Recombinant (ChAdOx1, MV), antibody Phase 2: Inactivated, DNA</td>
<td></td>
</tr>
</tbody>
</table>
Annexe 4: Pathogens priority lists

WHO pathogens priority lists

The WHO R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. Its aim is to fast track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large-scale crises.

The R&D Blueprint works based on a list of identified priority diseases. These are diseases that pose a public health risk because of their epidemic potential and for which there are no, or insufficient, countermeasures.

For each of these diseases, R&D roadmaps and, where relevant, target product profiles (TPPs) and generic protocols are developed through broad and open consultations with leading experts and other stakeholders. In addition, efforts to strengthen national regulatory and ethics bodies to respond to public health emergencies are being implemented.

- COVID-19
- Crimean-Congo haemorrhagic fever
- Ebola virus disease and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome
- Nipah and henipaviral diseases
- Rift Valley fever
- Zika
- “Disease X”

Source: https://www.who.int/teams/blueprint/who-r-and-d-blueprint-for-epidemics

WHO neglected tropical diseases (NTDs) are a diverse group of 20 conditions that are mainly prevalent in tropical areas, where they mostly affect impoverished communities and disproportionately affect women and children. These diseases have devastating health, social and economic consequences for more than one billion people.

- Buruli ulcer
- Chagas disease
- Dengue and chikungunya
- Dracunculiasis
- Echinococcosis
- Foodborne trematodiases
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Other deep mycoses
- Mycetoma, chromoblastomycosis
- Onchocerciasis
- Rabies
- Scabies and other ectoparasitoses
- Schistosomiasis

Source: https://www.who.int/health-topics/neglected-tropical-diseases

Partnerships for African Vaccine Manufacturing (PAVM) Framework for Action

The PAVM conducted a qualitative assessment that led to the identification of 22 diseases broken down as:

- Ten legacy diseases, which typically have high volumes of vaccines available, primarily produced by Indian manufacturer with low unit prices. These vaccines can offer economy of scale if produced on the African continent.
- Six expanding diseases, which typically do not yet have commoditized vaccines, or have vaccines with relatively higher prices, with some products still in development that are not yet licensed.
number of diseases endemic to Africa are included, and the development of vaccines against these
diseases is of high importance for the African continent.

- Six outbreak diseases, which typically have vaccines with unpredictable demand driven by
outbreaks, often with higher prices due to lower scale and urgent need. These diseases are
prioritized to quickly meet the required need for vaccines in times of outbreaks.

<table>
<thead>
<tr>
<th>Legacy diseases</th>
<th>Expending diseases</th>
<th>Outbreak diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hepatitis B, Diphtheria, Tetanus, Whooping Cough</td>
<td>• HPV</td>
<td>• Ebola</td>
</tr>
<tr>
<td>• Tuberculosis</td>
<td>• Pneumococcus</td>
<td>• Influenza</td>
</tr>
<tr>
<td>• Measles</td>
<td>• Rotavirus</td>
<td>• Chikungunya*</td>
</tr>
<tr>
<td>• Yellow fever</td>
<td>• COVID-19</td>
<td>• Rift Valley Fever*</td>
</tr>
<tr>
<td>• Cholera</td>
<td>• Malaria</td>
<td>• Lassa</td>
</tr>
<tr>
<td>• Typhoid</td>
<td>• HIV*</td>
<td>• Disease X*</td>
</tr>
<tr>
<td>• Meningococcus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Diseases for which there is currently no vaccines.

Source: https://africacdc.org/download/partnerships-for-african-vaccine-manufacturing-pavm-framework-for-action

SUMMARY OF CANDIDATE PATHOGENS AND INFECTIOUS DISEASES FOR AN mRNA VACCINE

<table>
<thead>
<tr>
<th>Viruses/diseases</th>
<th>Bacteria</th>
<th>Parasitic worms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya</td>
<td>Buruli ulcer</td>
<td>Dracunculiasis</td>
</tr>
<tr>
<td>Crimean-Congo haemorrhagic fever (CCHF)</td>
<td>Cholera</td>
<td>Echinococcosis</td>
</tr>
<tr>
<td>CMV</td>
<td>Leprosy</td>
<td>Foodborne trematodiases</td>
</tr>
<tr>
<td>Dengue</td>
<td>Mycobacterium</td>
<td>Lymphatic filariasis</td>
</tr>
<tr>
<td>Ebola</td>
<td>tuberculosis</td>
<td>Onchocerciasis (river blindness)</td>
</tr>
<tr>
<td>Emerging non-polio enteroviruses</td>
<td>Plague</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>Rickettsia (epidemic typhus)</td>
<td>Soil-transmitted helminthiases</td>
</tr>
<tr>
<td>HIV hMPV/PIV3</td>
<td>Trachoma</td>
<td>Taeniasis and cysticercosis</td>
</tr>
<tr>
<td>HSV-2</td>
<td>Yaws</td>
<td></td>
</tr>
<tr>
<td>Influenza A &amp; B (Flu)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lassa fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marburg virus disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle East respiratory syndrome coronavirus (MERS-CoV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nipah and henipaviral diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poliovirus (Enterovirus C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rift Valley fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe acute respiratory syndrome (SARS-CoV-2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>West Nile virus disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zika virus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Protozoan parasites

- Chagas disease
- Human African trypanosomiasis (Gambiense, Rhodesiense)
- Leishmaniasis (cutaneous and monocutaneous, visceral)
- Malaria

