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

Report of the WHO Science Council
Potential benefits and limitations of mRNA technology for vaccine research and development for infectious diseases and virus-induced cancers: report of the WHO Science Council

ISBN 978-92-4-008456-8 (print version)

© World Health Organization 2023

Acting as the host organization of the WHO Science Council. Some rights reserved. This work is available under the Creative Commons Attribution–NonCommercial–ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization. (http://www.wipo.int/amc/en/mediation/rules/).


Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris. Sales, rights and licensing. To submit requests for commercial use and queries on rights and licensing, see https://iris.who.int/.

Sales, rights and licensing. To purchase WHO publications, see https://www.who.int/publications/book-orders. To submit requests for commercial use and queries on rights and licensing, see https://www.who.int/copyright.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the Science Council to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO or the Science Council be liable for damages arising from its use. This publication contains the collective views of the members of the WHO Science Council and does not necessarily represent the decisions or policies of WHO.

Design and layout: Mr Shihab S Joi
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviations</td>
<td>iv</td>
</tr>
<tr>
<td>WHO Science Council</td>
<td>v</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>vi</td>
</tr>
<tr>
<td>Executive summary</td>
<td>vii</td>
</tr>
<tr>
<td>1. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>2. mRNA technology and its applications for vaccine R&amp;D</td>
<td>2</td>
</tr>
<tr>
<td>3. Key findings</td>
<td>6</td>
</tr>
<tr>
<td>3.1. Contributions of previous R&amp;D for mRNA vaccines to the success of COVID-19 vaccines</td>
<td>6</td>
</tr>
<tr>
<td>3.2. Issues of equitable access arising from the use of mRNA technology</td>
<td>8</td>
</tr>
<tr>
<td>3.3. Scientific and technological advantages and limitations to the use of the mRNA platform for vaccines</td>
<td>10</td>
</tr>
<tr>
<td>4. Recommendations for advancing mRNA vaccine technology</td>
<td>13</td>
</tr>
<tr>
<td>4.1. Assessing the value of mRNA technology in the context of a global vaccine strategy</td>
<td>14</td>
</tr>
<tr>
<td>4.1.1. Identifying pathogens of interest</td>
<td>15</td>
</tr>
<tr>
<td>4.1.2. Key indicators</td>
<td>15</td>
</tr>
<tr>
<td>4.1.3. Positioning mRNA vaccines within the existing R&amp;D and global health ecosystems</td>
<td>19</td>
</tr>
<tr>
<td>4.1.4. Assessing impact</td>
<td>20</td>
</tr>
<tr>
<td>4.2. Biological and technological improvements</td>
<td>21</td>
</tr>
<tr>
<td>4.3. End-to-end equitable development of mRNA technology</td>
<td>22</td>
</tr>
<tr>
<td>5. Conclusion</td>
<td>24</td>
</tr>
<tr>
<td>6. References</td>
<td>25</td>
</tr>
<tr>
<td>Annex 1: Methodology, consultation, and participants</td>
<td>30</td>
</tr>
<tr>
<td>Annex 2: Original WHO-Approved COVID-19 Vaccines: Key Features</td>
<td>31</td>
</tr>
<tr>
<td>Annex 3: Past and ongoing mRNA vaccine trials for infectious diseases and virus-induced cancers</td>
<td>32</td>
</tr>
</tbody>
</table>
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT-Accelerator</td>
<td>Access to COVID-19 Tools Accelerator</td>
</tr>
<tr>
<td>COVID-19</td>
<td>coronavirus</td>
</tr>
<tr>
<td>DALY</td>
<td>disability-adjusted life year</td>
</tr>
<tr>
<td>hMPV/PIV3</td>
<td>human metapneumovirus/parainfluenza virus type 3</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HPV</td>
<td>human papillomaviruses</td>
</tr>
<tr>
<td>LMIC</td>
<td>low- and middle-income countries</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Middle East respiratory syndrome coronavirus</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>RSV</td>
<td>respiratory syncytial virus</td>
</tr>
<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>TPP</td>
<td>target product profile</td>
</tr>
<tr>
<td>UTR</td>
<td>untranslated region</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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
President & Pro Vice Chancellor of Monash University Malaysia; 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 & Professor of Global Health, Columbia University, USA

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.

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

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

This report and enclosed recommendations have been developed by the World Health Organization (WHO) Science Council.

The WHO Science Council wishes to thank the many individuals and organizations who participated in planning meetings, the expert consultation, and the public consultation. Participants of the expert consultation with speaking roles are listed in Annex 1.

The development of this report was supported by the WHO Science Council Secretariat under the direction of Dr Anna Laura Ross (Head of WHO Science Council Secretariat, Unit Head for Emerging Technologies, Research Prioritization and Support), and the overall guidance of the WHO Chief Scientist (Dr Soumya Swaminathan, Dr John Reeder, Dr Jeremy Farrar).

A number of staff across the departments of WHO contributed to the expert consultation and creation of this report, namely (in alphabetic order), Hanan Balkhy, Donald Joseph Brooks, Veronique Bruniquel, Christopher Chadwick, Diana Chang Blanc, Gilles Forte, Martin Friede, Birgitte Giersing, Pierre Gsell, Claudia Nannei, Martin Nicholson, Fatima Serhan, Erin Sparrow, Marie Ange Wambo.

Dr Danny Sheath (Technical Officer) and Dr Roger Tatoud (Technical Consultant) supported the Science Council in concept development, desk review, and the writing of the report.
Executive summary

Introduction and background

The successful use of messenger RNA (mRNA) technology for the development of COVID-19 vaccines is fuelling interest in its potential for use in preventing, treating, or curing other health conditions. Hence, several mRNA vaccine candidates are being developed and tested, especially for other global infectious diseases, and the results will indicate whether the success seen with COVID-19 is replicable. Despite its benefits and promise, mRNA technology has certain drawbacks that require further investigation to determine its value and potential for having a positive impact on various health conditions on a global scale.

As a first step towards assessing the potential of mRNA technology for improving global health, the World Health Organization (WHO) Science Council has conducted an independent review of the role of this technology in the development of vaccines for the prevention of infectious diseases and virus-induced cancers. This report summarizes the Council’s findings on the advantages and limitations of the technology; it also provides recommendations to focus research efforts and guide global research and development (R&D) endeavours.

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

The Council’s report to the Director-General makes six recommendations for consideration by WHO and constituencies within its Member States.
Potential benefits and limitations of mRNA technology for vaccine research and development for infectious diseases and virus-induced cancers

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 consideration of mRNA technologies in strategies to control infectious diseases with vaccines, while recognizing the need to make existing and new vaccines accessible to all. For this, WHO should use existing structures and committees leading the organization’s vaccine strategy to regularly evaluate how new scientific developments impact the benefits and limitations (scientific and social) of mRNA technology, especially for pandemic preparedness and response.

2. Promoting the conduct of more research to address the limitations of mRNA technology.

**Recommendation 2**

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. This should include the identification of pathogens of interest for the development of mRNA vaccines and encourage mRNA vaccine development for pathogens associated with antimicrobial resistance, virus-induced cancers and agents likely to cause future pandemics.

