World Health Organization

WHO R&D Blueprint

COVID-19

Vaccines R&D Achievements Report

February 2020 – May 2021

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R&DBlueprint

Powering research
to prevent epidemics

Contents

1. Overall Summary

On 11-12 February 2020, WHO, in collaboration with the Global Research Collaboration for Infectious Disease Preparedness and Response (GLOPID-R) – an international network of funders to facilitate coordination and information sharing, organized a Global Forum on research and innovation for COVID-19 ('Global Research Forum').

In March 2020, the WHO R&D Blueprint group published a Coordinated Global Research Roadmap: 2019 Novel Coronavirus (https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap).

The following selected knowledge gaps in the vaccine research and development area were identified

1. Strength, duration of immunity, cellular immunity
2. Possibility of enhanced disease after vaccination
3. Animal models for prioritizing vaccines
4. Animal models for evaluating potential for vaccine-enhanced disease
5. Assays to evaluate immune response to vaccines
6. Design of late phase vaccine clinical trials

COVID-19 vaccines development has been unique. However, we still need rapid results in the context of major public health needs around the world; we need reliable results to support vaccine confidence to assure that speed doesn't lead to serious mistake and lastly we need equitable results that respect the rights and values of all people. Important and critical investigation is being coordinated by WHO to advance our understanding for safe and effective COVID-19 vaccines and to accelerate and coordinate the research, development and evaluation of candidate products. The Solidarity Vaccine Trial is being established to provide robust evidence from a wide range of settings globally on the efficacy of potential COVID-19 vaccines.

2. Aim

A key aim of the Vaccine R&D thematic area of the Roadmap has been to the collation of evidence and data on treatments, the coordination of research on candidate vaccines, providing platforms for sharing of data, and preparing to launch the Solidarity Vaccine Trial.

Three specific objectives underpinned the Vaccine research agenda:

- *Objective 1: To continuously identify vaccine candidates for clinical evaluation and landscape the scientific evidence*
- *Objective 2: To develop multicentre Core Protocols for a standardized approach to assess the efficacy and safety of candidate vaccines in clinical trials*
- *Objective 3: To coordinate and collaborate internationally to implement clinical trials, for evaluation of safety and efficacy of candidate vaccines.*

3. Key Achievements

3.1. Global Coordination: Multiple efforts have been made to enhance coordination of COVID-19 vaccine research, to avoid unnecessary duplication of efforts, to promote standardized approaches that ensure the comparability of results, and to provide platforms for sharing of data. Support has included development of a repository list of laboratories holding COVID-19 isolates, ensuring the availability of animal models, and developing standardized protocols and preferred characteristics of a vaccine.

3.2. Leading the Experts: Multiple expert working groups were established to promote greater coordination in COVID-19 vaccine-related R&D. These include groups focusing on:

- **Target product profiles**: Was developed through a consultation process with key stakeholders in human and animal health. It is intended to guide and prioritize the development of vaccines The document, available on the RD Blueprint page: https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines, describes the preferred characteristics of a COVID-19 vaccine.

- **Animal models**: In February 2020 the World Health Organization (WHO) R&D Blueprint convened a group of experts to develop preclinical models of Severe Acute Respiratory Syndrome (SARS)-CoV-2 infection. Since its inception, the goal of this WHO COVID Modeling group (WHO-COM) has been to accelerate the development of COVID-19 vaccines and therapeutics by rapid sharing of data among member scientists worldwide. In addition, due to concerns raised about the possibility of vaccine-associated enhanced disease (VAED), which was associated to enhancement of respiratory disease, predominantly in the lower respiratory tract, after vaccination against infections in the past (VAERD), or antibody-mediated disease enhancement (ADE) after vaccination, a main focus

of the group was to assess VAERD and ADE in animal models. In September 2020, the WHO-COM authored a review on COVID-19 animal models (Munoz-Fontela et al., 2020), which reflected a summary of the achievements at that time and was supported by publications authored by the members of the group. Specific achievements are as follows

