

# COVID-19 Research and Innovation

Powering the world's pandemic response – now and in the future

February 2022



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# Introduction and acknowledgements

In modern times science has played a critical and frontline role in combatting epidemics and pandemics.

The development of effective COVID-19 vaccines, treatments and public health interventions alone has provided humanity with some hope for the future.

This updated report once again brings a spotlight to the immense and tireless global research effort to control COVID-19.

The global coordination and support for the world’s leading scientists and experts does not always grab the media headlines. But it has been key in underpinning the important initiatives and breakthroughs detailed in this report.

The following pages detail not only the successes but also the priority research tasks and lessons learned that are critical in the next phase of the pandemic - as the world strives to move to ‘endemic’ status.

Crucially the report also focuses on how global research actions and platforms that are bolstering our response to COVID-19 right now, can also be deployed in the future to help the world rapidly combat new threats from viruses and other pathogens.

We again wholeheartedly thank the patients, volunteers and their families who have participated in each and every study.

Every single participant makes a difference to this incredible global effort. And we applaud all the funders and partners across the world - as without their support none of this work would be possible.

Finally, we remember the millions of people who have lost their lives to this devastating disease, along with their loved ones and every community affected.

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# Acronyms and abbreviations

**ACT-A** ACT-Accelerator

**AFRO** WHO Africa Region

**BSI** hospital-acquired bloodstream infection

**CC** WHO Collaborating Centre

**CEM** cohort event monitoring

**COMET** Core Outcome Measures in Effectiveness Trials

**CoP** correlate of protection

**COS** Common Outcome Set

**COVID-19** Coronavirus Disease 2019

**C-TAP** COVID-19 Technology Access Pool

**EURO** WHO Europe Region

**EMRO** WHO Eastern Mediterranean Region

**EUL** WHO Emergency Use Listing

**FAO** Food and Agricultural Organization

**GMP** good manufacturing practice

**GOARN** Global Outbreak Alert and Response Network

**GPP** Good Participatory Practice

**HAI** health care-associated infection

**HCF** high case fatality

**HCW** health care worker

**HH** hand hygiene

**IFR** infection fatality rate

**IOA** Integrated Outbreak Analytics

**IPC** infection, prevention and control

**IS** International Standard

**IU** International Unit

**LMIC** low- and middle-income country

**MENA** UNICEF Middle East and North Africa region

**MIS-C** Multisystem inflammatory syndrome in children

**mRNA** messenger RNA

**NRA** national regulatory authority

**NISBC** National Institute for Biological Standards and Control

**OECD** Organisation for Economic Co-operation and Development

**OIE** World Organization for Animal Health

**PAHO** Pan-American Health Organization

**PHSM** public health and social measure

**PPE** personal protective equipment

**RCCE** Risk Communication and Community Engagement

**R&D** Research and Development

**REACT** WHO Rapid Evidence Appraisal for COVID-19 Therapies

**RNA** Ribonucleic Acid

**SARS-CoV-2** severe acute respiratory syndrome coronavirus 2

**SEARO** WHO South-East Asia Region

**STAG-IH** Strategic and Technical Advisory Group for Infectious Hazards

**STV** Solidarity Trial Vaccines

**STT** Solidarity Trial Therapeutics

**TPP** Target Product Profile

**UHC** universal health coverage

**UN** United Nations

**UNICEF** United Nations Children's Fund

**VOC** variant of concern

**VOI** variant of interest

**WHO** World Health Organization

**WPRO** WHO Western Pacific Region

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**The global coordination and support of the world's leading scientists and experts does not always grab the media headlines. But it has been key in underpinning the important initiatives and breakthroughs detailed in this report.**

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# 1. R&D achievements summary

At the request of its 194 Member States in May 2015, the World Health Organization (WHO) convened a broad network of experts to develop an [R&D Blueprint for Action to Prevent Epidemics](#). A global strategy and preparedness plan was developed to allow for the rapid activation of research before and during epidemics.

Its aim is to fast-track the availability of effective tests, vaccines, medicines and social science that can be used to save lives and avert large-scale crisis, enhancing traditional epidemiology and public health responses with knowledge and skills from a number of areas.

WHO has defined as a [priority](#) to harness the power of science, research innovation, data and digital technologies as critical enablers of the other priorities – for health promotion and disease prevention, for early diagnosis and case management, and for the prevention, early detection, and rapid response to epidemics and pandemics.

The [UN Research Roadmap](#) for the COVID-19 Recovery provides a framework for leveraging the power of science in support of a better socio-economic recovery and a more equitable, resilient and sustainable future.

Furthermore, the World Health Assembly agreed on December 2021 to launch negotiations for an agreement to fight pandemics. The 194 Member States of the World Health Organization reached a [consensus](#) to kickstart the process to draft and negotiate a convention, agreement or other international instrument under the Constitution of the World Health Organization to strengthen pandemic prevention, preparedness and response.

Follows is a summary of the latest research achievements in COVID-19 across all the thematic areas.



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## SARS-CoV-2 at the human-animal interface

- Evaluations were carried out on the susceptibility of multiple animal species to SARS-CoV-2 infection. Studies were conducted in controlled conditions, both in vivo and in vitro, to inform on the susceptibility, pathogenicity and transmission in candidate species. Additional investigations were conducted around naturally infected cases of multiple species, including in zoos.
- The investigation of the COVID-19 outbreak in minks informed risk assessment at the global level and supported the development of biosafety guidance.
- Thanks to the networks of experts in molecular analysis of animal coronavirus, immediate knowledge sharing enabled informed decision-making during significant events such as the emergence of Omicron (and the hypothesis of its animal origin), or the recent outbreak associated with Syrian hamsters sold as pets.
- Studies have been carried out to explore the risk of transmission along the food chain, including in traditional markets, in a variety of global settings.
- Other achievements include the development of methods to quantify infectious particles of SARS-CoV-2; evaluation of virus persistence and infectivity during food processing; quantification in water and food matrices, on various products and under variable environmental conditions.
- Based on the experiences from countries, recommendations were developed to inform decisions on possible improvements to the resilience and readiness of food control and management systems during COVID, as well as guidance for competent authorities for the development of communication and awareness campaigns in at risk areas, including traditional markets.

## Epidemiology of COVID-19 focusing on past and current trends, drivers of transmission and severity, and epidemiological research gaps

- Rapid knowledge-sharing through various activities including (1) generic ready-to-use epidemiological investigation protocols available for country use under the WHO Unity Studies initiative; (2) a dashboard that systematically monitors and synthesizes findings of serosurveys around the world, in partnership with SeroTracker; (3) the Solidarity II knowledge share programme on sero-epidemiological studies, with over 55 meetings and workshops attended by an average of 90-100 participants per meeting across the world; (4) the Unity monthly scientific seminar for all countries in two major regions (AFRO and EURO) since mid-2020; and (5) over 50 meetings with key modelling partners to better understand and share knowledge about transmission dynamics.
- Capacity-building: countries in all regions have received technical support to build epidemiological capacity, enhance protocol development and statistical analysis. Scientific writing workshops have also been organized in different regions.
- To facilitate studies, some low-income countries have been provided with serological assays, laboratory equipment, serology reference panels and WHO International Standards (ISs) (antibody).
- Equipment for whole-genome sequencing has also been introduced into countries that previously lacked the capacity for such analyses.
- Development of study protocols: through Unity Studies, ten generic epidemiological investigations protocols were available for country use under the WHO Unity Studies initiative, covering a range of research questions that needed

to be answered, and allowing for those to be approached in a comparable manner globally.

- All protocols were adapted regularly to incorporate new findings. Through Solidarity II, serological testing standardization was made possible, with the developing study protocols such as the HARMONY study for the implementation of WHO antibody ISs.
- Analytical approaches have been developed to examine epidemiological, genomic sequencing, and contextual data to better characterize trends, transmission characteristics and disease severity, and short-term projections.

## Outbreaks should be detected and prevented at an early stage: A hub for pandemic and epidemic intelligence

- To better address pandemic and epidemic risks and to share knowledge with all countries, the WHO Hub for Pandemic and Epidemic Intelligence has been established to strengthen intelligence specifically for pandemics and epidemics by striving for better data, better analytics, and better decisions. Embedded in WHO's Health Emergencies Programme and building on consultations with hundreds of experts from different disciplines, sectors, and regions, it will leverage WHO's unique convening power across nearly 200 countries to foster global solutions that benefit all.

## Research on public health and social measures and their impact

### Key achievements

- Launch of the new WHO initiative to measure the effectiveness and impact of PHSMs during health emergencies.
- Development of a draft logic model on PHSMs to guide research and decision-making.

- Initiation of a global database for primary studies measuring the impact and effectiveness of PHSMs.
- Initiation of an umbrella review of the effectiveness and impact of PHSMs during COVID-19.
- Initiation of case studies to analyse the implementation challenges and enablers during COVID-19 .

## Infodemiology: Progressing on the public health research agenda for managing infodemics

- Publication of public health research agenda for managing infodemics.
- Joint call for papers on infodemiology.
- Establishment of five working areas of collaboration towards measurement of burden of infodemic.
- 5th WHO infodemic management conference on burden of infodemic measurement.
- Trained 750+ infodemic managers from 132 countries in infodemiology and evidence-based approaches to infodemic management.
- Development of methods and tools for automated social listening of conversations in social media and other digital public data sources: (in development) Field infodemiology guide for field responders.
- Joint call for papers on infodemiology and Field infodemiology guide for field responders.
- Evidence mapping and gap analysis reviewing implementation of the public health research agenda, infodemic management frameworks and interventions.
- Development of evidence-based scalable social inoculation interventions.

## Vaccines: Research and development priorities

- The working group on vaccine prioritization established criteria for the selection of vaccines for clinical trials and for the prioritization of the most promising candidates for inclusion in the Solidarity Trial Vaccines.
- The Target Product Profile for COVID-19 vaccines was reviewed and updated.
- Significant progress has been achieved towards a better understanding of transmission, virulence, identification of immune markers that predict protection for many vaccines, vaccine regimens, and seroepidemiology needs among other topics.
- Research groups have shared their experiences and data on the development of immune assays, materials and reagents for the evaluation of immunity to SARS-CoV-2 virus or SARS-CoV-2 vaccines and there were general trends observed across many studies.
- Animal model research played a chief role in the characterization of the pathogenesis, transmission and immunology of SARS-CoV-2 variants of concern.
- An important effort has been directed to engineer animal models that would mimic these important disease drivers.
- Guidance and lessons learned regarding volunteer challenge studies with SARS-CoV-2 were updated.
- A large, international, randomized clinical trial platform, the Solidarity Vaccines Trial, was launched in September 2021 in Colombia, Mali and the Philippines with more than 30 research sites.

- 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 identified. This was possible thanks to an extensive collaboration and cooperation between multiple stakeholders.

## Advancing the clinical care pathway: Outbreak research response centred around the patient

- Development and publication of core outcome measures for COVID-19 clinical trials with input from researchers from 25 countries around the world, with a minimal Common Outcome Set (COS) for COVID-19 trials, to capture clinical and virologic data that could be reported in a common manner to facilitate pooling data across multiple sources.
- Contribution to a separate COMET initiative to create a core outcome measure set for studies of COVID-19.
- A model of a prospective meta-analysis to pool grouped data from recently completed and ongoing clinical trials of potential treatments for COVID-19 was developed and the process published.
- A working group with leadership from LMICs is undertaking a study to determine the best respiratory support approaches to optimize the use of oxygen in LMICs.
- The COVID-19 Platform was established as an online data repository of anonymized, individual level clinical data of hospitalized COVID-19 cases to improve the global understanding of the presentation, risk factors, treatments, and outcomes of patients hospitalized with COVID-19 and those after acute illness with mid- and long-term consequences. The platform includes clinical data from over 550,000 hospitalized cases from 39 countries around the world.

- A WHO coordinated study of severe COVID-19 in children.
- A prospective cohort study investigating maternal, pregnancy and neonatal outcomes for women and neonates infected with SARS-CoV-2
- Safely introducing new therapeutics into clinical practice
- Classification matrix for COVID-19 Severity

## Research and development for treatments of hospitalized patients

- In the first six months, the Solidarity Therapeutics Trial generated conclusive evidence on the effectiveness of repurposed drugs for the treatment of COVID-19.
- In August 2021, WHO launched Solidarity PLUS, the new and current stage of the trial, which is an unprecedented global collaboration for COVID-19 R&D with thousands of researchers in 52 active countries.
- Based on available data, three new drugs - artesunate, imatinib, infliximab – were selected by the WHO Advisory Group on Therapeutics Prioritization for COVID-19, an expert group set up with the aim of establishing an independent process to advise WHO on the selection of therapeutics for COVID-19.
- Active enrolment in the trial is ongoing and co-sponsorship with participating Member States has been strengthened, by robust collaboration between multiple hospitals in countries around the world: national coordinators and principal investigators in each country supporting participating hospitals nationwide, in the preparation and conduct of the trial (from ethical and regulatory approvals, to the supply of study drugs, to scientific advice as well as to trial monitoring).

## Critical needs for outpatients and for the design of outpatient therapeutic trials

- Facilitation of large-scale collaborations and information sharing, leading to critical decisions, in particular regarding dose selection as well as selection of study arms and evaluation of therapeutic agents as combinations.
- Framework for pooled data analysis based on common measures across studies and information about comparable endpoints under development.
- Major issues pertinent to the design of outpatient trials and the interpretation and external validity of study outcomes have emerged from discussion sessions.

## Moving from rhetoric to reality: placing communities at the centre of health emergency readiness and response

- Advanced primary evidence generation related to social and behavioral dynamics including, for example, on PHSMs, vaccine uptake, COVID-19 home care, psychosocial impacts, policy responses, evidence-informed policy, health workers, infection prevention and control, sexual and reproductive health and ethics of scarce resource allocation.
- Informed WHO guidance through integration of evidence from social sciences.
- Global consultation on community centred approaches to health emergencies.
- Global and local level analyses and advocacy on the broader impacts of COVID-19.

- Advanced research for inclusive, person-centred response actions and structural mechanisms for wider engagement such as tools for rapid assessment of contextual vulnerability, community mapping, engagement of civil society organizations.
- Development of research protocols, tools, mechanisms and research infrastructure for standardized, systematic collection of data.
- Training and capacity development, together with network development and formalization to collect and share data including.

## IPC research during the pandemic: Pointing to an opportunity for saving lives and money

- Estimating the cost-effectiveness of IPC interventions: a global modelling study conducted by the Organization for Economic Co-operation and Development (OECD) and WHO assessed the effectiveness and cost-effectiveness of IPC interventions aimed at reducing transmission of SARS-CoV-2 among HCWs.
- Improving PPE effectiveness and addressing shortages.
- Identifying the role of the environment in tTransmission.

## Ethics and research

- Developing and contributing to WHO guidance documents and policy briefs on COVID-19.
- Specifying principles for research in public health emergencies.
- Hosting the WHO Pandemic Ethics & Policy Summit (6 Dec 2021).
- Dissemination and outreach activities.