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

**Recommendation 3**

WHO should use its reputability and trustworthiness to address the misinformation and disinformation about mRNA vaccines that are influencing vaccine hesitancy to improve current and future vaccine uptake, with the goal of improving public health.

4. Promoting the conduct of more research to address the limitations of mRNA technology.

**Recommendation 4**

WHO should take a leading role in identifying biological and technological improvements relevant to mRNA technology (including cold-chain requirements) and then in identifying pathogens with high priority for development of vaccines using mRNA technology. This includes advocating for and supporting 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.

5. Ensuring end-to-end equitable development and access to mRNA technology.

**Recommendation 5**

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

“mRNA technologies in strategies to control infectious diseases with vaccines should be emphasized, while recognizing the need to make existing and new vaccines accessible to all”
Recommendation 6

WHO is encouraged to draw the lessons from the experience of the ACT-Accelerator and to include, as appropriate, mRNA vaccines as part of its future medical countermeasures mechanism to tackle pandemic threats. In addition to these recommendations, it is crucial to improve the conditions that restrict the manufacturing, distribution, and accessibility of vaccines in LMICs, to allow the advancement of vaccines based on mRNA technology and to prevent creating further health disparities. It is important 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 mRNA technology can benefit the health of humankind.

The six recommendations are intended to support the sustainability of vaccine development and manufacturing infrastructure, and equitable access to vaccines developed using mRNA technology. The Science Council strongly encourages a critical approach and continued investment in basic and applied research to overcome the impediments of mRNA technology and to fully realize its potential.

“All recommendations are intended to support the sustainability of the vaccine development and manufacturing infrastructure and the equitable access to vaccines developed using mRNA technology”
1. Introduction

The remarkable and rapid development of COVID-19 vaccines based on messenger RNA (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 some of the technology’s limitations accentuated social health inequalities while exposing the unequal power dynamics between wealthy nations and low- and middle-income countries (LMICs).

During an in-person meeting in Geneva in July 2022, the World Health Organization (WHO) Science Council agreed to conduct an independent review of the uses and safety of mRNA technology, and the value and power of this technology 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 reignited interest in developing vaccines for a range of conditions and pathogens with pandemic potential. In parallel, while recognizing production and supply constraints, WHO has established an mRNA technology transfer hub to increase mRNA vaccine production capacity in underserved regions and thus promote regional health security.

It is vital to ensure that the development and use of mRNA technology aligns with existing vaccine research and development (R&D) strategies, and that its use is targeted towards the most pertinent applications. Hence, as an initial step towards assessing the potential of mRNA technology for improving global health, the WHO Science Council has conducted an independent review of the technology’s potential for success in preventing infectious diseases and virus-induced cancers (2,3).

This report presents the Council’s key findings, highlighting both the advantages and limitations of mRNA technology, providing suggestions to focus research efforts, and making recommendations to guide global R&D endeavours. The aim is to assist WHO in its efforts to promote the sustainable development and accessibility of mRNA technology, so that mRNA-based applications can benefit the health of humankind.
2. mRNA technology and its applications for vaccine R&D

RNA was discovered in the early 1940s. mRNA is one of many types of RNA involved in cellular functions. mRNAs contain genetic information encoding cellular and viral proteins, and they direct the synthesis of those proteins on ribosomes, the protein synthesis factories in cells (4).

Extensive research has been conducted to understand the function of mRNA and to find applications for mRNA in research and health. More than 30 years ago, mRNA was considered as a potential tool for creating new drugs, and it has a long history of product development, including for vaccines (5). However, major roadblocks to its use were the poor stability of mRNA synthesized in cell-free systems and the innate immune response it triggered once delivered into the body. Further research in the mid-2000s led to the development of stable and less immunogenic mRNA molecules (5–7). These breakthroughs opened the door to using mRNA in vaccine R&D (8–12).

The mRNA platform has several potential R&D applications such as the rapid design and production of vaccines for infectious diseases in humans and animals, the protection of crops against viruses (13) and therapeutic applications (cancers and regenerative therapies (14)). All these applications are currently undergoing clinical testing.

mRNA has been a valuable tool for COVID-19 vaccine R&D, with mRNA vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) developed and administered more rapidly than any other vaccines; the mRNA vaccines to SARS-CoV-2 demonstrated the safety and efficacy of the approach (15) (Annex 2). 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 that encode 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 synthesized and formulated for injection. Once introduced into 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 (6,8,16,17) (Box 2).

In addition, efficient delivery of synthetic mRNA requires a packaging and delivery system that will protect it against degradation by nucleases, to allow efficient cellular uptake, intracellular release and translation into proteins (18). Although various delivery systems are in development, the most clinically advanced comprises encapsulation of the mRNA in lipid nanoparticles (19).

### Box 1. Different types of mRNA molecules

- Synthetic mRNA usually contains five regions from the 5' to the 3' end: 5' cap, 5' untranslated region (UTR), an open reading frame that encodes the immunogen, 3' UTR and a poly (A) tail. Based on their physical and genetic characteristics, mRNAs are categorized as non-replicating, self-amplifying, trans-amplifying, and circular (20).
- Non-replicating mRNA encodes only the immunogen of interest, whereas self-amplifying mRNA 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 self-amplifying mRNA can produce a large amount of immunogen (21).
- Alternatively, self-amplifying mRNA can be delivered as two mRNAs (trans-amplifying RNA), one encoding the replicase and the other the immunogen of interest, thereby reducing the size of the mRNA.
- Circular mRNAs are produced by joining the 5' and 3' ends, protecting the RNA product from exonuclease activity, extending its stability and longevity, and stimulating the production of the immunogen of interest. Circular mRNAs do not need capping of the 5' end and polyadenylation of the 3' end; also, circularization reduces the innate immunogenicity of the mRNA.

### Box 2. mRNA modifications, adapted from Pardi et al., 2018

Several modifications of the mRNA molecule contribute to its critical quality attributes that dictate its ability 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.
- The 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 (16).
- Separation or purification techniques such as RNase III treatment and fast protein liquid chromatography (FPLC) purification decrease immune activation and increase translation.
- Optimization of the sequence or codon (or both) increases translation.
- Modulation of target cells (e.g. through co-delivery of translation initiation factors) alters translation and immunogenicity.
The use of mRNA technology to develop vaccines predates the COVID-19 pandemic (7,22) but following the success of mRNA-based COVID-19 vaccines there was rapid expansion in R&D of vaccines for other pathogens driven by academic institutions and governmental and nongovernmental organizations, in collaboration with pharmaceutical companies (8,10,23). The potential value of mRNA vaccines for infectious diseases and virus-induced cancers has previously been reviewed (8–11,24,25) (Table 1). So far, the only mRNA technology-based vaccines to receive emergency-use authorization by WHO are the COVID-19 vaccines. Current research focuses on linear non-replicating mRNA; it primarily targets infectious diseases caused by viruses and virus-induced cancers that have simpler structural and genomic characteristics than bacteria and protozoans, making it easier to design effective immunogens (see Section 3.3) (Table 1).