What has been achieved?	Specific points
1) Portfolio of models to assess pathogenesis, transmission and SARS-CoV-2 immunity and to accelerate therapeutic and vaccine development. Unprecedented data sharing avoided unnecessary experiment repetition. Organs on chip technology surfaced as an alternative to animal modelling for several applications.	1- Mouse models: Generation of transgenic and knock-in mouse models expressing human ACE2 (Bao et al., 2020). Mouse adaptation of SARS-CoV-2. Development of outbred mice and mice with human immune system (Leist et al., 2020). 2- The hamster model emerged as the small animal model of choice for preclinical vaccine and therapeutic development (Sia et al., 2020). 3- Ferrets, cats and hamsters have been widely utilized to understand SARS-CoV-2 transmission (Zhou et al., 2021). 4- Rhesus, cynomolgus and African green monkeys have been the model of choice to study SARS-CoV-2 induced pneumonia. In this model preclinical vaccine data matched phase I, II clinical data remarkably (Munster et al., 2020).
2) Immunology studies showed no evidence of VAERD and served to investigate biomarkers and vaccine correlates of protection.	1- Ferrets and rhesus macaques immunized with alum-adjuvanted formalin-inactivated vaccines showed no evidence of VAERD. 2- Re-infection studies showed that immunization of rhesus macaques provides protection against re-infection (Chandrashekar et al., 2020). 3- Studies in rhesus macaques suggest that levels of neutralizing antibodies between 100-500 GMT are a

What has been achieved?	Specific points
	correlate of protection. These studies also highlighted CD8 T cells an important component of vaccine immunity (McMahan et al., 2021).
3) Assessment of VOC transmission, pathogenesis and immune escape. This also reinforced the importance of virus sharing.	1- Passive transfer studies and vaccination + challenge studies indicate that, despite significant drops in antibody neutralization, all vaccines tested in animal models still confer protection to VOC challenge (Fischer et al., 2021). 2- Emerging VOCs show enhanced transmission in competition studies with prototypic strains in animal models (Zhou et al., 2021). 3- Some VOCs (e. g. B.1.135) seem to show lower pathogenicity in animal models. These findings suggest that as VOCs adapt to humans, animal models may need to be refined (Nuñez et al., 2021).
4) Secondary reservoir identification, species tropism is unprecedented	1- Ecological studies indicate that the host-range of SARS-CoV-2 is greater in comparison for example with other beta-coronaviruses. Several mammalian species including cats, bank voles, mink, tigers, racoon dogs, great apes, tree shrews and deer can be infected with SARS-CoV-2 and spread infection to other members of the same species. These studies strongly suggest that anthropozoonosis can help to maintain SARS-CoV-2 in nature (Oude Munnink et al., 2021).

What has been achieved?	Specific points
5. The importance of viral working stock propagation has been highlighted in several months of collaborative international work and data sharing by a WHO R&D Blueprint subgroup. This has been summarised into a short publication (accepted and in press in NPJ-Vaccines). This publication provides a cautionary note about ensuring working stocks are not compromised by the accidental generation of mutations and/or deletions in laboratory working stocks.	Vero cells appear to permit the generation and preferential proliferation of mutations or deletions, especially at region of the genome coding for the furin cleavage site of the Spike protein. Vero/SLAM cells, which contain a plasmid encoding antibiotic resistance and the measles receptor, appear to restrict this viral genome diversity. The importance of ensuring working stocks of virus are true to the original clinical isolate has been emphasised and reinforced by this collaborative study (Funnell et al., 2021)
6. The refinement, reduction and replacement of animal research has been constantly on the working group's agenda. Data sharing has resulted in reduced requirement for animal studies and refinement has occurred by sharing data around clinical symptoms and pathology. Replacement options in the form of differentiated tissue in microphysiological systems (MPS) have also been developed and their power emphasised in publications showing analogous data outputs to those seen during *in vivo* studies.	Studies showing the value of MPS have been published which demonstrate that some potential antiviral or therapeutic drugs which gave false positive signals in in vitro assays using Vero cells failed in both in vivo challenge studies and MPS systems. This emphasised the potential utility of MPS in the context of drug development and testing using MPS opposed to contemporary in vitro assay which use undifferentiated Vero cells (Funnell et al., 2020, Touret et al., 2020).

- **Assay development**:

  In March 2020, the WHO R&D Blueprint group published a Coordinated Global Research Roadmap: 2019 Novel Coronavirus (https://www.who.int/publications/m/item/a-coordinated-global-research-roadmap). A key research priority identified in the report was "To develop and standardize assays to support vaccine development, particularly to support the evaluation of immune responses and to support clinical case definition. Basic reagents should be shared to accelerate the development of international standards and reference panels that will help support the development of ELISAs, pseudovirion neutralization and PCR assays." Pursuant to this objective, the WHO convened an international working group on COVID-19 viruses, reagents and immune assays, which has met on a weekly basis since that time. Early topics of the group included status updates on the development and availability of SARS-CoV-2 viral isolates and other critical reagents and discussions of the potential for cross-reactivity between SARS-CoV-2, SARS-CoV-1 and MERS-CoV based on available sequence/modelling data. The meetings then transitioned to data presentations on the development of immune assays, cross reactivity, duration of immunity, assay comparisons, and assay harmonization, based on antibody standards. In the last year, there has been a great deal achieved in this area. Below is an overview of some of the chief accomplishments.