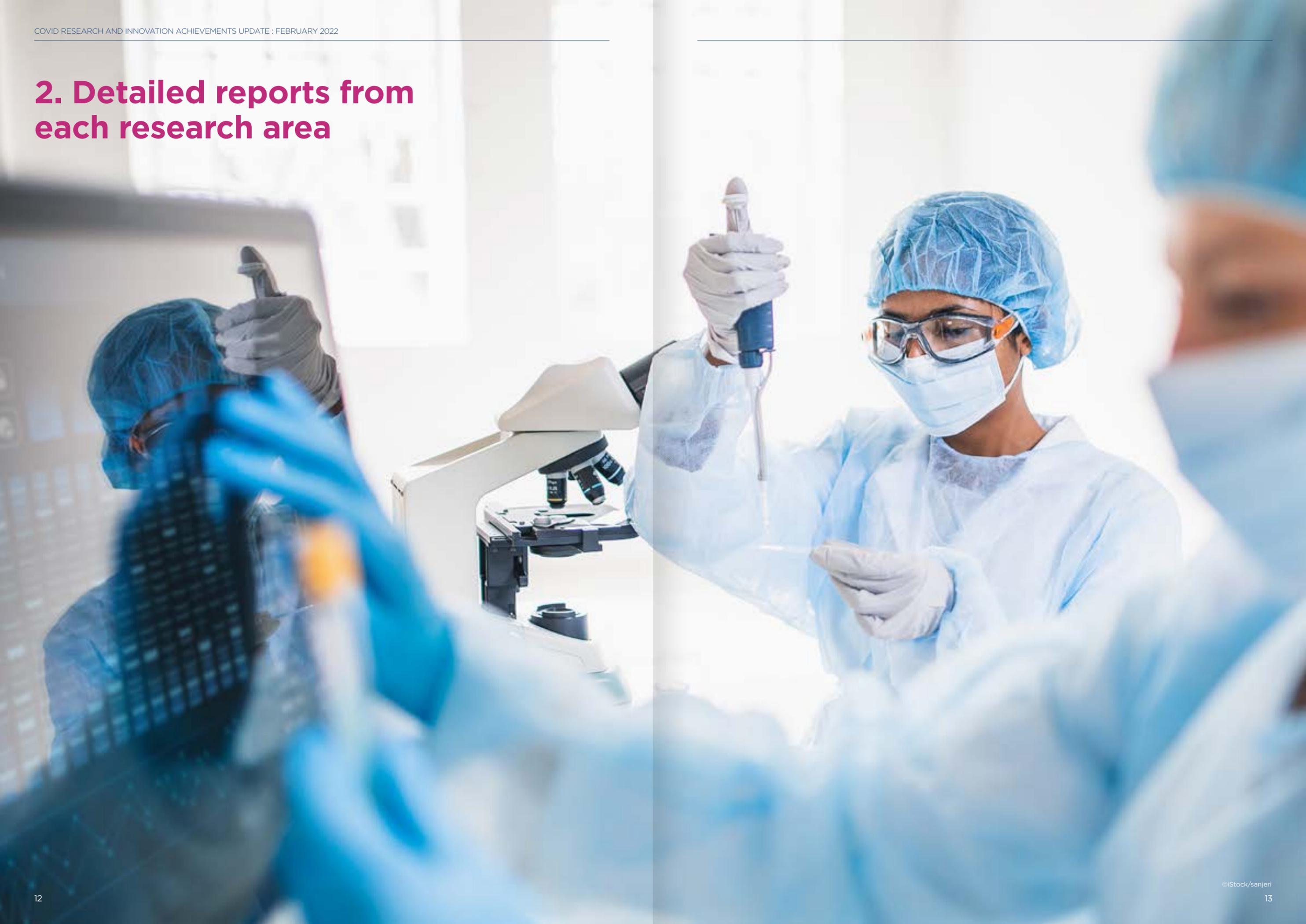
## Regulatory science and convergence between national regulatory authorities

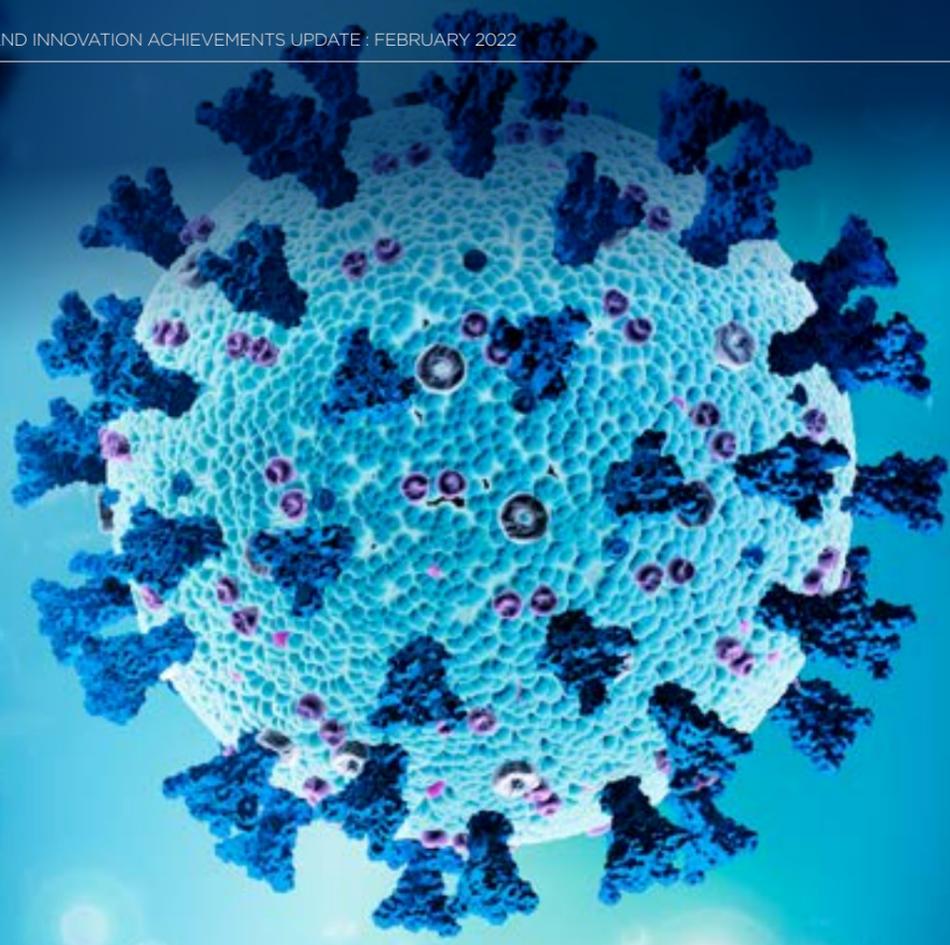
- In 2021, WHO assessed and recommended nine additional COVID-19 vaccines for Emergency Use Listing (EUL) with approval of 25 drug substance and 41 drug product manufacturing sites and evaluation of over 200 post-EUL changes.
- Assisted 40 self-benchmarking and completed five formal benchmarking (GBT) of regulatory systems, with follow-up of 11 NRAs on the implementation status of institutional development plans and provided technical support to over 15 NRAs Issued four global medical products alerts.
- Thus, sharing of WHO EUL dossiers and reports with NRAs under confidentiality agreement and implementing reliance concept facilitated timely regulatory decision-making without compromising the independent evaluation of quality, safety and efficacy of COVID-19 vaccines has been essential.

## WHO International Units: A common language in evaluation of the immune response to vaccines

- 1st WHO International Standard and Reference Panel for the anti-SARS-CoV-2 antibody were established by the WHO Expert Committee on Biological Standardization (ECBS).
- 1st WHO International Standard for SARS-CoV-2 RNA was established by the WHO ECBS.

## 2. Detailed reports from each research area





# 1 SARS-CoV-2 at the human-animal interface

## Overall summary

WHO continues to work closely with partners in the animal health sector to advance the understanding on the origins of the virus, monitor the circulation of the virus in animal populations and develop strategies to prevent transmission between animals and humans including future spillover.

Research projects resulted in critical advances in our knowledge on the susceptibility of animals, survival capacities of the virus on food associated surfaces and water matrices, contamination in the food chain or behaviour risk factors for spillover and transmission in specific communities or occupational groups more at risk.

This knowledge is of critical importance to assess risks associated with contaminated surfaces, establishment of animal reservoirs in wildlife and other animals at the vicinity of humans, as well as the evolution of SARS-CoV-2 in animal hosts and emergence of variants.

Despite the ongoing efforts, there are still substantial knowledge gaps related to these risks, and the coordination of this area is more important than ever.

## Aim

The key aim of animal and environmental research thematic area is to better understand SARS-CoV-2 in animals and the environment, including the potential transmission routes between animal and humans; the role of animals in the persistence and evolution of the virus; and reducing the risk of transmission at the human-animal interface.

## Objective 1 Susceptibility of animals, risks of creations of reservoirs and of reverse spillover to humans

### Key achievements

Evaluations were carried out on the susceptibility of multiple animal species to SARS-CoV-2 infection. Studies were conducted in controlled conditions, both in vivo and in vitro, to inform on the susceptibility, pathogenicity and transmission in candidate species.

These studies allowed the characterization of the efficiency of cell receptors of different animal species to bind SARS-CoV-2, as well as the analysis of genotype and phenotype variations (expression pattern of host proteins) in the course of infection.

Additional investigations were conducted around naturally infected cases of multiple species, including in zoos. This was associated with the validation of diagnostic tools for animal samples (incl. serological tests); development of guidance material for safe sampling and testing; transfer of technology in multiple countries hosting potentially susceptible animals.

Recent data suggest the transmission and persistence of SARS-CoV-2 in wild population of Cervids in North America.

Analysis conducted confirmed the sustained transmission of various variants, including Omicron, in wild white-tailed deer populations, resulting from multiple human-to-deer infections.

Reverse transmission from animal to humans has been observed during the 2020 outbreak in mink farms (cf R&D Blueprint report, April 2021).

More recently, another case of reverse transmission involving Syrian hamsters traded as pets was described in Hong Kong and discussed with the expert group of the World Organisation for Animal Health (OIE) and the UN Food and Agriculture Organisation (FAO).

### Contribution to our understanding of SARS-CoV-2 transmission

The COVID-19 pandemic is driven by human-to-human transmission of SARS-CoV-2, but the virus is also known to infect multiple animal species, including domestic animals, free-ranging, captive or farmed wild animals.

To date, all reported cases in animals have been associated with a likely transmission from humans.

With the wide spread of SARS-CoV-2 among humans, there is increased risk of infections in naive and possibly susceptible animal populations, including novel human variants that have mostly not been tested in animals.

**The COVID-19 pandemic is driven by human-to-human transmission of SARS-CoV-2, but the virus is also known to infect multiple animal species, including domestic animals, free-ranging, captive or farmed wild animals.**



In particular, cats have been shown to excrete the virus and while transmission to humans has never been demonstrated, the scarce testing, sequencing and epidemiologic investigations related to pets make reverse spill overs hard to detect.

Although current evidence indicates that wildlife does not play a significant role in the epidemiology of SARS-CoV-2 in humans, allowing its uncontrolled spread and maintenance in animal populations also amplifies the risk of endemicity in animals and viral evolution, potentially resulting in the emergence of new variants.

**There is an urgent need to intensify research on animal susceptibility and pathology, as well as surveillance and molecular analysis including genetic sequencing in animal populations.**

**Objective 2 Evolution of the virus in animal populations and the possible emergence of new variants**

**Key achievements**

The large outbreak of COVID-19 in minks allowed, among others, the analysis of the diversity of viral evolution in novel animal hosts, the follow-up of the circulation of mink variants in human populations and their public health impact, the description of associated mutations and possible increased affinity for human cell receptors, the investigation of contamination of the environment of infected farms and possible transmission routes.

The investigation of the outbreak informed risk assessment at the global level and supported the development of biosafety guidance.

Thanks to the networks of experts in molecular analysis of animal coronavirus, immediate knowledge-sharing enabled informed decision making during significant events such as the emergence of Omicron (and the hypothesis of its animal origin), or the recent outbreak associated with Syrian hamsters sold as pets.

**Contribution to our understanding of SARS-CoV-2 transmission**

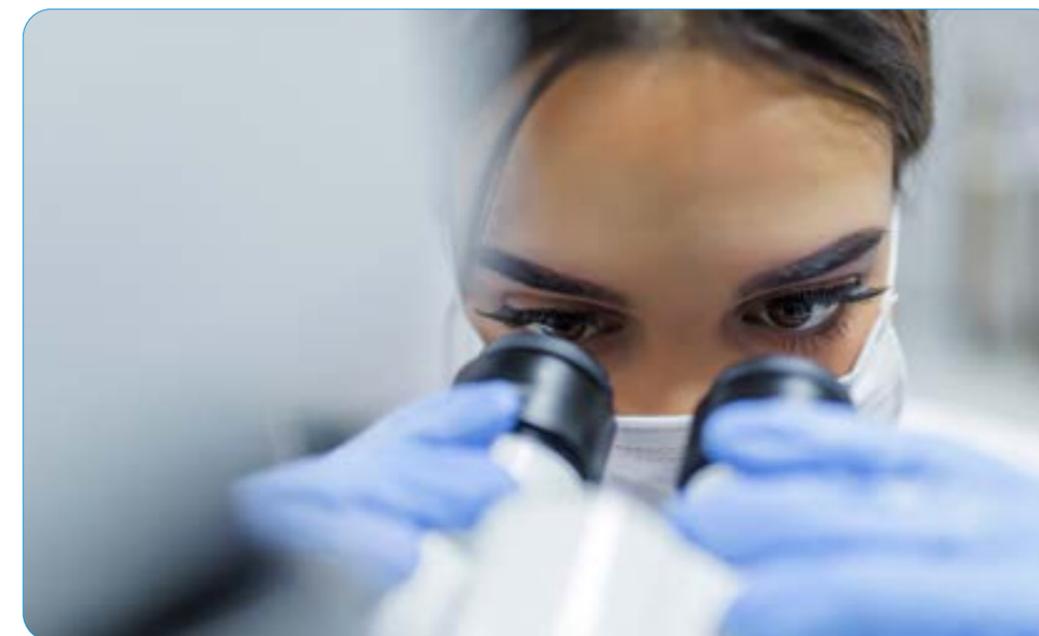
The control of possible animal reservoirs reduces selection pressure associated with spillover and genomic variations of the circulating viruses.

It has been seen during the outbreak in mink farms, when new variants emerged which were transmitted to humans, but fortunately have gradually faded out.

New and sometimes rare or unique mutations have also been observed in recently characterized viruses in different naturally or experimentally infected animal species.

It is critical to develop sequencing capacities for animal samples in order to monitor the genetic evolution and identify mutations known to have particular consequences for the epidemiology and pathogenicity of the virus.

The recording of mutations observed in virus isolated from the various animal species helps to explore the origin of new variants.



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**Objective 3 Risks linked to traditional markets and food of animal origin**

**Key achievements**

Studies have been carried out to explore the risk of transmission along the food chain, including in traditional markets, in a variety of global settings.

Other achievements include the development of methods to quantify infectious particles of SARS-CoV-2; evaluation of virus persistence and infectivity during food processing; quantification in water and food matrices, on various products and under variable environmental conditions.

Based on the experiences from countries, recommendations were developed to inform decisions on possible improvements to the resilience and readiness of food control and management systems during COVID, as well as guidance for competent authorities for the development of communication and awareness campaigns in at risk areas, including traditional markets.

**Contribution to our understanding of SARS-CoV-2 transmission**

There is no evidence that SARS-CoV-2 has any direct impact on food safety, nor that it is transmitted to a significant extent through food or food packaging materials.

However, some consequences of the disruptions caused by COVID-19 and of the efforts to minimize the spread of the illness may have had or may have indirect influences on the ability of governments, businesses and consumers to control and manage food safety risks. Sharing of experience was found very useful in this context.

Activities conducted other activities conducted contributed to reinforced country's risk-based food inspection activities, to assess critical points and behaviours increasing risks of transmission in food markets, to develop risk communication and awareness-raising adapted to different audiences, with a special focus on traditional markets where live animals are sold.