Most mRNA vaccines are in the early phases of clinical testing (Phase 1 and 2). Completed early phase trials of preventive vaccines against chikungunya (26), rabies (27) and Zika (28) have shown that the vaccines tested were safe, well tolerated and induced a good immune response, including the production of neutralizing antibodies. Influenza, cytomegalovirus, and respiratory syncytial virus mRNA vaccines are at the most advanced stage of clinical testing (Phase 3). In January 2023, Moderna announced that its mRNA-1345 vaccine against respiratory syncytial virus (RSV) was 83.7% effective in a late-stage trial at preventing at least two symptoms of the cold-like disease caused by the virus in adults aged 60 years and over. The efficacy of this mRNA vaccine is comparable to that of the Pfizer Prefusion F Protein vaccine (29), and Moderna plans to file for regulatory approval globally in the first half of 2023. Despite proposals for therapeutic vaccines against human papillomaviruses (HPV)-induced cancers (30,31); and pre-clinical evidence for efficacy in mouse models (32,33), further studies are required to establish the value of this approach to the treatment of cervical cancer and other HPV-induced malignancies.

A few clinical studies are also investigating self-amplifying RNA. The results of ongoing clinical studies will provide important information for the future development and use of the mRNA platform for vaccine R&D.

<table>
<thead>
<tr>
<th>Table 1. Most advanced clinical development stage(^a) of mRNA vaccines in development for the prevention of infectious diseases and virus-induced cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preclinical trial</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>• Ebola fever</td>
</tr>
<tr>
<td>• Lassa fever</td>
</tr>
<tr>
<td>• Marburg virus disease</td>
</tr>
<tr>
<td>• MERS-CoV</td>
</tr>
<tr>
<td>• Yellow fever</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus; hMPV/PIV3: human metapneumovirus/parainfluenza virus type 3; MERS-CoV: Middle East respiratory syndrome coronavirus; HPV: human papillomaviruses; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

\(^a\) As defined by the International Clinical Trials Registry Platform (ICTRP).
As with other outbreaks in the past, the COVID-19 pandemic has underscored the gross inequity that exists in access to health products, especially vaccines. The pandemic confirmed that LMICs are highly vulnerable because most advanced technologies and vaccine manufacturing capacity remain concentrated in a few high-income countries. The ubiquity and costs of the COVID-19 pandemic have focused attention on equitable access and the need to invest in long-term regional health security.

Announced on 21 June 2021, the objective of the WHO mRNA technology transfer programme is to build capacity in LMICs to produce mRNA vaccines, by providing information, developing skilled human capital, and strengthening national regulatory capabilities.

The programme operates via a global collaborative network that comprises a hub for technology development and transfer in South Africa (a consortium with the South Africa Medical Research Council, Afrigen Biologics and Vaccine and The Biovac Institute) and multiple partners in LMICs. These LMIC partners will receive the technology and contribute to its optimization and further development, sharing with the network the improvements and innovations achieved. To ensure sustainability of the investment being made by various governments and partners, the programme encourages the expansion of the mRNA vaccine pipelines to routine products that are adapted to the local needs and meet governments’ priorities for nationally funded disease control programmes. This will allow the continuous use of the technology, keep the equipment maintained and the workforce engaged, and apply and update quality control and assurance systems, so that the relevant capacity and skills will be available in the event of a new outbreak.

List of the 15 partners to demonstrate the geographical scope of the programme:

- South Africa
- Kenya
- Brazil
- Indonesia
- India
- Egypt
- Nigeria
- Ukraine
- Bangladesh
- Senegal
- Tunisia
- Serbia
- Pakistan
- Vietnam
- Argentina

https://www.who.int/initiatives/the-mrna-vaccine-technology-transfer-hub
3. Key findings

The success of mRNA vaccines for infectious diseases is largely based on experience with COVID-19 vaccines, which are the only safe and efficacious preventive mRNA vaccines that have been 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 (14,34). This lack of experience is a significant limitation to our current knowledge of the potential of mRNA vaccines for other infectious diseases and virus-induced cancers.

This part of the report summarizes the findings and observations from a desk and literature review of existing, in-development and forward-looking applications of mRNA-based vaccines for infectious diseases and virus-induced cancers. It also draws on two public consultations conducted to gather feedback on the advantages and limitations of mRNA technology and determine how it could best 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 the success of COVID-19 vaccines;
- issues of equitable access arising from the use of mRNA technology; and
- scientific and technological advantages and limitations to the use of the mRNA platform for vaccines.

3.1. Contributions of previous R&D for mRNA vaccines to the success of COVID-19 vaccines

Two COVID-19 vaccines – from Moderna and Pfizer-BioNTech – provided the first demonstration that it was possible to develop a safe and effective vaccine based on mRNA technology. The development of these vaccines was complex and challenging, and a host of factors contributed to their rapid development (6,35). These factors included
decades of related, formative research in virology, immunology, and structural biology; meaningful community engagement, which was central to the success of clinical testing; collaborations between researchers; and the availability of unprecedented funding, driven by a global focus on finding a solution to a critical global health threat (5,36). The following points provide more detail on the factors that contributed to the rapid development of these vaccines:

- **Existing mRNA vaccine R&D**: The development of mRNA vaccines built on at least four distinct lines of research in the fields of molecular biology, lipid chemistry, microbiology, and immunology (6). In the case of COVID-19, research on similar viruses (e.g. SARS and Middle East respiratory syndrome [MERS]) (37) and HIV (38), and the development of cancer vaccines (39,40) supported the rapid and efficient development of effective vaccines.

- **Research skills and infrastructure**: Vaccine researchers quickly pivoted to use the expertise gained during the development of other vaccines. The established clinical research infrastructure and enthusiastic participation of thousands of trial volunteers also played a crucial role in the rapid development of COVID-19 mRNA vaccines (41).

- **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 invested over $18 billion of US public funds in six vaccine candidates over 2 years (42); this was equivalent to more than 20 years of investment in HIV vaccine research (43).

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

Several other COVID-19 vaccines were also quickly developed using different platforms (44–46), emphasizing the continued importance of traditional vaccine strategies, especially for infectious disease response (Annex 2).

Importantly, there was a strong scientific rationale for the feasibility of a COVID-19 vaccine, based on existing data and knowledge. For example, it had long been known that antibodies binding to the epitopes of the avian coronavirus infectious bronchitis virus spike protein could neutralize the virus (47,48), and more recently it had been shown that an mRNA vaccine is translated into an immunogenic protein that can elicit functional antibodies (49). Previous work to stabilize the viral spike protein of other viruses such as MERS, RSV and HIV was also critical for the development of a highly stable and immunogenic SARS-CoV-2 protein. (50,51)

It is tempting to believe that future vaccines based on mRNA technology will be produced with similar ease and within a similar time frame. 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, the current mRNA technology still faces several challenges and limitations (discussed in more detail in Section 3.3) that must be considered before using the platform more widely for vaccine R&D.