What has been achieved?	Specific points and References
1. Viruses and other key reagents such as expression plasmids, proteins and antibodies have been made widely available through repositories such as BEI Resources, NIBSC and the European Virus Archive as well as directly from lab to lab, as well as commercial sources.	1- The major repositories have a number of SARS-CoV-2 stocks available, including Variants of Concern. Expression plasmids for SARS-CoV-2 proteins are available from BEI resources and have also been distributed widely between laboratories. Here are the links to the SARs-CoV-2 reagents in these repositories: BEI Resources: https://www.beiresources.org/BEIHighlights1.aspx?ItemId=79&ModuleId=14004 NIBSC: https://www.nibsc.org/science_and_research/idd/cfar/covid-19_reagents.aspx European Virus Archive: https://www.european-virus-archive.com/evag-news/sars-cov-2-collection 2- In addition, there are a very large number of commercial sources now available for SARS-CoV-2 proteins, hyperimmune serum, convalescent plasma and serum, monoclonal antibodies and other key reagents.
2. Multiple assays have been developed to measure binding antibodies against full-length Spike protein, portions of the Spike protein such as RBD, or the N protein. This includes multiple formats such as ELISA and ECL assays.	1- ELISAs were developed and described early by several members of the assays group. There were different antigens used including full length Spike protein, the S1 or RBD portions of the Spike protein or Nucleocapsid protein. Here are several examples: Stadlbauer et al 2020 SARS-CoV-2 *Seroconversion in Humans: A Detailed Protocol for a Serological Assay, Antigen Production, and Test Setup* Curr Protoc Microbiol. 2020 Jun;57(1):e100. doi: 10.1002/cpmc.100 Amanat et al 2020 *A serological assay to detect SARS-CoV-2 seroconversion in humans* Nat Med. 2020 Jul;26(7):1033-1036. doi: 10.1038/s41591-020-0913-5

What has been achieved?	Specific points and References
	Okba et al 2020 *Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease Patients*. Emerg Infect Dis. 2020 Jul;26(7):1478-1488. DOI: 10.3201/eid2607.200841 Freeman et al 2020 *Validation of a SARS-CoV-2 spike protein ELISA for use in contact investigations and serosurveillance*. bioRxiv. 2020 Apr 25;2020.04.24.057323. DOI: 10.1101/2020.04.24.057323 Johnson et al 2020 *Evaluation of a novel multiplexed assay for determining IgG levels and functional activity to SARS-CoV-2* Journal of Clin. Virol. 130, Sept 2020, 104572 https://doi.org/10.1016/j.jcv.2020.104572 2 - There are now a wide range of ELISA and other binding assays available from public health, academic and commercial laboratories. These include multiple technologies, formats (total Ig, IgG, IgM, IgA) and antigens. There are several use cases for these assays including diagnostics, seroepidemiology studies, and support for development of vaccines and therapeutics. Many of these assays have now been qualified and validated. As of May 7, 2021, There are 76 that have been granted EUA status by the US FDA. (https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-serology-and-other-adaptive-immune-response-tests-sars-cov-2#individual-serological) 3 – There have been several independent performance assessments of major commercial assays, including from FIND, the National Institutes of Health and Public Health England. FIND evaluation of SARS-COV-2 antibody detection kits https://www.finddx.org/sarscov2-eval-antibody/

What has been achieved?	Specific points and References
	FDA EUA authorized serology test performance https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance *Evaluation of sensitivity and specificity of four commercially available SARS-CoV-2 antibody immunoassays* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/898437/Evaluation__of_sensitivity_and_specificity_of_4_commercially_available_SARS-CoV-2_antibody_immunoassays.pdf 4 – Some assays have been developed specifically for use in low resource settings, such as an HA inhibition assay. Townsend et al 2021 *A haemagglutination test for rapid detection of antibodies to SARS-CoV-2* Nature Communications volume 12, Article number: 1951 (2021) https://www.nature.com/articles/s41467-021-22045-y
3. Wild-type virus neutralization assays, pseudovirus neutralization assays and surrogate neutralization assays are available and being used to assess neutralizing antibody titers. In many cases, good correlation is observed between binding assays and neutralization, although this is influenced by the format of the assay.	1 – Wild type viral neutralization assays (wtVNA) are the gold standard, but most technically challenging and only able to be performed in BSL-3 laboratories. The first wtVNAs were described from labs in China Zhou et al 2020 *A pneumonia outbreak associated with a new coronavirus of probable bat origin* Nature volume 579, pp. 270–273(2020) https://www.nature.com/articles/s41586-020-2012-7 2 – Pseudovirus neutralization assays (psVNA) have been developed with multiple backbones including lentiviruses and vesicular stomatitis virus (VSV). These have huge logistical advantages since BSL-3 is not required and there is no need to have the actual virus sample, just the sequence. Multiple studies have shown that the