## Key benefits

The research results as well as the regular exchanges with WHO's counterparts in the animal health sector, mainly FAO and OIE and their ad hoc groups of experts, contributed to assess risks jointly conducted during the period, especially on the role of wild and domestic animal in the transmission of COVID-19.

The investigations in animal populations explored the infection with SARS-CoV-2 or related coronaviruses in multiple animal species and in several countries, also helping to establish local capacities to test animal samples.

Susceptibility of some animal species and genotype and phenotype variations of SARS-CoV-2 virus when infecting animals

were explored in controlled conditions but during outbreaks in animals (e.g. the outbreak in mink farms in North Europe and elsewhere). During detected outbreaks in domestic and wild animals, new variants emerging as a result of the spillover and the genetic diversity of circulating strains were characterized.

More fundamental research on the expression pattern and function of host proteins involved in SARS-CoV-2 infection in animals and their impact on susceptibility of animal species was also part of this work.

## Key outputs

- Initial assessment of the susceptibility of multiple animal species, including free-ranging, captive or farmed wild animals, main livestock animals and pets
- Molecular mechanisms linked to susceptibility have been described (mainly binding capacities of the virus with host cell receptors) for several species.

Certain species of particular concern have been identified and have (occasionally) been investigated.

However, many species of possible interest remain to be investigated, especially wildlife and animals in the global south, and other species in the vicinity of humans (including pets such as dogs and cats) would need to be analysed, also considering currently prevailing SARS-CoV-2 variants.

- Description of the first reverse transmission events and associated evolution of the virus through identification of associated novel mutations and genetic signatures
- Guidance, training and implementation of risk communication campaigns as well as awareness raising on traditional markets in different context over the world
- Definition of key pillars to limit the impact of COVID-19 on food safety in traditional markets and improve good hygiene practices through regulations, inspection, training, community awareness and communication on risks



# 2 & 3

## Virus natural history, transmission and diagnostics – and novel diagnostics to inform better strategies for prediction, prevention, detection, and control of pandemic diseases

### Overall summary

Key work has been carried out to facilitate the understanding of SARS-CoV-2 replication kinetics, cell tropism, and virus evolution. Significant progress has also been made in the development and introduction of new diagnostics and the monitoring of their accuracy and impact.

Both commercial and non-commercial molecular assays have been widely used to screen for emerging variants, to inform testing strategies, and provide COVID-19 surveillance.

**Antigen-detection rapid diagnostic tests are available from dozens of manufacturers, including a handful that have passed WHO review and Emergency Use Listing (EUL).**

Finally, global sequencing capacity continues to increase, enabling more geographically representative and rapid information availability. Collectively, this work has contributed to the monitoring and assessment of emerging SARS-CoV-2 variants at a global scale, and informed national COVID-19 control measures.

### Aim

A key aim of the virology R&D thematic area of the global roadmap has been to improve understanding of the SARS-CoV-2 natural history, transmission

dynamics and diagnostics to increase access to rapid near-patient testing and to support national and global decision-making on COVID-19 control.

### Objective 1 The development of products to improve clinical processes, support containment measures, and improve clinical management

#### Key achievements

#### Dissemination and use of reliable antigen rapid tests

Rapid antigen tests continue to be a valuable tool for the early detection of cases for earlier clinical care and prevention of onward transmission as well as monitoring of disease trends in populations. Some evidence suggests they may be better proxies for infectiousness than highly sensitive PCR, which can remain positive for weeks after virus can no longer be cultured from respiratory tract samples.

**With continued virus evolution, it is critical to have robust data to inform whether accuracy of existing diagnostic tools are maintained.**

#### Continued monitoring of the accuracy of antigen-detection tests and PCR assays with emergence of VOCs

Diagnostics drift threat is minimized by recommending PCR assays targeting multiple genes and conserved regions which are relatively stable (e.g. ORF1ab).

#### Improvements in diagnostic capacities continues at national and subnational levels

This has happened with expanded use of PCR-based testing and AgRDTs. Timely diagnosis facilitates earlier access into the clinical care pathway leading to more opportunities to provide patients with recommended COVID-19-specific therapeutics.



**Objective 2 To understand how the virus spreads, cellular tropism, viral shedding, and the natural history of disease to support clinical management and the development of interventions. Continuous assessment of viral parameters for new variants through COVID-19 laboratory reference network and a dramatic increase in sequencing uptake and early sharing of data in publicly available databases**

**Key achievements**

Testing remains a critical component to the COVID-19 global strategy and as the virus evolves, continuous re-evaluation of how the virus spreads, shedding, the natural history of disease in support of clinical management and development of interventions is essential.

More transmissible variants have challenged the global response and reinforced the need for strong lab surveillance, robust research to assess differences in virus behaviors and scientific collaboration to evaluate results for public health decision-making.

COVID-19 laboratory networks provide vital information about the circulation of SARS-CoV-2 and the emergence of variants, which are assessed as variants of interest (VOIs) or variants of concern (VOCs) by the WHO Technical Advisory Group for Virus Evolution (formally known as the Virus Evolution working group).

**Objective 3 Develop tools and methods to monitor phenotypic change and potential adaptation**

**Key achievements**

Early warning system and rapid multidisciplinary assessment of emerging variants; establishment of TAG-VE to advise WHO on circulating VOCs and VOIs.

has been a global collaborative effort and has enabled a systematic and rapid way to understand the potential impact of variants.

The assessment of emerging variants

**Objective 4 Immunity – To support public health measures, clinical management and development of interventions vital for tracing spread of the virus and informing vaccine development efforts.**

**Key achievements**

Up-to-date estimates of population immunity (vaccine + infection-derived) and the establishment of TAG-CO-VAC to advise WHO on impact of emerging VOCs on vaccines.

Routine review and interpretation of available data on effectiveness and impact of VOCs on existing vaccines is critical to ensure continued implementation of effective countermeasures.

**Objective 5 Disease modelling to supports clinical management and development of interventions by researching transmission dynamics and diagnostics**

**Key achievements**

Development of new disease models such as organoids and respiratory tract models.

For the latest VOCs, disease models (e.g. organoids) have proven very helpful to complement experimental data using animal models, to better understand viral tropism, replication and disease course.

**Key benefits**

Work in this theme has helped to generate evidence on the impact of the continued evolution of the virus on the trajectory of the pandemic.

Results from global implementation also continue to provide key data to support effective and efficient implementation within national health systems.

**Key outputs**

**Diagnostic access and implementation**

- Five Antigen Rapid Diagnostic Tests approved by WHO for emergency use: [https://extranet.who.int/pqweb/sites/default/files/documents/220223\\_EUL\\_SARS-CoV-2\\_product\\_list.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/220223_EUL_SARS-CoV-2_product_list.pdf)
- To secure equitable access to tests, the COVID-19 Diagnostics Consortium including ACT-A partners has procured over 49 million molecular tests and over 107 million rapid antigen tests for LMICs.
- OpenWHO courses on ‘Implementation of SARS-CoV-2 antigen-detection rapid tests’ and “SARS-CoV-2 antigen rapid diagnostic testing” launched, through a collaboration between WHO and FIND
- Update of WHO interim guidance on the use of antigen-detection rapid diagnostic tests: <https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays>
- Release of WHO interim guidance on national SARS-CoV-2 testing strategies and diagnostic capacities <https://www.who.int/publications/i/item/WHO-2019-nCoV-lab-testing-2021.1-eng>

**Mechanisms for understanding impact of emerging variants and assess spread**

- Formal establishment of TAG-VE: <https://www.who.int/groups/technical-advisory-group-on-sars-cov-2-virus-evolution>
- Establishment of naming scheme for variants: <https://www.nature.com/articles/s41564-021-00932-w>
- Establishment of TAG-CO-VAC: [https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-\(tag-co-vac\)](https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac))
- Interim statement on COVID-19 vaccines in the context of the circulation of the Omicron SARS-CoV-2 variant from the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC)
- Launch of draft WHO Global Genomic Surveillance Strategy for Pathogens with Pandemic and Epidemic Potential and public consultation meeting

# 4 Epidemiology of COVID-19 focusing on past and current trends, drivers of transmission and severity, and epidemiological research gaps

## Overall summary

At the start of any outbreak, epidemic or pandemic, it is critical to understand the key epidemiologic parameters of the pathogen.

From the outset of this pandemic, a fundamental focus of WHO's work has been to understand the transmission characteristics of SARS-CoV-2 and severity of COVID-19.

As we enter the third year of COVID-19, these questions remain fundamental to inform and optimize the global, national and subnational responses.

Key questions of transmission, severity and susceptibility remain critical as SARS-CoV-2 evolves and new variants emerge.

**Important and critical research was carried out by WHO to advance our understanding through strong surveillance, early investigations and targeted high-quality epidemiological studies across the globe.**

All of this has been and continues to be facilitated through the coordination of technical and research networks. An example of this is the work WHO has coordinated on better understanding of SARS-CoV-2 seroprevalence.

The WHO Unity Studies, launched in January 2020, is a global sero-epidemiological investigations standardization initiative which aims to support standardized collection of early key epidemiological parameters and understand the extent of SARS-CoV-2 infection globally. This initiative has facilitated high-quality epidemiological and seroprevalence studies across all WHO regions.

As of December 2021, 103 countries have started implementing at least one sero-epidemiological investigation using WHO Unity Studies generic protocols – AFRO (27), EMRO (15), EURO (36), PAHO (9), SEARO (6), WPRO (11). Sixty-three percent of these were in low-and middle-income countries (LMICs).

In partnership with SeroTracker, a programme dashboard is publicly available that systematically monitors and synthesizes findings of serosurveys around the world.

A number of meta-analyses and modelled estimates of the extend of SARS-CoV-2 infections have been produced, both at global (and regional levels [link](#)) and have been used to inform local, regional and national responses.

The WHO Solidarity II collaboration, launched in March 2020, is a global collaborative programme that promotes the implementation of serological research, focusing on research coordination and standardization of serological testing for SARS-CoV-2.

This programme facilitates collaboration between public health agencies and academic institutions that has focused on research coordination and standardization of serological testing, complementing the Unity Studies initiative, and further helping to better understand the epidemiology of SARS-CoV-2.

Additionally, detailed analyses of epidemiological trends and geographically representative sequence data, together with coordination with modelling networks, have informed WHO technical and scientific advisory groups, and the WHO R&D Blueprint. This has been to enhance our understanding of the epidemiological characteristics of new variants of concern (VOCs), and rapidly inform such groups for decision-making.

**Together Unity and Solidarity II initiatives have contributed to better understand the true extent of infection and immunity in populations, and have increased capacities significantly in high, middle- and low-income countries to carry out enhanced surveillance and research for high threat respiratory pathogens democratizing such capacities into the hands of local public health professionals.**

## Aim

The overall aim of the epidemiological studies thematic area of the coronavirus roadmap has been to develop, implement and coordinate activities to help better understand the transmission characteristics of SARS-CoV-2 and severity profile of COVID-19, including new variants.

### Objective Understand the transmission dynamics of SARS-CoV-2

# 1

This included (1) the consolidation and implementation of generic protocols for first few COVID-19 cases and their close contact, population-based sero-epidemiological investigations, assessing household transmission, assessing risk factors for infection of health care workers; (2) analyses of available seroprevalence data to better understand evolution of seroprevalence over time – globally and regionally and nationally – as well as by age, risk groups, occupations and rural/urban locations; (3) ongoing analyses of epidemiological trends and

genomic sequencing data, particularly for each new emerging variant of concern (VOC), to better understand their transmission characteristics; (4) coordinating and convening regular meetings with key modelling partners to share early findings on transmission dynamics; and (5) coordination of research to improve standardization of serological and performance of assays, including in the context of new variants, to help understand and interpret seroprevalence studies.

### Objective Describe disease severity and mortality

# 2

This included ongoing comparative analyses of available data on severity and mortality associated with each of the VOCs to understand their intrinsic virulence, as well as the impact of immunity (from vaccination and/or past infection) on these outcomes.

### Objective Evaluate control and mitigation measures

# 3

This included (1) promoting, facilitating and supporting studies in countries with limited resources and expertise, and to build capacity in COVID-19 epidemiology; (2) collating and compiling detailed data on public health and social measures

(PHSMs), visualizing and analysing those data to help better understand the impact of PHSMs on the epidemiology of SARS-CoV-2.



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## Key achievements across all objectives

**Rapid knowledge-sharing** through various activities including (1) generic ready-to-use epidemiological investigation protocols available for country use under the WHO Unity Studies initiative; (2) a dashboard that systematically monitors and synthesizes findings of serosurveys around the world, in partnership with SeroTracker; (3) the Solidarity II knowledge share programme on sero-epidemiological studies, with over 55 meetings and workshops attended by an average of 90-100 participants per meeting across the world; (4) the Unity monthly scientific seminar for all countries in two major regions (AFRO and EURO) since mid-2020; and (5) over 50 meetings with key modelling partners to better understand and share knowledge about transmission dynamics.

**Capacity-building:** countries in all regions have received technical support to build epidemiological capacity, enhance protocol development and statistical analysis. Scientific writing workshops have also been organized in different regions.

**As of December 2021, 103 countries have started implementing at least one sero-epidemiological investigation using WHO Unity studies generic protocols, with the majority of them (63%) being in LMICs.**

To facilitate studies, some low-income countries have been provided with serological assays, laboratory equipment, serology reference panels and WHO International Standards (ISs) (antibody).

Equipment for whole-genome sequencing has also been introduced into countries that previously lacked the capacity for such analyses.

**Development of study protocols:** through Unity Studies, ten generic epidemiological investigations protocols were available for country use under the WHO Unity Studies initiative, covering a range of research questions that needed to be answered, and allowing for those to be approached in a comparable manner globally.

All protocols were adapted regularly to incorporate new findings. Through Solidarity II, serological testing standardization was made possible, with the developing study protocols such as the HARMONY study for the implementation of WHO antibody ISs.

### Data analysis

Analytical approaches have been developed to examine epidemiological, genomic sequencing, and contextual data to better characterize trends, transmission characteristics and disease severity, and short-term projections.

### Key benefits

Understanding the extent of infection and immunity in the population is critical to better grasp the dynamics of SARS-CoV-2 transmission and help prepare and tailor surveillance and control moving forward.

One of the key challenges to evaluation of the epidemiology at a global level is the variability in data, the limited data from a number of settings, and lack of comparability of data owing to differences in methodologies used.

**The Unity Studies initiative has helped improve standardization and comparability of serological data, with over 100 countries having implemented at least one sero-epidemiological investigation using the generic protocols.**

A collaboration with 14 assay manufacturers with the largest market share and technical support of over 40 clinical research teams across the world helped create the foundation for the first standardization framework for serological testing for SARS-CoV-2

**Large systematic review and meta-analyses of seroprevalence data have been undertaken to characterize seroprevalence over time – globally and regionally and nationally – as well as by age, risk groups, occupations and rural/urban locations.**

Solidarity II further contributes to harmonizing tools used for serological studies, and helps coordinate research as the pandemic enters a new phase.

Those initiatives will help us to understand seroprevalence levels in light of new variants, vaccination coverage, waning immunity, and implications for transmission and severity moving forward.

The ongoing collection of detailed data on PHSMs helps us build our knowledge of how different approaches have impacted on transmission dynamics, and further explore the effectiveness of these measures such measures.