“Existing mRNA technology still faces several challenges and limitations that must be considered before using the platform more widely for vaccine R&D”
3.2. Issues of equitable access arising from the use of mRNA technology

The remarkable accomplishment of developing COVID-19 vaccines in less than a year (52) illustrates the significant potential of human innovation, strong medical research capabilities and private industry infrastructure, when backed by considerable public investment – from basic research to substantial funding along the entire R&D and production process.

However, the benefits from this success were not distributed equally; this highlighted and sometimes worsened social inequalities. As of May 2023, 70% of the world population has received at least one dose of a COVID-19 vaccine since WHO declared SARS-CoV-2 a pandemic on 11 March 2020; however, 3 years after that declaration, only 29.1% of people in low-income countries had received at least one dose of a COVID-19 vaccine, whilst 24.5% had received complete primary series (53). Although precise information about the use specifically of mRNA-based vaccines in LMICs has proven difficult to obtain, many factors (summarized in Box 3) explain why access to those vaccines was less than for vaccines prepared in more traditional ways and far lower in LMICs than in more affluent countries.

The COVID-19 pandemic has occurred against a backdrop of existing social and economic health inequality; this led to a highly 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 (54,55).

Although mechanisms were put in place to ensure fair and equitable access through the Access to COVID-19 Tools Accelerator (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” (56).

Several barriers to access to COVID-19 health products, including vaccines, have been identified in LMICs. Barriers include market forces; unavailability, inaccessibility, and unaffordability of the products; an incompatibility between the agenda of donors and the funding available; unreliable health and supply systems; (57) and vaccine nationalism (58). The numerous challenges in accessing mRNA vaccines in LMICs are outlined in Box 3.

The challenge of delivering vaccines on an unprecedented scale and as quickly as possible affected all types of vaccines. However, in the case of mRNA vaccines, intellectual property barriers and ultra-cold-chain requirements were two particularly 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 that limit equitable access and fair allocation, and potentially impede future R&D. It is estimated that there are more than 80 patents surrounding mRNA COVID-19 vaccines; these patents cover all aspects of mRNA technology, from design to encapsulation and manufacturing methods and techniques (59,60).

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:

- Limited storage and transportation infrastructure: Many countries lack the necessary stable electricity supply, storage capacity and transportation infrastructure

\[1\] See https://www.who.int/initiatives/act-accelerator
to maintain ultra-low temperatures. There are a limited number of locations where the vaccines can be stored, which in turn can 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; this can result in wastage if doses are not used within a certain time frame.

Wealthier countries with better storage capacities, stable electricity supply, and transportation infrastructure were readily able to purchase and distribute the vaccines, while many LMICs struggled to access them.

---

**Box 3: Key factors influencing access to mRNA COVID-19 vaccines in LMICs**

1. **Affordability:** Several LMICs could not afford to purchase COVID-19 mRNA vaccines because of the costs involved in purchasing doses of vaccine and injury insurance (required to avoid manufacturer’s liability), and in setting up storage and distribution. With only two companies producing and selling mRNA vaccines, the lack of competition created no incentives for manufacturers to lower prices.

2. **Financial status:** In the early stages of the COVID-19 vaccine rollout, many LMICs were not at the front of the queue for obtaining vaccines from pharmaceutical companies, owing to their poor buying power in this sector.

3. **Market exclusion:** mRNA vaccine manufacturers unilaterally determined which countries would be allowed to license and market their vaccines. In the first 3 years of the COVID-19 pandemic, one manufacturer had not sought regulatory approval for its mRNA vaccine in any country in Africa, effectively precluding countries on that continent from purchasing their vaccine directly.

4. **Vaccine testing:** Many LMICs have little prospect of being involved in vaccine R&D (including clinical trials of mRNA vaccines) because of their poorly developed clinical trial infrastructure. Some pharmaceutical companies, for instance, tested their mRNA vaccines entirely in the USA.

5. **Access to intellectual property (IP):** Those LMICs that did have vaccine-manufacturing capabilities were not able to secure access to mRNA vaccine IP and production expertise for local manufacture of vaccines. Government agencies that funded the research that led to the IP did not stipulate or enforce sharing of IP under exceptional circumstances (e.g., a pandemic). Lack of IP access contributed – either directly or indirectly – to LMICs having limited access to mRNA vaccines.

6. **Low production capacities in LMICs:** Without access to IP and manufacturing expertise, even those LMICs that have vaccine production capability could not produce mRNA vaccines locally. Although some LMICs produce large quantities of low-cost generic medications for AIDS treatment under voluntary or compulsory licenses, the manufacturers of mRNA vaccines chose not to provide voluntary licenses for LMICs. This effectively precluded local production of mRNA vaccines in LMICs.

7. **Cold storage:** The low temperature cold storage requirements of mRNA vaccines presented a significant challenge for vaccine storage and distribution in many LMICs.

8. **Multidose vials:** Since mRNA vaccines are provided in multidose vials, there was significant wastage during the COVID-19 pandemic when the number of people awaiting vaccination did not match the doses available. This wastage increased the cost per dose used and affordability.
3.3. Scientific and technological advantages and limitations to the use of the mRNA platform for vaccines

The strategy of using nucleic acids to produce immunogen within the human body differs from conventional vaccine approaches, which rely on directly administering antigens to elicit immune responses. Although several vaccines based on DNA (61) have been developed, mRNA vaccines can have a number of advantages over recombinant and DNA vaccines (62) and over killed or live attenuated pathogens and pathogen subunits (8,23).

mRNA technology offers notable benefits from an R&D perspective; nevertheless, current scientific and technological constraints can limit the development of vaccines, which may impede realization of the full potential of this technology (23,63–65). Work is ongoing to address some of these challenges, and there is a clear need for more investment in research to realize the full benefits of the mRNA platform for vaccines.

This section discusses some of the promising features and known limitations of mRNA vaccines (summarized in Box 3).

**Design and immunogenicity**

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

mRNA vaccines are currently delivered intramuscularly, subcutaneously or intradermally using a conventional needle and syringe. However, patches and subcutaneous formulations that are needle free are being developed (66), and preclinical testing of intranasal delivery is under investigation (67). The mechanisms that induce immune responses associated with immunogenicity and reactogenicity remain largely unknown and warrant further studies (68). mRNA vaccines have a high translation efficiency (69), 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 (70–72). In addition, mRNA vaccines have an inherent adjuvant effect (73). The formulation mRNA vaccines affect their efficacy – some formulations can boost the immune response whereas others can be detrimental and have clinical side effects or can lead to reduced expression of the immunogen of interest (9).

The respiratory tract and oral mucosa are the primary points of entry for airborne viruses, and mucosal immunity plays a critical role in preventing infections and reducing transmission. mRNA vaccines trigger a robust immune response that protects against severe disease caused by a range of COVID-19 variants; however, these vaccines do not effectively stimulate mucosal immunity, thus increasing the risk of breakthrough infections by highly transmissible variants (e.g., Omicron variants) (74,75).