What has been achieved?	Specific points and References
	neutralization activity in these assays correlate with wtVNA. One example is shown below. Bewley et al 2021 Quantification of SARS-CoV-2 neutralizing antibody by wild-type plaque reduction neutralization, microneutralization and pseudotyped virus neutralization assays. Nature Protocols Apr 23, 2021 https://doi.org/10.1038/s41596-021-00536-y 3 – Surrogate neuralization assays have been developed which assess antibody disruption of RBD binding to purified hACE2. These also have been shown to correlate well with wtVNA and psVNA. Tan et al 2020 *SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction* Nature Biotechnology Vol 38 | September 2020 | 1073–1078 https://doi.org/10.1038/s41587-020-0631-z
4. A WHO International Standard (IS) for anti-SARS-CoV-2 immunoglobulin was developed by NIBSC and approved by the WHO Expert Committee on Biological Standardization in December 2020. There are also secondary standards available from several	1- The International Standard is available for order from the NIBSC catalog, item 20/136 (https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=20/136). It consists of a pool of plasma samples collected from 11 donors with high Ab titer who had recovered from SARS-CoV-2 infection prior to May 2020. The samples were reported by a member of the assays group to be higher in IgM than IgG. 2 – A collaborative study was run with 50 laboratories from 14 countries in order to generate data to support the standard. The report of the Expert Committee on Biologicals Standardization is published in the WHO Technical Report Series 1030.

What has been achieved?	Specific points and References
sources including the US National institutes of Health.	(https://extranet.who.int/pqweb/medicines/who-technical-report-series) 3 - The intended use of the International Standard is for the calibration and harmonisation of serological assays detecting anti SARS-CoV-2 neutralising antibodies. The assigned unitage for neutralizing assays is 1000 IU/mL. The preparation can also be used as an internal reference reagent for the harmonisation of binding antibody assays. For binding antibody assays, an arbitrary unitage of 1000 binding antibody units (BAU)/mL can be used to assist the comparison of assays detecting the same class of immunoglobulins with the same specificity (e.g. anti - RBD IgG, anti-N IgM, etc). Full instructions for use are contained in the product insert (https://www.nibsc.org/documents/ifu/20-136.pdf). 4 – The National Institutes of Health SARS-CoV-2 secondary serology standard is available at https://frederick.cancer.gov/seronet/serology-standard .
5. wtVNA and psVNA have been established in multiple laboratories for the WHO Variants of Concern (VOC) as well as for several Variants of Interest (VOI) to assess changes in neutralization activity for convalescent and vaccine sera.	1- Recent publications and pre-prints have shown impacts on neutralization due to the current WHO VOCs (B.1.1.7, B.1.35 and P.1). Most assays have demonstrated some loss in neutralization activity with each variant of concern, with the greatest loss observed so far with VOC B.1.351. Of note, these are non-validated assays which are early in development and are using different panels of sera. Shen et al *SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines* Cell Host & Microbe 29(4) 14 April 2021 pp. 529-539 https://www.sciencedirect.com/science/article/pii/S1931312821001025 Cele et al Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma Nature. 2021 May;593(7857):142-146 DOI: 10.1038/s41586-021-03471-w Dejnirattisai et al., *Antibody evasion by the P.1 strain of SARS-CoV-2*, Cell 184, 1–16 May 27, 2021 https://doi.org/10.1016/j.cell.2021.03.055

What has been achieved?	Specific points and References
	Wang et al *Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7* Nature volume 593, pages130–135(2021) https://www.nature.com/articles/s41586-021-03398-2 Yadav et al *Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees* Biorxiv April 23, 2021 doi: https://doi.org/10.1101/2021.04.23.441101 Garcia-Beltran et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity Cell vol 184, issue 9, 29 April 2021 Pages 2372-2383.e9 https://www.sciencedirect.com/science/article/pii/S0092867421002981
6. Assays to assess T cell responses to SARS-COV-2 infection as well as vaccination have been established in multiple laboratories. These have also been applied to VOCs.	1 – Several studies have demonstrated robust T cell responses to SARS-CoV-2 infection and have also demonstrated that T cell responses are associated with disease severity. Sette and Crotty *Adaptive immunity to SARS-CoV-2 and COVID-19*. Cell. 2021 Feb 18;184(4):861-880 doi: 10.1016/j.cell.2021.01.007. Rydyznkski Moderbacher et al *Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity* Cell. 2020 Nov 12;183(4):996-1012.e19. DOI: 10.1016/j.cell.2020.09.038 2- There is substantial evidence of cross-reactive T cells from previous human coronavirus infections, although their role in protection is unclear. Ogbe et al 2021 *T cell assays differentiate clinical and subclinical SARS-CoV-2 infections from cross-reactive antiviral responses* Nature Communications **2**, Article number: 2055 (2021) https://www.nature.com/articles/s41467-021-21856-3 Lipsitch et al *Cross-reactive memory T cells and herd immunity to SARS-CoV-2*. Nat Rev Immunol 2020 Nov;20(11):709-713. doi: 10.1038/s41577-020-00460-4.