**With increasing population immunity decreasing disease severity, finding the right balance between PHSM implementation to limit burden, and what is needed to control transmission during new flare ups, will be critical.**

### Key outputs

#### Continued strengthening of our understanding of SARS-CoV-2 transmission dynamics

- With data available as of December 2021, global SARS-CoV-2 seroprevalence was 45.2% by mid-2021. Seroprevalence rose steeply in the first half of 2021 due to infection in some regions (e.g. 29.9% to 70.1% in Africa) and vaccination and infection in others (e.g. 5.6% to 94.9% in the Americas high-income countries), but remained low in others (e.g. 2.5% in the Western Pacific). In 2021 Q2, median seroprevalence to cumulative incidence ratios were 2.9:1 in HICs and 45.3:1 in LMICs. Children 0-9 years and adults aged 60 years+ were at lower risk of seropositivity than adults 20-29.
- Despite this, Omicron has spread rapidly across the globe, faster than any other variant, and in previously immunized populations given its immune escape properties.

#### Better understanding of severity

- The infection fatality ratio (IFR) has steadily decreased over time, mostly as a result of more preserved immunity (from vaccination and/or past infection) against severe disease than infection, earlier diagnosis and use of available therapeutics by trained health workers. Further, Omicron appears intrinsically less severe than previous variants.
- IFR increases by age and is higher for people with underlying conditions, and will be higher among unvaccinated individuals.

- SARS-CoV-2 spreads mostly between people in close contact through infected droplets and aerosols and at or around the time an infected person develops symptoms. However, people with and without symptoms can transmit the virus.
- Long-range aerosol/airborne transmission can occur in specific settings where aerosol generating procedures are conducted and also in indoor settings where there is poor ventilation.

**Superspreading events for SARS-CoV-2 have been common throughout the pandemic and tend to occur in settings with poor ventilation, enclosed spaces with close and prolonged interpersonal contact.**

#### Understanding effectiveness of public health and social measures

- Timely and early implementation of a combination of measures is critical to limit transmission.
- Gathering prospective data on social contact patterns is a useful complement to surveillance and PHSM data to know better the impact of interventions.
- Data on adherence/coverage and acceptability of measures are very useful but remain scarce.
- In a multivariate model using pre-vaccination data as part of the meta-analyses of seroprevalence data though Unity Studies, stringent public health and social measures were associated with lower seroprevalence.

# 5 Outbreaks should be detected and prevented at an early stage: A hub for pandemic and epidemic intelligence

## Summary

### A new understanding of pandemic and epidemic risks

To better address pandemic and epidemic risks and to share knowledge with all countries, the WHO Hub for Pandemic and Epidemic Intelligence has been established to strengthen intelligence specifically for pandemics and epidemics by striving for better data, better analytics, and better decisions.

Embedded in WHO's Health Emergencies Programme and building on consultations with hundreds of experts from different disciplines, sectors, and regions, it will leverage WHO's unique convening power across nearly 200 countries to foster global solutions that benefit all.

# Better data, better analytics, better decisions

## Key characteristics

- The WHO Hub for Pandemic and Epidemic Intelligence is a global platform for pandemic and epidemic intelligence, creating shared and networked access to vital multi sectoral data, driving innovations in data analytics and building the communities of practice needed to predict, prevent, detect, prepare for and respond to worldwide health threats.
- It is a new global collaboration of countries and partners worldwide, driving innovations to increase availability and linkage of diverse data; develop tools and predictive models for risk analysis; and to monitor disease control measures and infodemics.

## Background

WHO and the Federal Republic of Germany established the new global hub for pandemic and epidemic intelligence, data, surveillance and analytics innovation in May 2021.

Based in Berlin and working with partners around the world, the hub will lead innovations in data analytics across the largest network of global data to predict, prevent, detect prepare for and respond to pandemic and epidemic risks worldwide.

The WHO Hub for Pandemic and Epidemic Intelligence is part of WHO's Health Emergencies Programme and will be a new collaboration of countries and partners worldwide, driving innovations to increase availability and linkage of diverse data; develop tools and predictive models for risk analysis; and to monitor disease control measures, community acceptance and infodemics.

Critically, the WHO Hub will support the work of public health experts and policy-makers in all countries with insights so they can take rapid decisions to prevent and respond to future public health emergencies.

Working with partners globally, it will drive a scale-up in innovation for existing forecasting and early warning capacities in WHO and Member States.

At the same time, the WHO Hub will accelerate global collaborations across public and private sector organizations, academia, and international partner networks.

It will help them to collaborate and co-create the necessary tools for managing and analysing data for early warning surveillance. It will also promote greater access to data and information.

The WHO Hub for Pandemic and Epidemic Intelligence is a global platform for pandemic and epidemic intelligence, creating shared and networked access to vital multi sectoral data, driving innovations in data analytics and building the communities of practice needed to predict, prevent, detect, prepare for and respond to worldwide health threats.

- It will enable partners from around the world to collaborate and co-create the tools and data access that all countries need to prepare, detect and respond to pandemic and epidemic risks.



## What is its mission?

The mission of the WHO Hub is to build a system of collaborative intelligence enabling better decisions to avert and manage pandemic and epidemic risks

The WHO Hub will foster collaborations across the world to use the best technology and data to detect and understand risks about future epidemics and pandemics.

## Why now?

The world continuously faces pandemic and epidemic risks: the faster we can detect and the better we can respond to those risks, the safer the world is. The WHO Hub will provide needed support as we continue to face COVID-19, and to prepare for the next health emergencies.

**The world cannot manage the next pandemic with tools tailored to past pandemics. We need a new approach and a new way of working with partners from across disciplines to achieve stronger pandemic and epidemic intelligence.**

## How will the WHO Hub work?

The WHO Hub will strengthen pandemic and epidemic intelligence through better data, better analytics, and better decisions across all aspects of public health emergencies at national and local levels.

As a global collaboration of partners from multiple sectors, the WHO Hub is designed to enable innovators to co-create tools and used linked data that all countries need to prepare, detect and respond to pandemic and epidemic risks.

It will drive innovations to increase the availability and linkage of diverse data, develop tools and predictive models for risk analysis, improve public health decision-making, and monitor disease control measures and infodemics.

## The WHO Hub will:

- enhance access and linkage across multiple data sources necessary to generate signals and insights on disease emergence, risks, evolution, and impact
- develop state-of-the-art tools to process, analyse and model data for prediction, detection, assessment and response
- connect and catalyse institutions and existing networks developing disease outbreak solutions for the present and future; and
- provide WHO, our Member States, and partners with collaborative tools to underpin better and faster decisions on how to address outbreak signals and events.

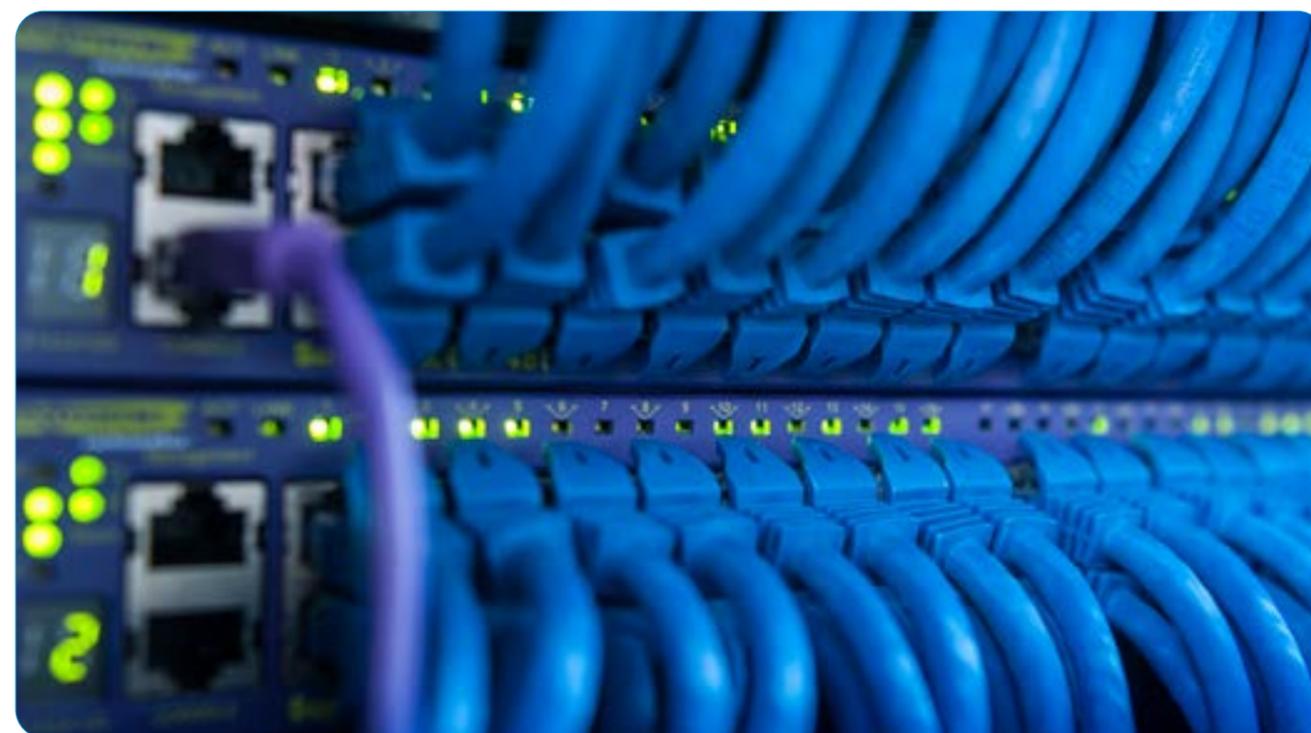
All aspects of pandemic and epidemic intelligence will be developed and adapted continuously through the hub's collaborative intelligence approach, including technical, governance, ethical and other dimensions.

To ensure that demand drives innovation and leads to tailored decisions that meet the context-specific needs of Member States, the WHO Hub will facilitate the convergence of their capacities, boost existing competencies, and develop new ones.

## What is collaborative intelligence?

The world cannot manage the next pandemic with tools tailored to past pandemics. We need a new approach and a new way of working with partners from across disciplines to achieve stronger pandemic and epidemic intelligence.

Collaborative intelligence is the essence of WHO's new approach. Collaboration is needed to bring clarity to risk information and increase interaction with partners and stakeholders. It fosters global trust between countries by promoting greater exchange of data, information



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and insights for pandemic and epidemic intelligence to improve policies and decision-making for pandemics and epidemics preparedness..

## Who will the WHO Hub serve locally, nationally and globally?

By linking local, national and global initiatives together, the WHO Hub will anchor its work in the needs of stakeholders everywhere, at all levels. It will work for all regions, Member States, institutions, and individuals around the world. The WHO Hub will also work closely with national and local authorities and with WHO Regional and Country Offices.

The WHO Hub is part of the WHO Health Emergencies Programme and will strengthen Member States' data sharing capacities and enable partners from around the world to collaborate and co-create the necessary tools to manage and analyse data for early warning surveillance.

## What types of data will be assessed in the WHO Hub?

The WHO Hub will work with a wide range of data sources to better understand the context, occurrences and predictors of epidemic and pandemic risks. Data sources will include traditional disease surveillance data, such as case data and laboratory data.

These will be complemented with data on environmental factors, such as rainfall or vegetation coverage; social factors such as health-seeking behaviour, health and risk literacy, and cultural beliefs about disease causation and prevention; economic factors such as travel patterns and trade routes; and human and animal interactions in agriculture and nature, as well as consumption, production and sale of wildlife.

The collaborative intelligence trust architecture will enable insights that combine both open (publicly available) and closed (not publicly available) data from both private and public sources.



# 6 Research on public health and social measures and their impact

## Overall summary

Public health and social measures (PHSMs) are a key strategy to reduce the transmission of pathogens with epidemic or pandemic potential.

PHSMs include non-pharmaceutical interventions that can be taken by individuals, institutions, communities, local and national governments and international bodies to slow or stop the spread of an infectious disease, such as COVID-19. Individuals can, for example, engage in behaviours such as frequent handwashing, covering coughs and sneezes, wearing a mask and keeping a physical distance from other people. Authorities and communities can enact measures such as contact tracing, isolation of cases and contacts, school measures, business closures, restricting public gatherings, travel bans and cordon sanitaire.

PHSMs can prevent individuals from being exposed to the virus, decreasing the number of people who will become sick, require hospitalization or die from the disease. PHSMs reduce the pressure on the health care system and buy time to develop pharmaceutical interventions such as vaccines and medication.

PHSMs have significant consequences for individuals and societies, including on health, social and economic aspects. To ensure the intervention burden of PHSMs does not outweigh the benefits, decision-makers need to have a thorough understanding of how the measures work in different contexts, combinations and durations.

In June 2021, WHO launched a new multi-year initiative to measure the effectiveness and social, health and economic impact of PHSMs during health emergencies. The main outcomes of the PHSM initiative will be a research framework including a global monitoring system on PHSMs as well as a decision-making tool facilitating the evidence-based and systematic implementation of measures during health emergencies.

To date, a WHO internal steering group and an external working group on PHSMs under the Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH) have been created to provide technical guidance and ensure alignment across all levels of the organization.

In September 2021, a global technical consultation with over 60 global experts was organized to review the existing evidence on PHSMs and identify research priorities for the future. A draft version of a logic model and flexible taxonomy on PHSMs has been developed and will be submitted for further internal and external review.

A draft research agenda has been developed and discussed at the consultation and will be finalized through an iterative online consultation process. A global evidence review and the development of a database for primary studies evaluating the effectiveness and impact of PHSMs are underway. Further, country case studies to analyse implementation challenges and enablers are being prepared.

## Aim

Despite widespread application of PHSMs during the COVID-19 pandemic, there is much to learn about their use, implementation and effectiveness.

The PHSM initiative aims to strengthen the global evidence base on PHSMs to inform the development of action-oriented guidance, mechanisms and tools for decision-makers.

**In June 2021, WHO launched a new multi-year initiative to measure the effectiveness and social, health and economic impact of PHSMs during health emergencies.**

## Objective Strengthen the global evidence base on PHSMs

# 1

### Key achievements

Launch of the new WHO initiative to measure the effectiveness and impact of PHSMs during health emergencies running from June 2021 to April 2024

Global technical consultation on measuring the effectiveness and impact of PHSMs during health emergencies with over 60 international experts (31 August to 2 September 2021)

Call for research on PHSMs in the WHO Bulletin

Global research agenda on PHSMs (draft version discussed at global consultation, further consultations planned)

Development of a logic model on PHSMs to guide research and decision-making (draft version, will be submitted for further review)

Initiation of a global database for primary studies measuring the impact and effectiveness of PHSMs

The main outcomes of the PHSM initiative will be a research framework including a global monitoring system on PHSMs as well as a decision-making tool facilitating the evidence-based and systematic implementation of measures during health emergencies.

**Objective 2 Establish a global PHSM monitoring system**

2

**Key achievements**

Development of a logic model on PHSMs to guide research and decision-making (draft version, will be submitted for further review)

Initiation of an umbrella review of the effectiveness and impact of PHSMs during COVID-19

Initiation of case studies to analyse the implementation challenges and enablers during COVID-19

Initiation of a global database for primary studies measuring the impact and effectiveness of PHSMs

**Objective 3 Support evidence-informed PHSM implementation at national and subnational levels**

3

**Key achievements**

Development of a logic model on PHSMs to guide research and decision-making (draft version, will be submitted for further review)

A better understanding of the effectiveness and impact of single PHSMs facilitates a more tailored and evidence-informed implementation of interventions, ensuring a balance between costs and benefits of said measures.