“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”
The experience with COVID-19 vaccines has raised the question of the durability of the protection conferred by mRNA vaccines due to waning immunity; that is, a decline in antibody levels that occurs over several months after vaccination and means that booster immunizations are needed to maintain effective antibody levels. Vaccine efficacy against symptomatic infection is reduced, but protection against severe disease is maintained, particularly in the context of hybrid immunity. Nevertheless, mRNA vaccines for COVID-19 confer longer protection than vectored vaccines against the disease (76,77).

The use of mRNA COVID-19 vaccines has also raised concerns about their effectiveness against variants that arise after immunization (78). Studies have shown reduced protection against COVID-19 variants in the absence of booster immunization (79–81). Although COVID-19 mRNA vaccines have been approved for use in children aged 6 months to 4 years (82), mRNA-based vaccines against other pathogens will require their efficacy to be assessed in specific populations, including people with depressed or compromised immunity, children, older people, those who are pregnant and those who are malnourished.

**Safety**

mRNA vaccines are non-infectious because they encode only a small portion of a pathogen. There is no evidence that DNA copies of the mRNA can integrate in the genome of the person receiving the vaccine, and the vaccines are degraded through normal cellular processes (62). In addition, the acquired immune response against an mRNA vaccine is limited and the vaccines have a good safety profile (83).

COVID-19 mRNA vaccines have raised safety concerns owing to potential anaphylactic reactions, possibly caused by pre-existing antibodies against PEGylated lipid in lipid nanoparticles (84–86). However, the incidence of anaphylactic reaction observed with mRNA vaccines is comparable to that seen with COVID-19 vectored vaccines and is within the range of mean anaphylaxis rates for commonly administered vaccines (87–89). Nevertheless, the possibility of such reactions contributed to vaccine hesitancy, and it may also affect vaccine efficacy. The implementation of a pharmacovigilance database would be useful to monitor mRNA vaccine efficacy and detect any rare and serious adverse events.

**Manufacturing**

Compared with other vaccines, manufacturing of mRNA is simpler because it has fewer steps in a cell-free environment, is relatively low cost and can be done 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 cost of less than US$1 per dose (90).

One of the factors limiting equitable access is that mRNA vaccine manufacture requires skills and expertise that are not yet widely available, meaning that manufacturing and distribution sites are concentrated in particular geographical areas. Also, downstream processing improvements are needed to address scalability and cost of

---

2 PEGylation is the process of modifying bioactive molecules with polyethylene glycol (PEG).
production (23). Finally, the cost and availability of raw materials (e.g. enzymes and other reagents needed to synthesize 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 (24,91).

Overall, 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, and the refining or improvement of existing immunogens through iterative design and testing. The technology could also be used as a proof of concept to support the development of conventional vaccines (e.g., protein-based vaccines), and for conducting preclinical testing or 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 will be needed as part of vaccine R&D.

---

**Box 4. The power and limitations of mRNA technology**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed and ease of design and redesign</td>
<td>Requires a known immunogen</td>
</tr>
<tr>
<td>Speed and ease of manufacturing</td>
<td>Durability and breadth of the immune response</td>
</tr>
<tr>
<td>Biological and clinical safety</td>
<td>Formulation and potential side effects</td>
</tr>
<tr>
<td>Inherent adjuvant effect</td>
<td>Manufacturing capacity and cost</td>
</tr>
<tr>
<td>Cellular and humoral immune response</td>
<td>Cold chain requirements</td>
</tr>
</tbody>
</table>
4. 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 reignited interest in developing vaccines for a range of conditions and for pathogens with pandemic potential, for which several clinical studies are ongoing (Annex 3). Thus, mRNA vaccines should be considered as an additional approach to existing vaccine development strategies. As with other vaccine platforms, the development of an mRNA vaccine needs to be assessed against unmet public health needs, existing prevention and treatment, and other public health interventions aimed 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 compared with other vaccine strategies for a particular pathogen?
- What is the added value of an mRNA vaccine for the prevention, control and
elimination of infectious diseases and virus-induced cancers compared with existing intervention?

In this section, the Science Council makes a series of recommendations to WHO and constituencies within its Member States (e.g. governments, academia, industry, health advocacy groups and professional societies) for assessing and advancing mRNA technology. The recommendations are addressed to WHO, vaccine developers and countries at all levels of economic development, to allow the benefits of mRNA technology to be experienced globally.

The Council’s recommendations are based on public reports, the experiences of its 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 the manufacturing, legal and social issues associated with use of the technology.

The recommendations focus 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; this report highlights these matters but does not aim to explore or address them in detail.

The Council makes recommendations that emphasize 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 limitations of mRNA technology; and
- ensure end-to-end equitable development and access to mRNA technology.

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

The mRNA platform’s flexibility and versatility enables rapid product design and manufacturing, and thus makes it a valuable tool for accelerating vaccine development. Although this report focuses on preventive vaccines, it is worth considering the use of mRNA for therapeutic vaccines. 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 or leading the evaluation of the added value of an mRNA vaccine within existing treatment and prevention strategies, and the evaluation of its competitive advantage over existing vaccines.

There are many pathogens for which an mRNA vaccine could be considered and many other vaccine platforms available. Therefore, mechanisms and a framework are needed to assess the value of 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, and the

“The recommendations focus on the potential of mRNA technology to contribute to the development of vaccines against infectious diseases and virus-induced cancers”
experience and expertise of stakeholders. Also, it should address challenges related to mRNA technology, the pathogens of interest and the purpose of using the technology (e.g., prevention, control, elimination, or pandemic preparedness and response). The framework should also enable regular reviews based on new evidence.

**Recommendation 1**

WHO should emphasize the need to include consideration of mRNA technologies in strategies to control infectious diseases with vaccines, while recognizing the need to make existing and new vaccines accessible to all. For this, WHO should use existing structures and committees leading the organization’s vaccine strategy to regularly evaluate how new scientific developments impact the benefits and limitations (scientific and social) of mRNA technology, especially for pandemic preparedness and response.

**4.1.1. Identifying pathogens of interest**

Several disease-causing pathogens and infectious diseases could be considered for the development of an mRNA vaccine. Consequently, global health organizations have designed strategies aimed at developing priority lists for pathogens and diseases, to support the necessary prioritization effort (92–94).

Most emerging infectious diseases in recent decades have been caused by zoonotic viruses and bacteria that spill over from animals to humans (95,96). Those that have caused significant epidemics globally include coronaviruses, haemorrhagic fever viruses, arboviruses, and influenza A viruses. Animal-to-human zoonotic disease transmission can be prevented (in some cases) by the vaccination of animals or humans, and there is value in developing vaccines for both when there is a known or potential risk of spillover (97). The development of a vaccine against West Nile virus provides an example of vaccine co-development. Other examples (e.g., rabies, Rift Valley fever, and Nipah virus) illustrate the potential for preventing zoonotic and emerging diseases by integrating veterinary and human medicine in a One Health approach (98).

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

**Recommendation 2**

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. This should include the identification of pathogens of interest for the development of mRNA vaccines and encourage mRNA vaccine development for pathogens associated with antimicrobial resistance, virus-induced cancers, and agents likely to cause future pandemics.