What has been achieved?	Specific points and References
	3- The variants of concern seem to have little effect on T -cell responses to SARS-CoV-2. Tarke et al *Negligible impact of SARS-CoV-2 variants on CD4 + and CD8 + T cell reactivity in COVID-19 exposed donors and vaccinees* bioRxiv . 2021 Mar 1;2021.02.27.433180. DOI: 10.1101/2021.02.27.433180 4- To address the potential for Vaccine Associated Enhancement of Respiratory Disease, vaccine developers analysed the Th1/Th2 responses to their vaccines, as Th2 biased responses have reportedly been associated with VAERD. Corbett et al SARS-CoV-2 *mRNA vaccine design enabled by prototype pathogen preparedness*. Nature volume 586, pages567–571(2020)
7. Duration of binding antibody, neutralizing antibody and T cell responses to SARS-CoV-2 infection has been assessed in multiple studies.	1 - Some studies have reported significant waning of antibody responses while others have reported relatively stable levels of antibody, although this seems to be dependent on the assay employed. Certain assays lose sensitivity over time and this seems to be dependent on the assay rather then the antigen. Muecksch et al *Longitudinal Serological Analysis and Neutralizing Antibody Levels in Coronavirus Disease 2019 Convalescent Patients* J Infect Dis. 2021 Feb 13;223(3):389-398. DOI: 10.1093/infdis/jiaa659 Longitudinal analysis 1 shows durable and broad immune memory after SARS2 Cohen et al *CoV-2 infection with persisting antibody responses and memory B and T cells* biorxiv doi: https://doi.org/10.1101/2021.04.19.21255739 2 - Durable T cell memory has been observed following SARS-CoV-2 infection.

What has been achieved?	Specific points and References
	Dan et al 2021 *Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection* Science 05 Feb 2021: Vol. 371, Issue 6529, eabf4063 DOI: 10.1126/science.abf4063 Cohen et al *CoV-2 infection with persisting antibody responses and memory B and T cells* biorxiv doi: https://doi.org/10.1101/2021.04.19.21255739
8. Conditions used to culture SARS-CoV-2 are critically important. Multiple passages in Vero cells can lead to the proliferation of mutations, especially of the Furin cleavage site in the Spike protein.	1 – Mutation or deletion of the furin cleavage site has been shown to lead to an attenuated phenotype *in vivo* and different *in vitro* properties. Klimstra et al *SARS-CoV-2 growth, furin-cleavage-site adaptation and neutralization using serum from acutely infected hospitalized COVID-19 patients*. JOURNAL OF GENERAL VIROLOGY Volume 101, Issue 11 21 August 2020 https://doi.org/10.1099/jgv.0.001481 Johnson et al Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis Nature volume 591, pages293–299(2021) https://www.nature.com/articles/s41586-021-03237-4 2 - A separate WHO working group on SARS-CoV-2 propagation was formed and a manuscript summarizing their findings has been accepted for publication (NPJVACCINES-01217R). This report highlights lessoned learned very early on in the pandemic and provides recommendation for best practice through agreement on findings from an international group of laboratories which used different viruses but saw similar effects during propagation. This lessons-learned report should help other laboratories ensure the quality and integrity of their SARS-CoV-2 working stocks and should reduce time to development of new vaccines, drugs and therapies.
9. In studies of antibody cross reactivity with other coronaviruses, there has been	Amanat et al 2020 *A serological assay to detect SARS-CoV-2 seroconversion in humans* Nat Med. 2020 Jul;26(7):1033-1036. doi: 10.1038/s41591-020-0913-5