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**Objective 4 Integrate PHSM assessments into health emergency preparedness activities**

4

**Key achievements**

Collaboration with WHO colleagues, to include PHSM elements in existing emergency preparedness tools and assessments

**Contribution to our understanding of SARS-CoV-2 transmission and control across all objectives**

A better understanding of the effectiveness and impact of single PHSMs facilitates a more tailored and evidence-informed implementation of interventions, ensuring a balance between costs and benefits of measures.

This will help decision-makers to choose the most effective interventions in a given context, reducing negative consequences and the need to apply a layered approach that results in a maximum limitation of the public's freedom.

A more nuanced and evidence-informed implementation of PHSMs is likely to increase public trust, uptake of and adherence to measures and hence increase their effectiveness.

## Key benefits

PHSMs have been a key strategy to curb transmission of SARS-CoV-2 and protect health systems from being overburdened.

However, the current approach to implementation using multiple measures at the same time in the absence of evidence on the effectiveness of single interventions in specific contexts, combinations and durations has led to prolonged lockdowns.

This has posed a significant burden on the health, social and economic aspects of individuals and societies.

A better understanding of the effectiveness and impact of single PHSMs facilitates a more tailored and evidence-informed implementation of interventions, ensuring a balance between costs and benefits of said measures.

This will help decision-makers to choose the most effective interventions in a given context, reducing negative consequences. A more nuanced and evidence-informed implementation of PHSMs is likely to increase public trust, uptake of and adherence to measures and hence increase their effectiveness.

The PHSM initiative aims to provide the necessary research framework to design and evaluate the effectiveness and impact of single PHSM interventions and different combinations of interventions.

This includes a set of study blueprints, ethical and implementation guidance harmonizing global research activities to ensure methodological robustness, replicability, and cross-country comparability, following the idea of the WHO Unity studies.

Data for action hubs will be established and trained to collect and analyse data on PHSMs during health emergencies. Insights derived from these studies will directly inform PHSM decision-making and hence make a significant contribution to the control of health emergencies.

**This will help decision-makers to choose the most effective interventions in a given context, reducing negative consequences.**

## Key outputs

- Global technical consultation on measuring the effectiveness and impact of PHSMs during health emergencies (31 August-2 September 2021), attended by over 60 international experts
- Working Group on PHSM established with a subset of STAG-IH members and external expert advisors to provide technical guidance on the PHSM initiative
- WHO internal steering group with representatives of all six regions and several HQ departments established to

ensure alignment of activities across the organization and benefit from broader in-house experience and expertise

- Draft version of the logic model to facilitate systematic thinking on PHSMs, to be submitted for further review
- Draft global research agenda on PHSMs, discussed at the global consultation and to be submitted for further review

All references and publications/further resources are available at the end of the report.



# 7 Infodemiology: Progressing on the public health research agenda for managing infodemics

## Overall summary

The COVID-19 pandemic has been accompanied by a COVID-19 infodemic: excess information, including false or misleading information, in digital and physical environments that has spread during a health emergency.

The infodemic is leading to confusion and risk-taking behaviours that can be harmful to health as well as erode trust in health authorities and public health responses.

WHO is developing tools to provide an evidence-based response to the infodemic to strengthen epidemic and pandemic response activities and is fostering the growth of the field of infodemiology. In the future, all emergencies and pandemics will be accompanied by infodemics that will be better addressed with the tools and insights developed today.

The digital information ecosystem intertwines social dynamics between people and communities and influences health behaviours – it swirls together health information of different quality, as well as misinformation, disinformation, and once accurate but now outdated information.

People are confused because of information overload and are frustrated by the inability to follow recommended guidance or have access to recommended health services, all while new scientific evidence is generated and reshapes the emergency response by health authorities.

Due to the multifaceted impacts of infodemics on health and society, understanding and controlling infodemics to support uptake of vaccines, public health and social measures, treatments and health behaviours is now a priority for many health authorities.

Individual actions can cumulatively lead to severe health impacts on communities, and a lack of interventions and policies can trigger catastrophic outcomes (e.g. overflowing emergency room admissions, popular opposition to health guidance, attacks on health workers or a collapse of trust in health authorities).

It has therefore become imperative to find ways to clearly discern and demonstrate the burden of infodemics on our individual and collective health outcomes so that interventions may be created to mitigate its harms.

In April 2020, WHO, in collaboration with partners and stakeholders, developed and published a framework for responding to the COVID-19 infodemic, which identified the need to apply multidisciplinary research and evidence to detecting, managing and responding to infodemics. This framework also called for evidence-based response and metrics to the COVID-19 infodemic.

Before 2020, researchers have explored the use of data produced and consumed on the web to inform public health officials, agencies and policy – the science behind infodemic management known as infodemiology.

However, the COVID-19 pandemic has accelerated and amplified an infodemic that has caused harm and sowed confusion, a new facet of pandemic response that many countries were not prepared to address effectively in its entirety.

Since the first WHO Infodemiology Conference in June-July 2020, the working definition of infodemiology has expanded beyond studying the digital information ecosystem to include an integrated understanding of the online-offline information exchange and interactions, and how they lead to behaviours and impact health outcomes.

Following the conference, several scientific journals partnered with WHO for a joint call for papers on infodemiology within the frame of the research agenda.

Three special infodemiology issues of these journals have been published to date. In addition, the Journal of Medical Internet (JMIR) was established; WHO staff serves on the editorial board.

Numerous other special calls for papers on infodemiology were issued and more research and public health collaborations on infodemic topics mushroomed across the world.

Similarly, funding on misinformation research has increased. Examples include US\$ 10 million for the Mercury Project global research consortium funded by the Social Sciences Research Council, and US\$ 10 million for research on mis- and disinformation by the National Science Foundation's Secure and Trustworthy Cyberspace (SaTC) programme.

Substreams of the WHO public health research agenda for managing infodemics were discussed in subsequent WHO infodemic management conferences including:

- a whole-of-society response to COVID-19 infodemic (Nov-Dec 2020)
- the current state of research and practice in social listening approaches to generate infodemic management insights (May 2021)
- the measurement of the burden of infodemic (November 2021)

## Aim

Despite widespread recognition of the importance of infodemic management in COVID-19 pandemic response, there is still much to learn about the use, implementation and effectiveness of infodemic management tools, methods and interventions, and how they are integrated into the emergency preparedness and response.

Promoting the science of infodemiology aims to strengthen the global evidence base on infodemic management to inform the development of action-oriented guidance, support options, mechanisms and tools for infodemic managers and emergency programme managers.

## Objectives

The specific objectives underpinned include:

### Objective 1 Establish an infodemiology research agenda

1

#### Key achievements

Publication of public health research agenda for managing infodemics

Joint call for papers on infodemiology

Establishment of five working areas of collaboration towards measurement of burden of infodemic

**In the future, all emergencies and pandemics will be accompanied by infodemics that will be better addressed with the tools and insights developed today.**

### Objective 2 Measure the burden of infodemic

2

#### Key achievements

Establishment of five working areas of collaboration towards measurement of burden of infodemic

5th WHO infodemic management conference on burden of infodemic measurement

(in development) Tools and protocol for measuring information diet and linking it to health outcomes

**WHO, in collaboration with partners and stakeholders, developed and published a framework for responding to the COVID-19 infodemic, which identified the need to apply multidisciplinary research and evidence to detecting, managing and responding to infodemics. This framework also called for evidence-based response and metrics to the COVID-19 infodemic.**

### Objective 3 Connect research to practice through a WHO infodemic management training programme and evidence-based infodemiologist toolbox

3

#### Key achievements

Trained 750+ infodemic managers from 132 countries in infodemiology and evidence-based approaches to infodemic management

WHO competence framework to develop a response workforce to manage infodemics, including a competence area in infodemiology

OpenWHO course on Infodemic Management 101, including infodemiology methods

Development of methods and tools for automated social listening of conversations in social media and other digital public data sources

(in development) Field infodemiology guide for field responders

### Objective 4 Promote implementation science, evidence generation and publication in infodemiology-related topics

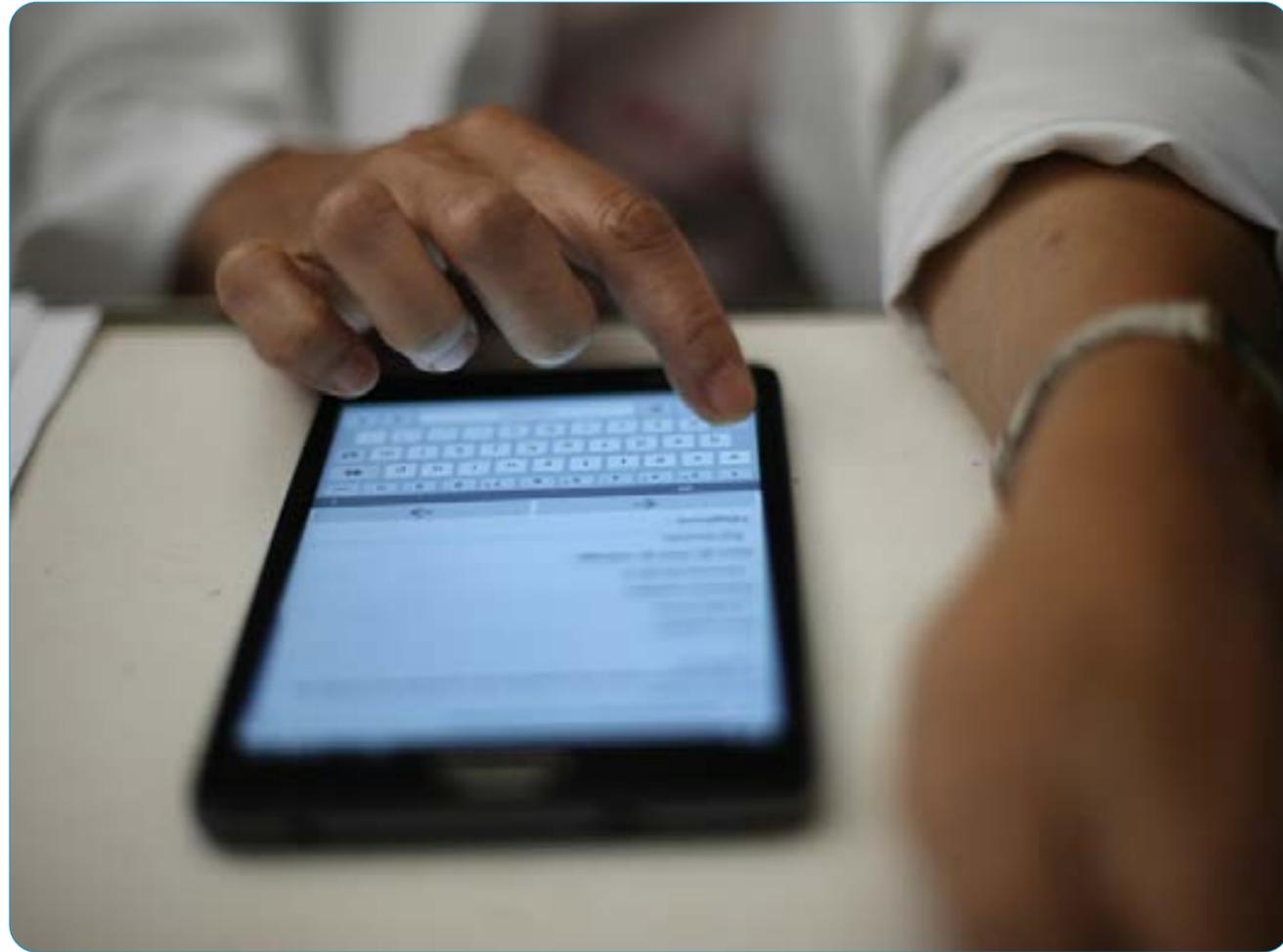
4

#### Key achievements

Joint call for papers on infodemiology (in development) Field infodemiology guide for field responders



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**Objective 5 Develop an evidence map and gap analysis for frameworks of interventions and infodemiologys**

5

**Key achievements**

Evidence mapping and gap analysis reviewing implementation of the public health research agenda, infodemic management frameworks and interventions (ongoing)

Development of evidence-based scalable social inoculation interventions (in development)

**Objective 6 Promote the development of ethical frameworks for infodemiology applied to social listening and infodemic management**

6

**Key achievements**

Development of an ethical framework for social listening and infodemic management (forthcoming)

**Contribution to our understanding of SARS- CoV-2 transmission and control across all objectives**

A better understanding of the form and impact of infodemic harms will facilitate a more tailored and evidence-informed implementation of infodemic management interventions.

Defining the factors that contribute to the infodemic across the information environment, individual cognition and behaviour, and health system and societal impacts in the changing trajectory of the pandemic, will help develop a bigger set of evidence-based tools and methods to respond to the infodemic.

Infodemiology helps us understand the interplay between individual behaviours and population health and how trust impacts adherence to PHSMs, uptake of diagnostics, therapeutics and vaccine demand.

Evidence-based infodemic management interventions support epidemic management and management of infodemic risk in communities during the pandemic, particularly vulnerable communities.

Infodemic management interventions used in the COVID-19 pandemic can build trust and community resilience against misinformation now that will pay dividends in preparedness of future emergencies.

**Key benefits**

A key focus area for fostering infodemiology is creating stronger linkages between the generation of infodemiology science in academia and public health practice.

The WHO public health research agenda for responding to infodemics frames this in five research streams:

1. Measuring and monitoring the impact of infodemics during health emergencies
2. Detecting and understanding the spread and impact of infodemics
3. Responding and deploying interventions that protect against the infodemic and mitigate its harmful effects
4. Evaluating infodemic interventions and strengthening resilience of individuals and communities to infodemics

5. Promoting the development, adaptation and application of tools for managing infodemics

Answering research questions within these workstreams can advance the evolution of infodemiology to continue to contribute to moving past COVID-19 and inform preparedness and response efforts.

Up until now, many infodemic management efforts have been sporadic, splintered and disproportionately focused on mis- and disinformation instead of the entire information ecosystem.

Meanwhile our growing understanding of the complex nature of infodemiology will lead to the development of a wider set of interventions and approaches to measure their effectiveness.



## Key outputs

- An ad hoc WHO technical consultation managing the COVID-19 infodemic: call for action, April 2020: <https://www.who.int/publications/i/item/9789240010314>
- WHO public health research agenda for managing infodemics, January 2021: <https://www.who.int/publications/i/item/9789240019508>
- 3rd WHO infodemic management conference: whole-of-society challenges and approaches to respond to infodemics, Nov-Dec 2020: <https://www.who.int/publications/i/item/9789240034501>
- 4th WHO infodemic management conference on advances in social listening, May 2021 (forthcoming, to be published on infodemic health topic website)
- 5th WHO infodemic management conference on measurement of the burden of infodemics, Nov 2021 (forthcoming, to be published on infodemic health topic website)
- WHO competency framework: Building a response workforce to manage infodemics, March 2021: <https://www.who.int/publications/i/item/9789240035287>
- 1st , 2nd, and 3rd WHO infodemic manager trainings (Nov 2020, June 2021, Nov 2021)

All references and publications/further resources are available at the end of the report.



# 8 Vaccines: Research and development priorities

## Overall summary

**Important and critical research was carried out by WHO to advance our understanding and inform the global public health community about safe and effective COVID-19 vaccines.**

This was achieved by accelerating and coordinating the research, development, and evaluation of candidate products, including vaccine effectiveness.

Current vaccines are based on wild-type antigens, but we have encountered many variants of concern (VOCs) including alpha, beta, gamma, delta, and now the emergence of omicron. Other variants have been regionally important, such as lambda and mu. Omicron combines reduced (though still significant) virulence, greater transmissibility, and significant evasion of previous immune responses, both from natural and vaccine-induced infection.