**4.1.2. Key indicators**

Developing an assessment framework to evaluate the value of mRNA technology for infectious diseases and virus-induced cancers requires identification of relevant indicators. These indicators must align with existing efforts in this field; also, they must account for factors such as burden of disease at global and regional levels, feasibility of biological and product development, and implementation and accessibility considerations. By carefully selecting appropriate indicators and applying them consistently, a comprehensive assessment framework can be established to effectively evaluate the potential of mRNA technology.
Box 5. 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 (e.g., is there a WHO R&D blueprint or is the disease on the list of WHO neglected diseases)?
- Are there vaccines already in development or available (mRNA or other types)?
- What is the advantage of an mRNA vaccine over other vaccines?
- What is the aim of the vaccination (prevention of transmission, infection, serious disease, or 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?
- Has the immune response been characterized?
- Are there animal models?
- Are there known correlates of protection and 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 preferred product characteristics and a target product profile 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 (or are breadth and speed of manufacturing more important, especially for seasonal epidemics)?
In the case of mRNA vaccines, three high-level indicators are important when evaluating the potential value of mRNA technology:

- burden of disease
- vaccine feasibility
- vaccine characteristics.

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 that can be used include the prevalence, incidence, mortality, morbidity, and financial cost of a disease (99).

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

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

**Vaccine feasibility**

Developing a vaccine is a significant, costly, and long-term endeavour; hence, it is critical for WHO to contribute 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 unknown
- Pathogen complexity, diversity, and variability
- Unknown correlate of protection
- Lack of relevant animal models
- Lack of optimized clinical immunological assays
- Vaccine-associated enhanced disease and immunopathogenesis
- Clinical testing difficult owing to sporadic outbreaks, geographies, or lack of infrastructure
- Need for complex immunization regimens
- Limited protection (low efficacy or short-term protection)
Two aspects of vaccine feasibility have been recognized previously (100):

- **Biological feasibility:** This considers progression of clinical development, existence of immunity from natural exposure, current understanding of mechanisms of immunity, known correlates of protection, and the 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 undertaking clinical development and setting up 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 evaluation of vaccine feasibility. These criteria are not tailored to mRNA vaccines; however, mRNA vaccines may present greater challenges than traditional vaccinology approaches that do not require the identification of individual immunogens (e.g., toxoid, whole inactivated or attenuated vaccines, which form the basis of vaccines against several infectious diseases).

<table>
<thead>
<tr>
<th>Table 2. Evaluating vaccine feasibility using a composite set of criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feasible</strong></td>
</tr>
<tr>
<td>One or more immunogens have been identified or can be identified</td>
</tr>
<tr>
<td>Animal models are available, enabling rapid preclinical testing</td>
</tr>
<tr>
<td>Clinical data support the efficacy of a vaccine</td>
</tr>
<tr>
<td>Target populations have been identified</td>
</tr>
<tr>
<td>Clinical testing can be conducted using existing infrastructure</td>
</tr>
</tbody>
</table>

**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 (76,77). Although mRNA COVID-19 vaccines are more efficacious than other types of vaccine and provide durable protection against severe disease, booster immunizations 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 depend
Recommendations for advancing mRNA vaccine technology

on the platform used. The need for multivalent vaccine and booster immunizations is an important aspect of a vaccine regimen, and it is best to assess platforms against immunological requirements.

When considering vaccine efficacy, it will also be important to determine the purpose of developing a vaccine. The required efficacy may differ, depending on whether a vaccine is used to control an epidemic; contribute to eliminating an endemic disease; prevent infection, severe disease, hospitalization, and death; or form part of epidemic preparedness and response.

Table 3 summarizes key criteria for assessing vaccine efficacy, durability, breadth, and regimen. Although the table is 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 3. Evaluating the value of an mRNA vaccine based on efficacy and immunization regimen |
|-----------------------------------|---------------------------------|--------------------------------|
| **Optimal**                       | **Acceptable**                  | **Not suitable**               |
| • Highly efficacious against existing pathogen strains and emerging variants | • Moderately efficacious against existing pathogen strains or emerging variants | • Limited efficacy against pathogen strains or emerging variants |
| • A multivalent vaccine is required | • A heterologous prime-boost vaccine regimen may be required | • A complex immunization regimen or repeated immunizations and boosters are required |
| • A vaccine could be rolled out broadly as part of an existing immunization agenda |

mRNA: messenger ribonucleic acid.

4.1.3. 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 4 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 emphasizes the need to carefully consider the position of an mRNA vaccine within 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”
Table 4. Potential for mRNA vaccine R&D to add value to existing vaccine R&D and within global health ecosystems

<table>
<thead>
<tr>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Limited prevention and treatment are available</td>
<td>• Prevention and treatment are available, but not always implementable or accessible</td>
<td>• Effective prevention and treatment are available</td>
</tr>
<tr>
<td>• No vaccine is available</td>
<td>• Few effective vaccines are available</td>
<td>• Other interventions exist that can be deployed rapidly and when needed to control the epidemic</td>
</tr>
<tr>
<td>• Limited vaccine R&amp;D</td>
<td>• Manufacturing is complex or limited, making vaccine costly</td>
<td>• Transmission and acquisition dynamics are not well described</td>
</tr>
<tr>
<td></td>
<td>• Active vaccine R&amp;D</td>
<td>• Effective vaccines are available</td>
</tr>
</tbody>
</table>

mRNA: messenger ribonucleic acid; R&D: research and development.

4.1.4. 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 nongovernmental organizations and the pharmaceutical industry, while identifying gaps in these agendas.

Table 5 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 to the refinement and enhancement of other vaccine strategies. The potential for success could also trigger interest in vaccine R&D at the discovery stage (e.g., to identify immunogens for further vaccine development). An mRNA vaccine could also make an important contribution to pandemic preparedness and response.

Table 5: Assessing the value of an mRNA vaccine based on its potential impact

<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 (global or regional)</td>
<td>• Complement existing public health interventions</td>
<td>• Would not significantly contribute to lower acquisition or severity of the disease, but may add to prevention in specific settings and populations</td>
</tr>
<tr>
<td>• Contribute to disease elimination</td>
<td>• Contribute to disease control</td>
<td></td>
</tr>
</tbody>
</table>

DALY: disability-adjusted life year.
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, which contributed to inequitable access. As a new technology, mRNA vaccines frequently raised concerns of safety and efficacy (101,102). 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 (103–105). 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, coupled with scepticism about its efficacy, contributed to a persistent vaccine hesitancy worldwide (106), limiting effective protection at individual and population level (107,108).

**Recommendation 3**

WHO should use its reputability and trustworthiness to address the misinformation and disinformation about mRNA vaccines that are influencing vaccine hesitancy to improve current and future vaccine uptake, with the goal of improving public health.