What has been achieved?	Specific points and References
little cross reactivity observed with seasonal human betacoronaviruses, some cross reactivity with MERS-CoV and the most cross reactivity with SARS-CoV.	Okba et al 2020 *Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease Patients*. Emerg Infect Dis. 2020 Jul;26(7):1478-1488. DOI: 10.3201/eid2607.200841 Freeman et al 2020 *Validation of a SARS-CoV-2 spike protein ELISA for use in contact investigations and serosurveillance*. bioRxiv. 2020 Apr 25;2020.04.24.057323. DOI: 10.1101/2020.04.24.057323 Hicks et al 2021 *Serologic Cross-Reactivity of SARS-CoV-2 with Endemic and Seasonal Betacoronaviruses* J Clin Immunol . 2021 Mar 16;1-8. DOI: 10.1007/s10875-021-00997-6
10. Neutralizing antibody and Fc functional antibody responses were both found to correlate with protection from SARS-CoV-2 disease in re-infection, adoptive transfer and vaccine studies in non-human primates.	McMahan et al Correlates of protection against SARS-CoV-2 in rhesus macaques Nature Nature volume 590, pages630–634(2021) https://doi.org/10.1038/s41586-020-03041-6 Chandrashekar et al SARS-CoV-2 infection protects against rechallenge in rhesus macaques Science 14 Aug 2020 vol 369(6505) pp. 812-817 https://science.sciencemag.org/content/369/6505/812#:~:text=Immunity%20from%20reinfection&text=generated%20rhesus%20macaque%20models%20of,protected%20against%20a%20second%20infection. Yu et al DNA vaccine protection against SARS-CoV-2 in rhesus macaques Science 10.1126/science.abc6284 (2020). www.sciencemag.org Corbett et al Immune Correlates of Protection by mRNA-1 1273 Immunization against SARS-CoV-2 Infection in Nonhuman Primates biorxiv doi: https://doi.org/10.1101/2021.04.20.440647

- **Clinical trial design**: Under the RD Blueprint Road of Action, WHO convened a group of experts in clinical trials, regulatory, and outbreak management, to agree on standard procedures to rapidly evaluate experimental vaccines during public health emergencies (PHEs) while maintaining the highest scientific and ethical standards. This guidance document details major vaccine study designs that could be used during outbreaks and PHEs of emerging and re-emerging pathogens for which there is no licensed vaccine.

  https://www.who.int/docs/default-source/blue-print/working-group-for-vaccine-evaluation-(4th-consultation)/ap1-guidelines-online-consultation.pdf

- **Core protocol development**: Drafted a core protocol (https://www.who.int/publications-detail-redirect/an-international-randomised-trial-of-candidate-vaccines-against-covid-19) for the global Solidarity vaccine trial with the aim of rapidly evaluate multiple candidate vaccines and provide sufficient evidence of safety and efficacy against COVID-19 to support decision-making about vaccine deployment.

- **Vaccine prioritization**: Establishing criteria for selection of vaccines for clinical trials and prioritizing the most promising candidates for inclusion. The group produced a table that outlines the criteria and the scoring system for assessing the inclusion of a candidate vaccine.

- **Human challenge studies**: The Advisory Group on Closely Monitored Challenge Models of Experimental COVID-19 Infection and Illness in Healthy Young Adult Volunteers developed a set of recommendations to inform the design and implementation of controlled human infection studies. Two groups have started human challenge studies with low risk healthy individuals (aged 18-30) to initially determine through dose escalation the target dose of challenge agent that will elicit an asymptomatic level of illness. The studies have received ethical approval and aim to assess antivirals and/or candidate vaccines and establish correlates of protection in previously infected individuals.

3.3. Research Forums: Online forums have been established to facilitate global discussions on key aspects of vaccine development and to encourage sharing of data and experiences. Forums have focused on key issues such as:

- **COVID-19 Vaccines: Knowledge gaps and research priorities:** The virtual forum took place on January 15, 2021. The main objective was to discuss the current

state of COVID-19 vaccine development and future research priorities and needs. In breakout groups and panel sessions, participants identified a range of priority research questions:

Area of research	Research questions
Closing gaps in knowledge about first-generation vaccines	What is the real-world effectiveness of first-generation vaccines? What is the duration of protection provided by first-generation vaccines? How effective are first-generation vaccines in special populations (e.g. children, pregnant women, the immunosuppressed)? What impact do first-generation vaccines have on viral shedding and transmission? What is the long-term safety of first-generation vaccines in real-world settings?
Generating evidence to inform programme design	What is the impact of different dosing schedules? What is the impact of combining different vaccines? How can local epidemiology be used to guide targeted vaccine use and integrated use of vaccines with other control measures?
Accelerating new vaccine development	What are the correlates of protection for different aspects of COVID-19? What impact do variants of concern have on the efficacy of first-generation vaccines?
Effective communication	What are the best approaches for communicating vaccine-related efficacy and safety information to general audiences?