The WHO has convened regular global consultations to discuss critical scientific issues, identify major knowledge gaps and move the research agenda forward. These meetings have focused on understanding the pathogenesis of SARS-CoV-2 and the emerging variants, identifying correlates of protection (CoPs), assessing the impact of VOCs on vaccine efficacy and effectiveness. Conclusions from these consultations resulted in strengthened evidence-based vaccination recommendations.

## Objective 1 Continuously identify COVID-19 vaccine candidates for clinical evaluation and scan the landscape of scientific evidence

### Key achievements

**Discussion on research methods and emerging evidence - Framework to evaluate new vaccines against COVID-19**

In order to contribute to increase supply of vaccines that meet the WHO Target Product Profile (TPP) criteria for effectiveness against severe disease, WHO is developing a framework to evaluate vaccines against currently circulating variants or for pan-sarbecovirus vaccines. This may also guide researchers and developers additional data needed for the assessment of new vaccines.

**The working group on vaccine prioritization established criteria for the selection of vaccines for clinical trials and for the prioritization of the most promising candidates for inclusion in the Solidarity Trial Vaccines.**

### Vaccine prioritization

Two candidate vaccines were included in the Solidarity Trial Vaccines. This trial is a large, international, randomized controlled clinical trial designed to concurrently evaluate the benefits and risks of multiple COVID-19 vaccines. In addition, the working Group on vaccine prioritization has reviewed more than 20 candidate vaccines.

### Target Product Profiles (TPPs)

**WHO has reviewed and updated the TPP for COVID-19 vaccines**

**The TPP has guided developers and researchers to target efforts on the development of COVID-19 vaccines.**

Revision of the TPP is in progress to update the preferred and minimally acceptable profiles for human vaccines in the changing epidemiological environment.

### Research landscape

The COVID-19 living map is an interactive database that provides instant access to all registered clinical trials (both randomized and non-randomized) being conducted worldwide on novel COVID-19 vaccines.

The COVID-19 candidate vaccine tracker and landscape provides a comprehensive mapping of all pre-clinical and clinical COVID-19 vaccine candidates in development worldwide.

In collaboration with scientific groups, such as the University of Bristol and Cochrane, data on the vaccine platform, schedule of vaccination, route of administration, developers, trial phase and clinical endpoints are gathered from various sources to monitor the progress being made in the research

and development of COVID-19 vaccine candidates. To date, there are approximately 339 vaccines being monitored, of which 144 are in clinical phase and 195 in the pre-clinical phase

The landscape of observational study designs on the effectiveness of COVID-19 vaccines provides an overview of observational studies which evaluate the COVID-19 vaccination in real-world settings. Approximately 400 studies are screened on a weekly basis and studies that assess vaccine effectiveness, including against VOCs, are identified. Data is collected on various endpoints including COVID-19 infection, disease, severe disease, hospitalization and mortality. The landscape currently lists 751 observational studies on vaccine effectiveness, including test-negative (n=78), cohorts (n=491), case-control (n=52).

The COVID-19 living evidence synthesis of trial results provides a constantly updated list of vaccine comparisons where data are available, as well as the general characteristics of each trial with an assessment of risk-of-bias (evidence synthesis and profile for phase 2-3 trials; risk-of-bias assessment for safety outcomes only for phase 1-2 studies).

This source of information is used by multiple stakeholders in both the non-scientific and scientific domain. Updated weekly, the landscape tracks the progress of each candidate vaccine from pre-clinical through Phase 1, 2, 3 and 4 studies, and provides links to published reports on the safety, immunogenicity and efficacy data. The COVID-19 candidate vaccine tracker and landscape provides an overview of the rapidly developing field regarding the diversity of vaccine technologies being developed which can potentially benefit specific populations, improve access and availability, and target specific VOCs.

The landscape of observational studies includes key features extracted on the study characteristics in terms of study design, sample size, study population, participants' characteristics (age, gender), intervention details (developer, strain, route of administration, schedule), location of study and key outcomes. This information has been used towards compiling data for a living systematic review of vaccine effectiveness on VOCs in 'real-world' settings, and for the critical appraisal and risk of bias of the observational studies. Study and participant characteristics, risk of bias data as well as outcome data are made publicly available at [https://covid-nma.com/vaccines/os\\_vaccines/](https://covid-nma.com/vaccines/os_vaccines/).

In addition, a recent review of data was published (*Considerations in boosting COVID-19 vaccine immune responses*, Krause et al, 2021) evaluating the effectiveness of COVID-19 vaccination against severe disease and confirmed SARS-CoV-2 infection. Findings from this analysis were used to inform public health decision-making on the use of boosters.

## Objective Facilitate global discussions on key aspects of vaccine development

# 2

### Key achievements Global coordination

Multiple efforts have been made to enhance coordination of COVID-19 vaccine research which facilitates unnecessary duplication of efforts, standardized approaches comparability of results, data sharing. More than 18 consultations to discuss critical scientific issues were held last year.

**Significant progress has been achieved towards a better understanding of transmission, virulence, identification of immune markers that predict protection for many vaccines, vaccine regimens, and seroepidemiology needs among other topics.**

### Using vaccine immune response data for public health and regulatory decision-making

Identifying immune markers that predict protection for many vaccines is essential for vaccine development. Outside of randomized controlled trials (RCTs), post-deployment confirmation, including large simple trials, could be used to rapidly estimate effectiveness, confirm safety, and identify a CoP. Additional clinical data collected during deployment could also support the use of correlates across a variety of vaccine regimens/schedules. The choice of immune markers, comparator vaccine, and statistical criteria can be made on a case-by-case basis depending on the characterization of the immune response from the vaccine candidate and the availability of comparator vaccines in-country.



WHO/Blink Media - Hannah Reyes Morales

**Vaccine research needs to achieve control of pandemic everywhere**

The Omicron VOC has been detected in many countries, and there needs to be a continued threat assessment (transmissibility, virulence, and the capacity for evading immunity in those previously vaccinated or infected). The resulting assessment will have implications for vaccine development, vaccine evaluation, and vaccine deployment.

It is critical to consider global implications as we adjust the research agenda to reflect the changing situation.

**Vaccine equity is not just a matter of fairness but is critical for controlling the pandemic everywhere.**

If new vaccines are developed against omicron or other variants, we need to make sure they are available for deployment in the developing world and they are available for testing of the next generation of vaccines. Additional data is needed on omicron-induced COVID--19 in groups with different levels and types of immunity.

Vaccines will likely continue to prove protective against severe disease caused by new variants. Boosting can increase both humoral and cellular responses. Variant-specific vaccines will need to be validated. Animal models (possibly also organoid systems) will provide valuable data on phenotypes of variants.

Regulators support immunobridging (to known effective prototype vaccine) as an approach to develop variant-specific vaccines. A full correlate of protection is not necessary to use immune responses in a productive way. Randomization (whether individual or small cluster) during deployment could yield essential information about vaccine effectiveness to meet these needs. Lead time plus lack of immediate availability makes randomized deployment more feasible.

**Evidence and implications of omicron evading immunity**

Despite milder disease, its rapid spread has the potential to overcome other responses and saturate health care systems. Therefore, it is important to critically appraise Omicron data and share this information widely across the global scientific community to create an integrated response to the pandemic

It seems evident that variants have greatest impact on neutralizing antibodies response, also cell-mediated immune responses are less susceptible but also important for protection against SARS-CoV-2. Many laboratories have reported reduced Omicron neutralization as compared to the ancestral virus and previous variants. This reduction has been observed in convalescent plasma and with several different vaccines.

Booster or additional exposure of vaccinees via infection increases neutralization, it may also increase the breadth of neutralizing response. Some studies show the response to boosters against Omicron may wane very quickly.

In terms of clinical data some studies show that vaccine effectiveness against symptomatic illness increase following a booster dose.

**Assays development achievements Standards**

**The first WHO International Standard (IS) for anti-SARS-CoV-2 immunoglobulin was established by the WHO Expert Committee on Biological Standardization on 10 December 2020.**

Since that time, the IS has been shipped to laboratories around the world, leading to the depletion of the standard in August 2021. Multiple secondary standards calibrated to the IS have been made available to bridge the gap until a new IS can be established (expected October 2022).



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Efforts to educate the research community on the use of standards included a training webinar in November 2021 ([https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/coronavirus-disease-\(covid-19\)](https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/coronavirus-disease-(covid-19))) and a new WHO manual for the establishment of national and other secondary standards ([https://cdn.who.int/media/docs/default-source/biologicals/call-for-comments/who-manual-secondary-standards-for-antibodiesv30012022.pdf?sfvrsn=8638882c\\_3](https://cdn.who.int/media/docs/default-source/biologicals/call-for-comments/who-manual-secondary-standards-for-antibodiesv30012022.pdf?sfvrsn=8638882c_3)).

As part of the training, it was emphasized that the IS can be used for calibration of assays for each VOC or Variant of Interest (VOI), but that comparisons or conversions cannot be made between variants and that units should be reported per isolate used.

In addition, the global research community has made a concerted effort to share reagents and protocols across approximately 150 labs worldwide.

**Variants of Concern (VOCs) and Variants of Interest (VOIs)**

The greatest challenge in the last year has been the proliferation of VOCs and VOIs. One of the early readouts for each new variant has been the assessment of neutralization of convalescent or vaccine sera. The wild type neutralization assays, pseudovirus neutralization assays, and surrogate virus neutralization assays that were developed in 2020 were all adapted to the new VOCs and VOIs as they emerged.

**Research groups have shared their experiences and data on the development of immune assays, materials and reagents for the evaluation of immunity to SARS-CoV-2 virus or SARS-CoV-2 vaccines and there were general trends observed across many studies.**

In summary, the fold reduction in neutralization compared to ancestral strains was relatively modest for alpha and gamma, slightly more for delta, and highest for beta, until the emergence of Omicron. There is an extremely high fold reduction in neutralization titres due to Omicron across all convalescent and vaccine samples tested, with many samples not being neutralized at all. Sera from individuals that were infected as well as vaccinated had higher titres over primary vaccination series alone. Neutralization titres from infection or vaccination were seen to wane over time.

However, additional doses, either homologous or heterologous boosters, were able to restore neutralization titres to peak levels and in some cases, higher than the peak following primary series. Early data for Omicron also indicates that infection of previously infected or vaccinated individuals leads to boosting of cross neutralizing antibodies, while infection of naïve individuals leads to poor neutralization of other variants.

Early animal data suggest that Omicron-specific vaccines do not generate broadly cross-neutralizing antibodies against other VOCs when used as a primary series. When used as boosters, some studies suggest that they do not offer an advantage over current vaccines.

The retention of non-neutralizing antibody functions and cellular immunity following vaccination likely continue to confer post-transmission protection against severe disease and death against VOCs.

#### Durability

In evaluating durability of antibody levels, there are assay-specific technical issues, such as assay format and immunoglobulin target, which influence the outcomes of these assessments.

In several studies, anti-spike, direct or total immunoglobulin assays demonstrated more stable, or increasing reactivity over time



than anti-nucleocapsid, indirect, or immunoglobulin assays. Durability has been determined in longitudinal cohorts as far out as 15 months post-infection and while neutralizing and antibody titres decreased over time, some studies have shown that they stabilize after several months. SARS-Cov-2-specific memory B and T cells have also shown persistence out to a year or more.

#### Correlates of Protection

Identifying CoPs, assessing new vaccines is critical to support vaccine pre-clinical and clinical development.

Several groups have shown that neutralizing or binding antibodies can serve as correlates of protection based on data reported across vaccine efficacy trials. There is also a proposed population-based threshold of protection based on immunoglobulin G anti-Spike antibody. Binding and neutralizing antibody levels were also shown as a correlate for specific vaccines. Most of these assessments were from trial data prior to the emergence of many of the VOCs, so additional data are needed in the context of more recent variants such as Omicron.

**In 2021, animal model research played a chief role in the characterization of the pathogenesis, transmission and immunology of SARS-CoV-2 variants of concern (VOCs).**

#### Animal model achievements Variants of concern (VOCs)

Studies in mice, hamsters, ferrets and non-human primates (NHPs), have demonstrated that none of the VOCs tested (alpha, beta, delta and Omicron), show enhanced virulence in these animal models, although increased production of proinflammatory cytokines was observed in hamsters infected with the alpha VOC. In the case of Omicron, and

despite conserved binding to animal model ACE2, the disease signs are very mild in all animal models.

**These findings suggest that, as SARS-CoV-2 adapts to humans, to some extent it loses capacity to cause disease in animal models.**

Recent studies in mice, hamsters, and NHPs show that animals previously infected or vaccinated against lineage A SARS-CoV-2 are protected against challenge with homologous as well as heterologous virus strains including all VOCs. VOCs also tend to show enhanced transmission in comparison with lineage A SARS-CoV-2 in competition studies performed in a number of models, including hamsters, ferrets, and white-tailed deer. Omicron outcompeted other VOCs in competition studies of transmission in the presence of immune pressure.

#### Age and co-morbidities

**In humans, the severity of COVID-19 with age and with co-morbidities, such as diabetes and cardiovascular disease, has been well established.**

**In 2021, an important effort has been directed to engineer animal models that would mimic these important disease drivers.**

Aged models, including NHPs, hamsters and mice suggested that viral pneumonia may persist longer in older animals, and that this persistence was associated with reduced humoral responses to infection and enhanced inflammation. Similarly, infection of diabetic animals, resulted in enhanced inflammation and delayed virus clearance. Further development of co-morbidity models is ongoing.

**Correlates of protection**

NHP studies have been key to investigate (CoPs) exerted by vaccination and natural infection.

These studies have demonstrated for example the importance of CD8 T cells, which contribute to protection when antibody levels are suboptimal, or start to wane. In general, animal model studies strongly suggest that correlates for long-term protection for an individual may

change over time or may include multiple immune parameters. Ongoing studies in the NHP model will be important to define immune thresholds for protection and immunobridging.

**Objective**

**3**

**Coordinate and collaborate internationally to implement clinical trials, for evaluation of the safety and efficacy of vaccines**

**Key achievements  
Human challenge studies**

The Advisory Group on Closely Monitored Challenge Models of Experimental COVID-19 Infection and Illness in Healthy Young Adult Volunteers.

**In 2021 the group met to update guidance and lessons learned regarding volunteer challenge studies with SARS-CoV-2.**

**Solidarity Trial Vaccines (STV) for vaccine evaluation**

**A large, international, randomized clinical trial platform was launched in September 2021 in Colombia, Mali and the Philippines with more than 30 research sites.**

Over 17,000 participants have been randomized. Two candidate vaccines are being evaluated in the trial with four more expected to enter in the coming months. The STV will also expand the implementation activities to two other countries.