**4.2. Biological and technological improvements**

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

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

Other areas of research relate to improving the effectiveness, safety, or ease of use of a mRNA vaccine, or to technological advancements in the manufacture of mRNA. They 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;
- further exploring the immunity elicited by mRNA vaccines at the molecular level;
- developing diverse vaccine formulations, including the use of adjuvants; and
- improving production processes to support manufacturing at scale and commercialization (23).

Research is already ongoing to advance mRNA technology in several of these areas for both preventive and therapeutic use (9,10,14).

Enhancing thermostability and reducing the complexity of cold-chain requirements for vaccines is crucial for improving global accessibility (109). Addressing the thermostability of new vaccines from the outset, as part of the TPP, is essential. Encouragingly, there is now a renewed focus on improving vaccine stability (110).
Preclinical studies are ongoing to develop thermo-stable mRNA vaccines (111,112), and two thermostable formulations have been licenced for emergency use: AWcoma in China, Mexico, Nepal and Indonesia; and GEMOVAC-19 in India. Further improvements may arise from the development of other types of mRNA platforms (e.g., self-amplifying, trans-amplifying and circular mRNA) that have advantages over non-replicating mRNA, such as higher and longer expression of the immunogen, better biological stability, increased longevity and reduced immunogenicity. For example, a preclinical study in mice showed that a self-amplifying mRNA vaccine against SARS-CoV-2 formulated with a nanostructured lipid carrier is stable at room temperature and can induce strong humoral immunity against the Alpha, Beta and Delta variants of concern (113). This work – which combined the development of a different type of mRNA and a different formulation – shows that mRNA technology can be improved, potentially leading to wider access to RNA vaccines for the current pandemic and the development of future mRNA vaccines.

**Recommendation 4**

WHO should take a leading role in identifying biological and technological improvements relevant to mRNA technology (including cold-chain requirements) and then in identifying pathogens with high priority for development of vaccines using mRNA technology. This includes advocating for and supporting 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.

**“WHO should take a leading role in identifying biological and technological improvements relevant to mRNA technology”**

4.3. **End-to-end equitable development of mRNA technology**

Experience with COVID-19 has shown that the development of a new technology can increase health inequality. Therefore, ensuring equitable access to both research outputs and mRNA technology is paramount to the development of mRNA vaccines, and efforts to ensure equitable access should take place alongside R&D. 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 mRNA technology more widely known and accessible. Overall, WHO should encourage others to join advocacy campaigns as part of its efforts to bring the benefits of mRNA technology to everyone in an effective, ethical, and equitable manner.

The benefits and limitations of mRNA technology should be communicated clearly and in a compelling fashion. Presentations should be balanced and should 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.

Depending on regional capabilities and the nature of the target condition, regionally based
diversification of R&D and manufacturing will be essential to addressing underserved or unmet needs. This will require further technology transfer and the commitment of governments to supporting and promoting local manufacture of vaccines. By investing in local production, countries can reduce their reliance on imported goods and services, which can be expensive and sometimes unreliable. In addition to creating job opportunities, local production can help to drive economic growth by increasing competitiveness in the value chain of production. By committing to supporting and promoting local production, countries can create job opportunities, boost the economy, and increase competitiveness in the global marketplace while improving access (114,115).

The development and use of mRNA technology could build on experience with the ACT-Accelerator. WHO and partners launched the ACT-Accelerator in response to the COVID-19 pandemic, to accelerate 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 the ACT-Accelerator experiences and identify key lessons for future pandemic preparedness and response (116). The Science Council encourages WHO 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.

**Recommendation 5**

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

**Recommendation 6**

WHO is encouraged to review and build on the experience of the ACT-Accelerator partnership, expanding its mission to include the development of vaccines against other infectious diseases and to contribute to pandemic preparedness.
5. Conclusion

With the success of COVID-19 mRNA vaccines, mRNA technology is leading a revolution in vaccine development. The speed and ease of development, as well as the safety and efficacy of mRNA vaccines, are generating hope and raising expectations that the platform will lead to the rapid development of new vaccines for existing and emerging infectious diseases.

However, there are clear challenges. The decision to engage in mRNA vaccine R&D should consider factors such as vaccine feasibility, burden of disease, and national and global public health agendas and strategies.

“The speed and ease of development, as well as the safety and efficacy of mRNA vaccines, are generating hope and raising expectations that the platform will lead to the rapid development of new vaccines for existing and emerging infectious diseases”
References


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


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


96. Polack FP, Harth V, Zink会出现错误的一部分。
References
Annex 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.

Stakeholder consultation: A virtual 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. Declarations of Interests (DOIs) were sought for all speaking participants on the agenda. Speakers who declared an interest were not deemed to influence the experts’ views in the context of the meeting. None of these stakeholders participated in the decision-making process relating to the development of this report nor the final content of the report.

<table>
<thead>
<tr>
<th>Speaking participants (listed on the agenda)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First name</strong></td>
</tr>
<tr>
<td>Hanan</td>
</tr>
<tr>
<td>Glenda</td>
</tr>
<tr>
<td>Adeeba</td>
</tr>
<tr>
<td>Jerome</td>
</tr>
<tr>
<td>Anna</td>
</tr>
<tr>
<td>Martina</td>
</tr>
<tr>
<td>Firdausi</td>
</tr>
<tr>
<td>John</td>
</tr>
<tr>
<td>Robin</td>
</tr>
<tr>
<td>Erin</td>
</tr>
<tr>
<td>Roger</td>
</tr>
</tbody>
</table>
### Annex 2. Original WHO-Approved COVID-19 Vaccines: Key Features