- Discussions also identified a range of needs to accelerate research on existing and second-generation vaccines:
    - Openness, collaboration and sharing

- Platform for data sharing
- Standardization of assays and agreement on preferred model systems.
- Data gathering from multiple sources.
- Global surveillance systems.
- Integration of clinical, in vitro and in vivo data.

- **SARS-CoV-2 variants: Knowledge gaps and research**. The virtual meeting took place on February 12, 2021. Developing and agreeing of an R&D agenda in response to existing and emerging SARS-CoV-2 variants. Assessing the implications of variants of concern for vaccine development and developing mechanisms to track and respond to them. The following priority areas of research were identified: (i) Detection of variants and the need for a global surveillance strategy to detect and track new variants of concern; (ii) Understanding the epidemiology and evolution of variants; (iii) Understanding variant biology and how mutations affect the biology of variant SARS-CoV-2 strains; (iv) understanding clinical impacts and consequences of infection with variants and (v) understanding the impacts on vaccine effectiveness. WHO is outlining the pathway to assess vaccines in the context of variants for current, modified and new vaccines.

  Additionally, sharing, standardization, data integration, capacity building, new diagnostic tools and leveraging trials and cohort studies, nomenclature, communication and global coordination were identified as important research facilitators.

- **COVID-19 Vaccines: Methodological approaches to assess effect on vaccine efficacy, effectiveness and impact**: Potential designs and methodological approaches for clinical trials and observational studies to assess the impact of variants on vaccine efficacy and effectiveness. Multiple vaccines are being rolled out globally and are pivotal to COVID-19 control. However, SARS-CoV-2 is prone to mutation and multiple variant strains have been identified. The key outcomes from this forums where (i) WHO must play a role in coordinating activities to identify the need for vaccines against new SARS-CoV-2 variants and the sequences that are most appropriate for global use; (ii) as vaccines are deployed, it will be essential to gather data on their performance against evolving variants; (iii) regulatory alignment at global level is important; (iv) communication should be prioritized to raise awareness of the challenges and ongoing activities.

- **Data and material sharing**: Encouraging more rapid sharing of data and virus samples for analysis.

3.4. **Agile Vaccine Research Working Group:** monthly meetings to provide updates of COVID-19 vaccine research progress with the ability to pivot given dynamic research needs and to facilitate rapid dissemination and open discussion of research protocols and emerging results. This forum provides space to vaccine developers and funders to share information on their research plans and priorities including those related to variants

3.5. **Mapping the Scientific Evidence:** The COVID-19 living map is an interactive database that provides instant access to all registered clinical trials (both randomised and non-randomised) being conducted worldwide on novel COVID-19 vaccines.

COVID-19 NMA initiative living map of vaccine. https://covid-nma.com/vaccines/mapping/

3.6. **Vaccine Tracker:** The WHO Vaccine Landscape and Tracker is a comprehensive COVID-19 vaccine landscape listing all the pre-clinical and clinical vaccine candidates being developed worldwide. Updated weekly, the landscape tracks the progress of each candidate vaccines from pre-clinical through to Phase 1, 2, 3 and 4 studies, as well as provides links to published reports on the safety, immunogenicity and efficacy data.

COVID-19 landscape and tracker of novel candidate vaccines

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

3.7. **Landscape of observational study designs for COVID-19 vaccination.** This landscape lists observational studies focusing on the effectiveness of COVID-19 vaccination in real world settings, assessing endpoints on immunity, infection, transmission, efficacy and safety.

https://www.who.int/publications/m/item/draft-landscape-of-observational-study-designs-on-the-effectiveness-of-covid-19-vaccination

3.8. **Regulatory coherence**: Regulators and the WHO prequalification team have maintained regular contact to align and coordinate activities. Specific guidelines have been developed to expedite the evaluation of modified vaccines targeting variants of concern. Multiple written standards are available as well as reference preparations. WHO has accelerated the process and nomenclature scheme for vaccines for variants has been developed. WHO provides regulatory support to countries to issue regulatory authorizations for vaccines supplied through COVAX facility.

3.9. **Vaccine Safety**. Guidance on the development of pharmacovigilance capacity to monitor vaccine safety, assessment of rare cases of side effects in vaccinated people and actively reviewing emerging evidence in collaboration with regulatory authorities. WHO is also coordinating research to help understand the risk of any emerging safety concern, such as background rates, potential mechanisms of action and possible mitigating measures.