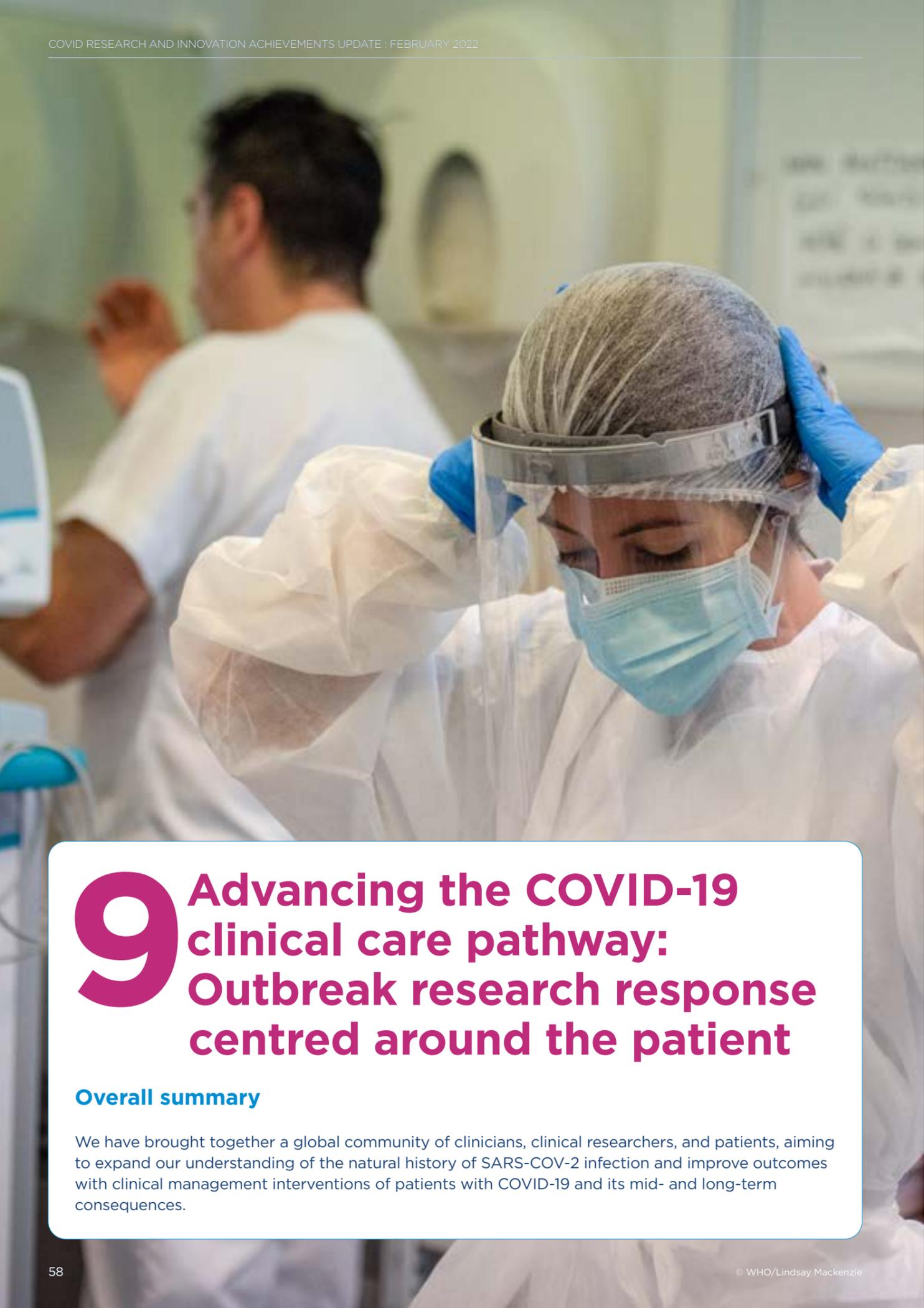
**Key benefits**

**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 identified. This was possible thanks to an extensive collaboration and cooperation between multiple stakeholders.**

Even so, additional vaccines are required to increase global supply, to provide products with additional desirable properties, and potentially to address SARS-CoV-2 VOCs.

**Key outputs**

See the list of references at the end of the report.



# 9 Advancing the COVID-19 clinical care pathway: Outbreak research response centred around the patient

## Overall summary

We have brought together a global community of clinicians, clinical researchers, and patients, aiming to expand our understanding of the natural history of SARS-CoV-2 infection and improve outcomes with clinical management interventions of patients with COVID-19 and its mid- and long-term consequences.

## Aim

The overall aim of the epidemiological studies thematic area of the coronavirus roadmap has been to develop, implement and coordinate activities to help better understand the transmission characteristics of SARS-CoV-2 and severity profile of COVID-19, including new variants.

### Objective To develop research tools for standardization

# 1

#### Achievements

##### Development of core outcome measures for COVID-19 clinical trials

With input from researchers from 25 countries around the world, we developed a minimal Common Outcome Set (COS) for COVID-19 trials, to capture clinical and virologic data that could be reported in a common manner to facilitate pooling data across multiple sources.

Many studies and trials around the world have utilized this COS in their work. WHO Working Group on the Clinical Characterization and Management of COVID-19 infection: A Minimal Common Outcome Measure Set for COVID-19 Clinical Research. *Lancet Infect Dis* 2020 Aug;20(8):e192-e197.

- With the Core Outcome Measures in Effectiveness Trials (COMET) initiative we are developing a core outcome set for studies of post-COVID-19 condition (manuscript in review). The importance of this work is described in the following publication: Studying the post-COVID-19 condition: research challenges, strategies, and importance of Core Outcome Set development. *BMC Medicine* 2022 Feb; 50.

- We contributed to a separate COMET initiative to create a core outcome measure set for studies of COVID-19. Tong A et al for the COVID-19-Core Outcomes Set (COS) Workshop Investigators: Core Outcomes Set for Trials in People With Coronavirus Disease 2019 *Crit Care Med* 2020 Nov;48(11):1622-1635.

#### Development of clinical case definitions

##### Post-COVID-19 condition

- We used a Delphi process with a diverse group of stakeholders to create a clinical case definition for post-COVID-19 condition. The initiative was described in the WHO Bulletin, Towards a universal understanding of post-COVID-19 condition. Bulletin of the World Health Organization, 99(12), 901-903 and the global definition published, Soriano JB et al for the WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis.* 2021 Dec 21;S1473-3099(21)00703-9. We are engaging with paediatric investigators on a similar definition for paediatric post-COVID-19 condition.

##### Mother-to-child transmission

- We conducted evidence synthesis and convened a WHO expert consultation to define a consensus initial classification system for the timing of vertical transmission and this was published in a WHO scientific brief, 'Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2'.

##### MIS-C

- WHO has convened a working group for multisystem inflammatory syndrome in children (MIS-C). Through a consensus approach, the MIS-C Working Group developed a preliminary clinical case definition for MIS-C which has been [published](#) on the WHO website. The case definition has been used widely by national governments and researchers.

## Objective 2 To coordinate knowledge syntheses efforts for reliable and trustworthy clinical guidance

### Achievements

#### Prospective meta-analyses of candidate therapeutics for COVID-19

We developed the model of a prospective meta-analysis to pool grouped data from recently completed and ongoing clinical trials of potential treatments for COVID-19 and published the process.

We have developed an agreement with JAMA Network that enables each PMA to be accompanied in the journal by relevant contributing trials.

The prospective meta-analyses are on the following topics:

- Protocol for steroids: Sterne JAC et al for the WHO COVID-19 Clinical Management and Characterization Working Group: Corticosteroid therapy for critically ill patients with COVID-19: A structured summary of a study protocol for a prospective meta-analysis of randomized trials. *Trials* 2020; Aug 24;21(1):734.
- Corticosteroid PMA: The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Systemic Corticosteroids for Critically Ill Patients with COVID-19: A Prospective Meta-analysis of Randomized Clinical Trials. *JAMA* 2020 Oct 6;324(13):1330-1341.
- Interleukin-6 Receptor Analysis PMA: WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group: Association between administration of interleukin-6 receptor antagonists and mortality among hospitalized patients with COVID-19: A prospective meta-analysis. *JAMA* 2021 Aug 10;326(6):499-518.

- Protocol for heparin/anticoagulation: [Prospective meta-analysis of randomized trials of anticoagulation therapy for COVID-19](#), Last updated December 2021.
- Heparin PMA: The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working group: A prospective meta-analysis of heparin (draft in process).
- Under consideration and development: A PMA on antiplatelet therapies and SGLT-2 inhibitors.

#### Living systematic review on COVID-19 and pregnancy

We have established a living systematic review of emerging evidence on COVID-19 during pregnancy. A dedicated website,[1] hosted by the University of Birmingham, UK (a WHO Collaborating Centre) was set up to disseminate the findings of the living systematic review and has been regularly updated.

The following were reviewed:

- Clinical presentation, prevalence, risk factors: Allotey J, et al; for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020 Sep 1;370:m3320. Updated results of the living systematic review on clinical presentation, prevalence, risk factors were published in March 2021. The second update has been submitted for publication.
- Mother-to-child transmission: Offspring SARS-CoV-2 positivity and timing of mother-to-child transmission: A living systematic review and meta-analysis (accepted in *BMJ*).

- Treatment: Giesbers S, et al;for PregCOV-19 Group. Treatment of COVID-19 in pregnant women: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2021 Dec;267:120-128. [1] <https://www.birmingham.ac.uk/research/who-collaborating-centre/pregcov/index.aspx>

#### Neurology and COVID-19: improving our understanding

This has been part of the activities of the ongoing Neurology and COVID-19 Forum, a collaborative network of international stakeholders that focuses on COVID-19 neurological surveillance, acute clinical care, follow-up, long-term impact and the provision of essential services.

It is summarized in a WHO scientific brief, based on the evidence that emerged from systematic or rapid reviews and meta-analyses commissioned by WHO (listed below).

- Garcia-Azorin D, Seeher KM, Newton CR, Okubadejo NU, Pilotto A, Saylor D et al. Disruptions of neurological

services, its causes and mitigation strategies during COVID-19: a global review. *J Neurooncol*. 2021;1-14. <https://doi.org/10.1007/s00415-021-10588-5>

- Misra S, Kolappa K, Prasad M, Radhakrishnan D, Thakur KT, Solomon T et al. Frequency of neurological manifestations in COVID-19: a systematic review and meta-analysis of 350 studies (submitted for publication). *medRxiv*. 2021:2021.04.20.21255780 <https://www.medrxiv.org/content/medrxiv/early/2021/04/23/2021.04.20.21255780.full.pdf>
- Beghi E, Giussani G, Westenberg E, Allegri R, Garcia-Azorin D, Guekht A, Frontera J, Kivipelto M, Mangialasche F, Mukaetova-Ladinska EB, Prasad K, Chowdhary N, Winkler AS. Acute and post-acute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions. *J Neurol*. 2021 Oct 21:1-10. doi: 10.1007/s00415-021-10848-4. Epub ahead of print. PMID: 34674005; PMCID: PMC8528941.



### Rehabilitation and COVID-19

Based on the evidence provided from Rapid Living Systematic Reviews on Rehabilitation and COVID-19 from Cochrane Rehabilitation and publications provided by the WHO COVID-19 Clinical Management network, a Scientific Brief on 'Rehabilitation needs of people recovering from COVID-19' was [published](#).

To further inform rehabilitation interim guidance for post-COVID-19 condition the following narrative syntheses and reviews are under development: Narrative synthesis of the evidence of rehabilitation interventions for selected impairments in post-COVID-19 Condition; and Systematic scoping review to describe health system, provider and patient characteristics to design rehabilitation care models for post-COVID-19 condition.

#### Living guidelines for COVID-19: Therapeutics, clinical management

We have established an innovative process to develop COVID-19 Living guidelines using innovative approaches to rapid evidence synthesis (LNMA and

PMA) and an electronic publication platform (MAGICapp) to develop trustworthy, transparent, rapid recommendations.

The therapeutics guideline is disseminated in three simultaneous platforms including WHO website, MAGICapp electronic publication platform and British Medical Journal; and translated into easy-to-use, visual tools in an [infographic](#) and COVID-19 clinical care pathway.

- [Therapeutics and COVID-19: living guideline \(who.int\)](#)
- [A living WHO guideline on drugs for covid-19 | The BMJ](#)
- [MAGICapp -](#)
- [Making GRADE the Irresistible Choice -](#)
- [Guidelines and Evidence summaries](#)
- [Living guidance for clinical management of COVID-19 \(who.int\)](#)
- [Therapeutics and COVID-19 \(who.int\)](#)  
[COVID-19 Clinical Care Pathway \(who.int\)](#)



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## Objective 3 To improve evidence surrounding supportive care interventions for COVID-19 (doing the basics well)

# 3

### Achievements

#### Optimizing respiratory support for COVID-19 in LMICs

**A working group with leadership from LMICs is undertaking a study to determine the best respiratory support approaches to optimize the use of oxygen in LMICs.**

This programme consists of two components:

- [WHO O2CoV2](#) is an international observational study on oxygen requirements and use in patients with COVID-19 in LMICs from all six WHO regions. It will inform an upcoming

WHO RCT of respiratory support strategies to minimize the need for mechanical ventilation. We have recruited 36 Principal Investigators from 24 countries; the study has launched in Lebanon, and is in various stages of onboarding elsewhere. Study protocol: <https://clinicaltrials.gov/ct2/show/NCT04918875> | [covidrespstudy@who.int](mailto:covidrespstudy@who.int)

- An initial protocol for a platform trial to determine optimal approaches to respiratory support has been drafted and will be customized based on the results of O2CoV2.

## Objective 4 To describe the changing natural clinical history of COVID-19

# 4

### Achievements

#### WHO Global Clinical Platform for COVID-19

The COVID-19 Platform is an online data repository of anonymized, individual-level clinical data of hospitalized COVID-19 cases to improve the global understanding of the presentation, risk factors, treatments, and outcomes of patients hospitalized with COVID-19 and those after acute illness with mid- and long-term consequences.

The platform includes clinical data from over 550,000 hospitalized cases from 39 countries around the world. A case report form to assess clinical manifestation of the post-COVID-19 condition has been developed and disseminated.

Technical products associated with the Global Clinical Platform:

- A statistical analysis plan (manuscript in preparation)
- Global report on clinical features and outcomes of COVID-19 in people living with HIV (link; late breaker abstract at the International AIDS Conference; manuscript under review by Lancet HIV) consequences.



- Country reports on clinical manifestations and outcomes of COVID-19 (Brazil, Cameroon, Colombia, Ghana, Jordan, Nigeria, Zimbabwe)
- WHO Global Clinical Platform Dashboard for COVID-19 ([link](#))
- Additional analyses addressing severity and mortality associated with the Omicron variant, clinical features and outcomes of COVID-19 in children and adolescents, clinical features and outcomes of COVID-19 in pregnant women, antimicrobial resistance and co-infections in patients hospitalized with COVID-19, and validation of mathematical modelling predicting disease severity in LMICs are in development.
- For more information see our website: [The WHO Global Clinical Platform for COVID-19](#)

**WHO coordinated a severe COVID-19 in children study**

This study evaluates the clinical characteristics of SARS-CoV-2 disease in neonates, children and adolescents hospitalized with COVID-19 or MIS-C in LMICS, using hospital network surveillance systems in four LMICs (Ethiopia, India, Pakistan, South Africa).

Children have been followed for three months post-hospital discharge. The study protocol is registered on the ANZ clinical trials registry (registration no ACTRN12621001154897) <https://www.anzctr.org.au/ACTRN12621001154897.aspx>.

The study ceased enrolment on 31 Dec 2021, with 3,870 children aged 0-19 years enrolled from April 2020 to Dec 2021. Three-month follow-up status is available to date for 2,741 (71%). Final follow-up, data cleaning and analysis are ongoing and will be complete in April 2022.

**A prospective cohort study investigating maternal, pregnancy and neonatal outcomes for women and neonates infected with SARS-CoV-2**

This study evaluates the prevalence, clinical spectrum and impact of SARS-CoV-2 on outcomes of pregnant or recently pregnant women. It will characterize the prevalence of SARS-CoV-2 RNA in amniotic fluid and breast milk, and follow clinical outcomes of women and their newborns up to six weeks after childbirth. The impact of vaccination will be evaluated.

Eleven countries are engaged: Argentina, Brazil, Burkina Faso, Chile, Georgia, Ghana, Kenya, Malawi, Pakistan, Philippines and Tunisia. The study enrolment started in June 2021 (Table). A total of 9,000 women have been screened of whom 5,500 were enrolled in different stages of pregnancy. Approximately 2,000 women have received at least one dose of a COVID-19 vaccine.