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Type of vaccine</th>
<th>Primary vaccination series (EUL)</th>
<th>Efficacy</th>
<th>Impact on transmission</th>
<th>Efficacy against variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMIRNATY/ BNT162b2 Pfizer-BioNTech COVID-19 vaccine (BioNTech Manufacturing GmbH)</td>
<td>mRNA (BNT162b2)</td>
<td>2 doses</td>
<td>95%</td>
<td>Modest impact on transmission</td>
<td>Effective against virus variants though for the Omicron variant, vaccine effectiveness against severe and mild disease after two doses is lower compared to Delta, and waning is more rapid</td>
</tr>
<tr>
<td>SPIKEVAX Moderna COVID-19 Vaccine (Moderna Biotech)</td>
<td>mRNA (mRNA-1273)</td>
<td>2 doses</td>
<td>94%</td>
<td>Modest impact on preventing mild infections and transmission, particularly in the context of Omicron</td>
<td>Effective against virus variants, though for the Omicron variant, vaccine effectiveness against severe and mild disease after two doses is lower compared to Delta, and waning is more rapid</td>
</tr>
<tr>
<td>Vaxzevria/EU Nodes AstraZeneca/ Oxford COVID-19 vaccine (AstraZeneca AB)</td>
<td>ChAdOx1-S recombinant</td>
<td>2 doses</td>
<td>83%</td>
<td>No substantive data available</td>
<td>Countries should assess the risks and benefits taking into consideration their epidemiological situation</td>
</tr>
<tr>
<td>Janssen COVID-19 vaccine/ Ad26.COV2-S recombinant (Janssen–Cilag International NV)</td>
<td>Ad26.COV2.S recombinant</td>
<td>1 dose</td>
<td>66%</td>
<td>No substantive data available</td>
<td>57% efficacy against moderate and severe disease (S. Africa only, 95% of cases due to B.1.351 variant)</td>
</tr>
<tr>
<td>Sinopharm/ BIBP COVID-19 vaccine (Beijing Institute of Biological Products Co., Ltd. - BIBP)</td>
<td>Inactivated virus</td>
<td>2 doses</td>
<td>79%</td>
<td>No substantive data available</td>
<td>86% efficacy against symptomatic COVID-19 and 100% against moderate and severe disease (UAE/Bahrain)</td>
</tr>
<tr>
<td>Coronavac (Sinovac Life Sciences Co., Ltd.)</td>
<td>Inactivated virus</td>
<td>2 doses</td>
<td>50%</td>
<td>No substantive data available</td>
<td>49% against PI variant in an observational study in Brazil</td>
</tr>
<tr>
<td>Nuvaxovid (Novavax CZ) Covovax (Serum Institute of India)</td>
<td>SARS-CoV-2 rS recombinant subunit</td>
<td>2 doses</td>
<td>90%</td>
<td>No sufficient evidence to date to evaluate the impact of the vaccine on transmission</td>
<td>90% against mild, moderate, or severe COVID-19 were Alpha, Beta and Delta were in circulation (USA/Mexico)</td>
</tr>
<tr>
<td>CONVIDECIA Vaccine (Ad5-nCoV) (CanSino Biologics)</td>
<td>Ad5-nCoV-S recombinant</td>
<td>1 dose</td>
<td>57%</td>
<td>Limited effect particularly against Omicron</td>
<td>Limited effect particularly against Omicron</td>
</tr>
</tbody>
</table>

Table prepared with information available from WHO (https://www.who.int/westernpacific/emergencies/covid-19/covid-19-vaccines accessed on 10 MAY 2023) and VIEW-hub, a collaboration between the WHO and the International Vaccine Access Center (IVAC) at Johns Hopkins Bloomberg School of Public Health. For detailed information on vaccine efficacy, see VIEW-hub (https://view-hub.org/vaccine/covid/product accessed on 10 MAY 2023).
### Annex 3: Past and ongoing mRNA vaccine trials for infectious diseases and virus-induced cancers

<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><strong>Chikungunya</strong></td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 1</td>
<td>VAL-181388 mRNA-1944</td>
<td>NCT03325075(26) NCT03829384(117)</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><strong>Cytomegalovirus (CMV)</strong></td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 3</td>
<td>mRNA-1647</td>
<td>NCT05085366</td>
<td>6 April 2026</td>
<td>Phase 2: Protein, peptides, recombinant (MVA, ALVAC) Phase 3: DNA</td>
</tr>
<tr>
<td><strong>Ebola</strong></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><strong>HIV</strong></td>
<td>Virus</td>
<td>Moderna/IAVI NIAID</td>
<td>Phase 1</td>
<td>mRNA-1644 mRNA-1644v2-Core BG505 MD39.3, BG505 MD39.3 gp151</td>
<td>NCT05414786 NCT05001373 NCT05217641</td>
<td>30 June 2023 11 April 2023 13 October 2023</td>
<td>Phase 3: Recombinant (Ad26, MVA), DNA, protein</td>
</tr>
<tr>
<td><strong>hMPV/PIV3</strong></td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 1</td>
<td>mRNA-1653</td>
<td>NCT03392389 NCT04144348</td>
<td>29 July 2019 31 March 2023</td>
<td>-</td>
</tr>
<tr>
<td><strong>Human papillomaviruses (HPV)</strong></td>
<td>Virus</td>
<td>pHion BioNTech SE</td>
<td>Preclinical</td>
<td>Therapeutic vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Influenza A &amp; B (flu)</strong></td>
<td>Virus</td>
<td>Pfizer BioNTech SE CureVac CureVac/GSK Moderna Pfizer Sanofi Pasteur</td>
<td>Phase 1</td>
<td>qIRV (22/23) CVSQIV VAL-506440 VAL-339851 mRNA-1010 mIRV, bIRV, qIRV soRNA MRT5410 MRT5407 MRT5413 mRNA vaccine</td>
<td>NCT05596734 NCT05252338 NCT05446740 NCT03076385(119) NCT05666639 NCT05052697 NCT05553301 NCT05550554 NCT05426174</td>
<td>13 December 2024 November 2022 25 January 2024 October 2018 13 August 2018 31 March 2024 27 January 2023 1 August 2023 2 August 2023</td>
<td>Several vaccines approved in 2022</td>
</tr>
<tr>
<td><strong>Lassa</strong></td>
<td>Virus</td>
<td>Moderna CureVac</td>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
<td>Preclinical: Recombinant, DNA, replicon particles, other vectors Phase 1: recombinant (VSV, MV)</td>
</tr>
</tbody>
</table>


## Annex 3: (contd.)

<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>Malaria</td>
<td>Protozoan</td>
<td>BioNTech SE</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>
</tr>
<tr>
<td>Marburg virus disease</td>
<td>Virus</td>
<td>CEPI Imperial College London</td>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
<td>Phase 1: DNA, recombinant (ChAd3, MVA)</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Virus</td>
<td>NIAD</td>
<td>Phase 1</td>
<td>mRNA -1215</td>
<td>NCT05398796</td>
<td>24 June 2024</td>
<td>Phase 1: Recombinant (VSV), protein</td>
</tr>
<tr>
<td>Rabies</td>
<td>Virus</td>
<td>CureVac</td>
<td>Phase 1</td>
<td>CV7202</td>
<td>NCT03713086(27)</td>
<td>23 November 2021</td>
<td>27 Licensed vaccines. Several candidates in development</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Virus</td>
<td>Moderna</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>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Virus</td>
<td>Multiple</td>
<td>Phase 4</td>
<td></td>
<td></td>
<td></td>
<td>11 vaccines have received WHO emergency use listing (EUL)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Bacteria</td>
<td>BioNTech SE</td>
<td>Phase 1</td>
<td>BNT164a1, BNT164b1</td>
<td>NCT05537038, NCT05547464</td>
<td>April 2025, April 2025</td>
<td>BCG, 16 candidates under active clinical development</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Virus</td>
<td>CureVac/ CEPI</td>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
<td>Stamaril (Sanofi Pasteur)</td>
</tr>
<tr>
<td>Varicella Zoster Virus</td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 2</td>
<td>VZV modRNA</td>
<td>NCT05703607</td>
<td>5 January 2030</td>
<td>Several licensed vaccines</td>
</tr>
<tr>
<td>Zika</td>
<td>Virus</td>
<td>Moderna</td>
<td>Phase 1 Phase 2</td>
<td>mRNA-1325 mRNA-1893</td>
<td>NCT04064905(28), NCT03514089(28), NCT04911761</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>
</tr>
</tbody>
</table>
Potential benefits and limitations of mRNA technology for vaccine research and development for infectious diseases and virus-induced cancers.