3.10. **Solidarity Vaccine trial**: Setting the stage for additional vaccine development and clinical evaluation the Solidarity Vaccine Trial will be launched as a large, international, randomized clinical trial platform to rapidly and efficiently evaluate the efficacy and safety of multiple candidate COVID-19 vaccines and to ensure that as many of the vaccine candidates still in development have the best chance of success. Its aims are to evaluate efficiently and rapidly (within 3–6 months of each vaccine's introduction into the study) the efficacy of multiple vaccines, helping to ensure that weakly effective vaccines are not deployed. High enrolment rates facilitated by flexible trial design and hundreds of study sites in high-incidence locations will yield results on short-term efficacy for each vaccine within just a few months of including that vaccine. Preparations are complete to initiate the trial in two countries in at least 15 trial sites with an anticipated enrolment rate of 2oo patients per site per week.

4. Efficacy of COVID-19 vaccines

Vaccine	Efficacy results available	
	Date of first released information	**Press release link**
Pfizer-BioNTech	09 November 2020	https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against
Sputnik V	11 November 2020	https://sputnikvaccine.com/newsroom/pressreleases/the-first-interim-data-analysis-of-the-sputnik-v-vaccine-against-covid-19-phase-iii-clinical-trials-/
Moderna	16 November 2020	https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy
AstraZeneca-University of Oxford	23 November 2020	https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html
Sinopharm	29 December 2020	https://www.biospace.com/article/china-s-sinopharm-claims-covid-19-vaccine-has-79-percent-efficacy/
Sinovac Biotech	13 January 2020	https://www.bbc.com/news/world-latin-america-55642648
Novavax	28 January 2021	https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
Johnson & Johnson	29 January 2021	https://www.jnj.com/johnson-and-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial
CanSino Biologics	08 February 2021	https://www.bloomberg.com/news/articles/2021-02-08/pakistan-says-cansino-s-covid-vaccine-shows-65-7-efficacy In China, administered to military personnel since June 2020.
Bharat Biotech	04 March 2021	https://www.pharmaceutical-technology.com/news/bharat-biotech-vaccine-efficacy/

Key Benefits

Safe and effective COVID-19 vaccines have been developed at unprecedented speed, with the first vaccinations taking place less than a year after SARS-CoV-2 was first identified. The speed of vaccine development has depended on extensive collaboration and cooperation between multiple stakeholders. Even so, further vaccines are still required to increase global manufacturing capacity, to provide products with additional desirable properties, and potentially to address SARS-CoV-2 variants of concern.

5. Key outputs

COVID-19 NMA initiative living map of vaccine. https://covid-nma.com/vaccines/mapping/

COVID-19 landscape and tracker of novel candidate vaccines

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Landscape of observational study designs for COVID-19 vaccination

https://www.who.int/publications/m/item/draft-landscape-of-observational-study-designs-on-the-effectiveness-of-covid-19-vaccination

Feasibility, Potential Value and Limitations of Establishing a Closely Monitored Challenge Model of Experimental COVID-19 Infection and Illness in Healthy Young Adult Volunteers, 2 December, 2020.

https://www.who.int/publications/m/item/feasibility-potential-value-and-limitations-of-establishing-a-closely-monitored-challenge-model-of-experimental-covid-19-infection-and-illness-in-healthy-young-adult-volunteers

An international randomised trial of candidate vaccines against COVID-19, 28 May 2020.

https://www.who.int/publications/i/item/an-international-randomised-trial-of-candidate-vaccines-against-covid-19

Global animal laboratories capacities to support vaccine and therapeutic evaluation, 13 August 2020.

https://www.who.int/publications/m/item/global-animal-laboratories-capacities-to-support-vaccine-and-therapeutic-evaluation

Criteria for COVID-19 vaccine prioritization, 17 May 2020.

https://www.who.int/publications/m/item/criteria-for-covid-19-vaccine-prioritization

WHO Target Product Profiles for COVID-19 Vaccines, 29 April 2020

https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines

WHO R&D Blueprint: novel Coronavirus: prospects for evaluating cross-reactivity of nCoV with SARS-CoV, 27 January 2020.

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https://www.who.int/publications/m/item/methodological-approaches-to-assess-variants-effect-on-vaccine-efficacy-effectiveness-and-impact

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https://www.who.int/publications/m/item/report-of-the-who-ag-on-human-challenge-studies

COVID-19 Animal Models ad hoc working group Summary of progress made by the WHO COVID-19 modelling ad hoc Expert working Group, 26 March – 1 June 2020.

https://www.who.int/publications/m/item/covid-19-animal-models---summary-of-progress-made-by-the-who-covid-19-modelling-(march-04-june-2020)

COVID-19 Reagents, Cross-reactivity and Immune Assays Working Group, 18 March – 1 April 2020.

https://www.who.int/publications/m/item/summary-of-progress-made-by-the-who-assays-for-vaccines-group-of-experts-(18-march-1-april)

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