Virus-induced cancers

- Epstein-Barr virus
- Hepatitis B and C
- Human herpes virus 8
- HIV
- Human papillomaviruses (HPV)
- Human T-lymphotrophic virus-1 (HTLV-1)
- Merkel cell polyomavirus (MCV)
### Annexe 5: Snapshot of vaccine R&D for priority diseases identified in the WHO R&D Blueprint

*Adapted from Sparrow et al., 2022 (www.clinicaltrials.gov – December 2022).*

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease burden</th>
<th>RNA portfolio</th>
<th>RNA vaccine stage of development</th>
<th>Other vaccines - most advanced development stage</th>
<th>Vaccine feasibility</th>
<th>Current disease management approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHF</td>
<td>The CCHF virus causes severe viral haemorrhagic fever outbreaks, with a case fatality rate of 10-40%. CCHF is endemic in Africa, the Balkans, the Middle East and Asian countries south of the 50th parallel north – the geographical limit of the principal tick vector.</td>
<td>X</td>
<td>x</td>
<td>Phase 1: Inactivated Preclinical DNA</td>
<td>Complex Target antigen for vaccine development not yet identified</td>
<td>General supportive care with treatment of symptoms is the main approach to managing CCHF in people.</td>
</tr>
<tr>
<td>Ebola</td>
<td>Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a rare but severe and often fatal illness in humans. The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks. In 2022 (as of 22 November 2022), there have been 141 confirmed cases of EVD, including 55 deaths (case fatality rate: 39%).</td>
<td>Moderna Preclinical</td>
<td>Ervebo, recombinant (FDA approved, WHO Pre-Qual) Zabdeno-and-Mvabea recombinant (EMA approved)</td>
<td>Feasible Licensed vaccines and multiple vaccines in clinical development</td>
<td>Supportive care – rehydration with oral or intravenous fluids – and treatment of specific symptoms improve survival. A range of potential treatments, including blood products, immune therapies and drug therapies, are currently being evaluated. Two monoclonal antibodies (Inmazeb and Ebanga) were approved for the treatment of Zaire ebolavirus (Ebolavirus) infection in adults and children by the US FDA in late 2020.</td>
<td></td>
</tr>
<tr>
<td>Lassa fever</td>
<td>Lassa fever is known to be endemic in Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone and Nigeria, but probably exists in other West African countries.</td>
<td>Moderna CureVac</td>
<td>Preclinical Recombinant, DNA, replicon particles, other vectors</td>
<td>Diversity is a challenge but feasible; several studies ongoing; potential correlate of protection (CoP); WHO target product profile (TPP)</td>
<td>The antiviral drug ribavirin seems to be an effective treatment for Lassa fever if given early in the course of clinical illness. Prevention of Lassa fever relies...</td>
<td></td>
</tr>
</tbody>
</table>
countries, as well. The overall case-fatality rate is 1%. The observed case fatality rate among patients hospitalized with severe cases of Lassa fever is 15%. The number of Lassa virus infections per year in West Africa is estimated at 100,000 to 300,000, with approximately 5,000 deaths. Unfortunately, such estimates are crude because surveillance for cases of the disease is not uniformly performed.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Phase 1</th>
<th>Preclinical</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marburg virus disease</td>
<td>There are sporadic outbreaks. The average Marburg virus disease (MVD) case fatality rate is around 50%. Case fatality rates have varied from 24% to 88% in past outbreaks, depending on virus strain and case management.</td>
<td>CEPI, Imperial College London</td>
<td>Preclinical</td>
<td>Phase 1: DNA, recombinant (ChAd3, MVA)</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Since Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in April 2012, over 2,600 cases of the disease have been detected in 27 countries. Humans sporadically become infected through zoonotic transmission.</td>
<td>x</td>
<td>x</td>
<td>Preclinical (various) Phases 1: Recombinant (ChAdOx1 MVA, Ad5), DNA</td>
</tr>
<tr>
<td>Nipah and henipaviral diseases</td>
<td>The case fatality rate is estimated at 40% to 75%. This rate can vary by outbreak depending on local capabilities for epidemiological surveillance and clinical management. Due to incomplete reporting and underdiagnosis, the true fatality rate is likely higher.</td>
<td>NIAD</td>
<td>Phase 1</td>
<td>Feasible Clinical testing difficult due to sporadic outbreak; potential CoP</td>
</tr>
</tbody>
</table>

on promoting good “community hygiene” to discourage rodents from entering homes.
to its high mortality in humans, its zoonotic nature, the possibility of human-to-human transmission and the lack of an available vaccine, WHO has recognized it as a global health problem.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Clinical Testing</th>
<th>Feasible</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rift Valley fever</td>
<td>Rift Valley fever is an acute viral disease that affects domestic animals. While most human cases are relatively mild, a small percentage of people develop a much more severe form of the disease.</td>
<td>x</td>
<td>Feasible</td>
<td>Clinical testing difficult due to sporadic outbreak; animal models available; several strategies tested in animals</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Globally, as of 2 December 2022, there have been 640,395,651 confirmed cases of COVID-19, including 6,618,579 deaths, reported to WHO.</td>
<td>Multiple</td>
<td>Feasible</td>
<td>Vaccination, physical distancing, masking and quarantine have been applied.</td>
</tr>
<tr>
<td>Zika virus</td>
<td>In October 2015, Brazil reported an association between Zika virus infection and microcephaly. Outbreaks and evidence of transmission soon appeared throughout the Americas, Africa and other regions of the world. To date, a total of 86 countries and territories have reported evidence of mosquito-transmitted Zika infection.</td>
<td>Moderna</td>
<td>Feasible</td>
<td>Controlling the vector is taking place by working actively with national authorities, partners and communities to eliminate mosquito populations.</td>
</tr>
</tbody>
</table>