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**Objective**

**5**

**To conduct implementation research relevant to clinical characterization and management**

**Achievements**

**Safely introducing new therapeutics into clinical practice**

- As effective treatments are identified, their uptake is being evaluated. A cohort event monitoring (CEM) protocol has been developed to be used by LMICs to actively monitor the safety of molnupiravir. At least six countries will be supported to conduct the CEM study, and findings will be pooled into a repository at WHO HQ.
- We have developed collaborations with colleagues in pharmacovigilance, influence, antimicrobial resistance, and in the laboratory to develop a protocol to monitor for potential resistance to SARS-CoV-2 antivirals.

**Classification matrix for COVID-19 severity**

- An ongoing activity seeks to reassess and revise the severity classification for COVID-19 to ensure that the system is simple, broadly applicable, and adequately discriminatory between severity states, leveraging data collected through the WHO Global Clinical Platform.



# 10a

## Research and development for treatments of hospitalized patients

### Overall summary

Since the 18 March 2020 launch of the Solidarity Therapeutics trial, a large randomized controlled trial of treatments for COVID-19 in hospitalized patients, WHO, in close collaboration with participating Member States and partners around the world, helped evaluate drugs effects on important outcomes.

**In the first six months, Solidarity generated conclusive evidence on the effectiveness of repurposed drugs for the treatment of COVID-19.**

Four drugs were evaluated and following the enrolment of 14,221 patients, the results showed that remdesivir, hydroxychloroquine, lopinavir and interferon had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.

**In August 2021, WHO launched Solidarity PLUS, the new and current stage of the trial, which is an unprecedented global collaboration for COVID-19 R&D with thousands of researchers in 52 active countries.**

As of February 2022, over 1,000 patients have been randomized in 23 countries across the six WHO regions; while remaining countries are preparing to do so. Solidarity PLUS has been enrolling hospitalized patients to evaluate three new treatment arms, in the clinical management of COVID-19: artesunate, infliximab and imatinib, in addition to the local standard of care.

**These therapies were selected by an independent expert panel for their anti-inflammatory properties and their potential in reducing the risk of death in hospitalized COVID-19 patients.**

**“Finding more effective and accessible therapeutics for COVID-19 patients remains a critical need, and WHO is proud to lead this global effort,” said Dr Tedros Adhanom Ghebreyesus, WHO Director-General.**

**“I would like to thank the participating governments, pharmaceutical companies, hospitals, clinicians and patients, who have come together to do this in true global solidarity.”**

The drugs were donated for the trial by their respective manufacturers, through Letters of Agreement between WHO and the companies. Artesunate, produced by Ipca, is a derivative of artemisinin, an antimalarial drug extracted from the herb *Artemisia annua*. Imatinib, produced by Novartis, is a small molecule tyrosine kinase inhibitor, formulated as an oral chemotherapy drug used to treat certain types of cancer. Infliximab, produced by Johnson and Johnson, is a TNF alpha inhibitor, a chimeric monoclonal antibody that recognizes human TNF alpha.



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## Aim

The aim of Solidarity PLUS is articulated in four objectives below.

### Objective 1 **Continuously identify candidates for clinical evaluation and analyse the landscape of scientific evidence, while allowing for the addition of new treatments and discontinuation of ineffective treatments throughout the trial**

#### Key achievements

Four drugs were first evaluated - remdesivir, hydroxychloroquine, lopinavir and interferon: the results showed little or no effect on the mortality of hospitalized patients with COVID-19, providing critical evidence to inform clinical decision-making and treatment guidelines.

Based on available data, three new drugs - artesunate, imatinib, infliximab - were selected by the *WHO Advisory Group on Therapeutics Prioritization for COVID-19*, an expert group set up with the aim of establishing an independent process to advise WHO on the selection of therapeutics for COVID-19.

The panel considered various antithrombotics, antivirals, immunomodulators and monoclonal antibodies, and chose these drugs as they were considered to have the largest potential to reduce mortality.

The first four treatment arms were discontinued. Three new treatment arms added to the trial in addition to the local standard of care.

### Objective 2 **Continue to assess multiple treatments at the same time using a single protocol**

#### Key achievements

Robust results on safety and efficacy (or lack thereof) were delivered.

### Objective 3 **Recruit thousands of patients to generate robust estimates on the effect a drug may have on mortality - even moderate effects**

#### Key achievements

Active enrolment in the trial is ongoing.

### Objective 4 **Ensure a strong international coordination and collaboration to implement clinical trials for evaluation of the safety and efficacy of therapeutics**

#### Key achievements

Co-sponsorship with participating Member States strengthened, by robust collaboration between multiple hospitals in countries around the world.

National co-ordinators and principal investigators in each country supporting participating hospitals nationwide, in the preparation and conduct of the trial: from ethical and regulatory approvals, to the supply of study drugs, to scientific advice as well as to trial monitoring.

#### Key benefits

**Global platforms like Solidarity PLUS help the world prepare for future pandemics in establishing a new global approach to the robust evaluation of several therapeutics. The innovative approach is based upon simplicity, scale and access and collaboration.**

Enrolling patients in one single randomized trial helps facilitate the rapid worldwide comparison of unproven treatments and overcome the risk of multiple small trials not generating the strong evidence needed to determine the relative effectiveness of potential treatments. Through the Solidarity PLUS trial, researchers across the world are empowered and provided with opportunities to contribute their expertise and resources to the global research needs for COVID-19.

#### Key outputs

- Four drugs evaluated and discontinued
- 10+ new potential compounds considered by the WHO Advisory Group on Therapeutics Prioritization for COVID-19 and its technical panels, and three submitted for consideration to the Executive Group of the International Steering Committee of Solidarity PLUS
- Three new drugs selected by the Executive Group for inclusion into Solidarity PLUS with subsequently addition of three new arms to the platform;
- Identification and subsequent negotiations with manufacturers for study drugs donation with regulatory and access conditions carried out with final agreements reached in July 2021
- Solidarity PLUS launched in August 2021 with first randomized patient on 6 August 2021
- Manuscript on the final results for Solidarity period one completed and submitted for peer-review publication



# 10b Critical needs for outpatients and for the design of outpatient therapeutic trials

## Overall summary

Several initiatives were rapidly established to conduct large-scale and robust clinical trials, as flexible and adaptive platforms supporting the clinical evaluation of therapeutic candidates targeting particular patient groups and disease stages. Progress to date has been dependent on unprecedented levels of collaboration, at national, regional and global levels to ensure consistency in approaches, facilitating sharing of information, promoting alignment around shared visions, and creating opportunities for large-scale trials delivering robust evidence.

Potentially, greater coordination could be achieved especially in the early stages of clinical evaluation, to accelerate the development of a global pipeline of COVID-19 therapeutics, through closer alignment between major platforms, to reduce duplication of effort and focus efforts on shared priorities, while recognizing that some overlap is important in demonstrating replication of research results.

The COVID-19 Working Group on Outpatient Therapeutics Protocols was established with the intent to provide an opportunity to build on these existing initiatives to promote rapid, fluid and efficient information sharing and promote collaboration.

## Aim

The aim is to promote synergy and efficiency between the different outpatient treatment platform trials through coordinated interaction and exchange of information, to avoid duplication of effort and repetition of

errors, and to ensure the comparability of results to answer pertinent questions and better inform outpatient treatment policy, with the following three objectives:

### Objective 1 Share trial-specific information and best practices between trial platforms

# 1

#### Key achievements

Facilitation of large-scale collaborations and information sharing, leading to critical decisions, in particular regarding dose selection as well as selection of study arms and evaluation of therapeutic agents as combinations.

### Objective 2 Promote collaboration, standardized approaches, information sharing on therapeutic agents under evaluation and data sharing

# 2

#### Key achievements

Framework for pooled data analysis based on common measures across studies and information about comparable endpoints under development.

### Objective 3 Collaboratively deliberate on the ideal design, outcome measures and endpoints for outpatient treatment clinical trials, particularly in light of the disease dynamics

# 3

#### Key achievements

Major issues pertinent to the design of outpatient trials and the interpretation and external validity of study outcomes have emerged from discussion sessions.

## Key benefits

**The availability of effective outpatient treatment of COVID-19 is critical to the control of the pandemic, and outpatient trials whose clinical objectives are to limit progression, limit hospitalization and improve symptoms are essential for many communities.**

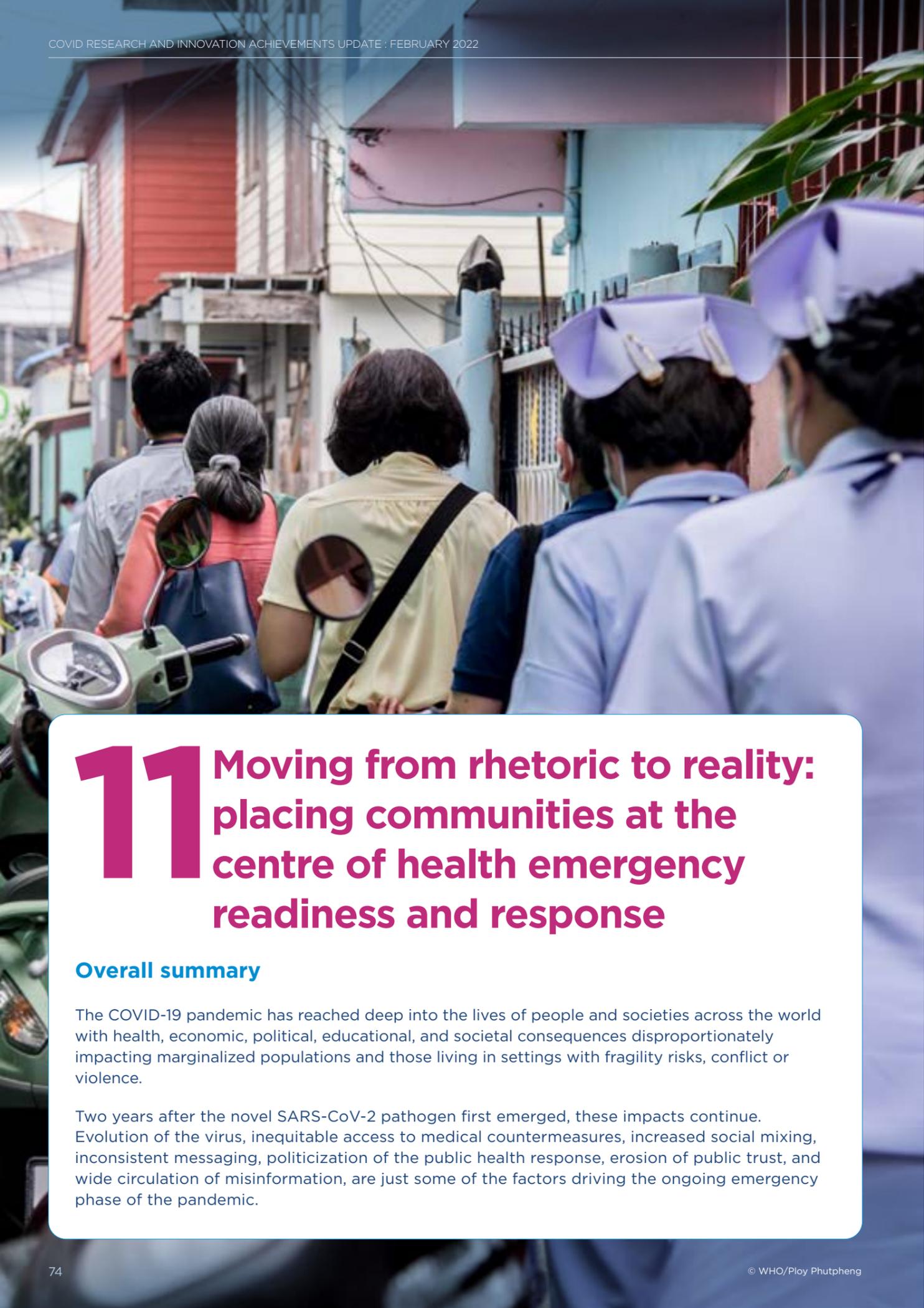
Effective outpatient treatment is likely to be cost-effective and alleviate the burden on the health system by reducing COVID-19-associated hospitalization and death, thereby freeing up medical facilities for other essential medical services. In the setting of a rapidly evolving COVID-19 pandemic, the usual scientific process of building one study on another with progressive endpoints is inefficient.

## Key outputs

- Development of a landscape of all endpoints across platform trials, recognizing that discussions about pooling endpoints across trial platforms have been largely restricted to the primary endpoints, which could limit the ability to do pooled data analysis. Instead, the focus should shift from comparing primary endpoints to ensuring common measures across studies and pooling information about comparable endpoints
- Identification of gaps and needs: for adjusting the clinical scales to capture to capture a broader range of patient conditions to compare study outcomes and the development of statistical analysis methods to leverage longitudinal ordinal outcomes; for consideration of the cost burden on the health system in addition to the quantification of clinical benefits
- Recognition that restricting enrolment to unvaccinated patients limits the external validity of outpatient treatment

Rather, data should be collected within platforms, and endpoints relevance assessed periodically depending on the external context. This type of innovation remains a significant challenge. The working group, comprised of trial platform experts across different regions of the world, contributes to addressing these challenges by sharing, and in its sessions, examined the evidence needed to inform policy change, discussed country-specific challenges, reflected on the selection of appropriate endpoints in a rapidly evolving pandemic with changes in the disease course and population susceptibility, commenced discussions of establishing a framework for data sharing among trial platforms, discussed the place of economic approaches in the evaluation of treatment outcomes, prepared a landscape of trial outcomes for comparability and commenced activities to address the gaps and challenges identified.

- trials. The applicability and the external validity of a study findings in an era of increasing vaccination coverage remain important considerations to be further discussed. Specifying the patient population that would most benefit from treatment is essential to document the evidence in this group in the trial, refraining from extrapolating widespread use in patients in whom it may not be beneficial
- Preliminary insights into study comparators over time, through an attempt to anticipate and track the changes in trial outcome rates over time across outpatient treatment trial groups, and possibilities for handling these changes through pre-specification of anticipated dynamics
- Flexibility in the timing of pre-specification of thresholds has been identified as an important determinant to address the dynamism of an evolving outbreak



# 11 Moving from rhetoric to reality: placing communities at the centre of health emergency readiness and response

## Overall summary

The COVID-19 pandemic has reached deep into the lives of people and societies across the world with health, economic, political, educational, and societal consequences disproportionately impacting marginalized populations and those living in settings with fragility risks, conflict or violence.

Two years after the novel SARS-CoV-2 pathogen first emerged, these impacts continue. Evolution of the virus, inequitable access to medical countermeasures, increased social mixing, inconsistent messaging, politicization of the public health response, erosion of public trust, and wide circulation of misinformation, are just some of the factors driving the ongoing emergency phase of the pandemic.

**Social science in outbreak response is a newer area in health emergency response and COVID-19 has seen progress in mainstreaming evidence production in this area, particularly in the use of socio-behavioural data.**

Credible, trustworthy data and evidence on the social, behavioural, cultural, political, and economic aspects of COVID-19 provide critical perspectives to tackle these and other challenges. The social science in outbreak response group advocates for and advances research to bring these much needed perspectives to inform policy and response action.

Social science evidence cuts across all pillars of outbreak response and across the health emergency cycle. This work is delivered across the three levels of WHO and in partnership with multiple academic groups, networks, and operational partners including the Risk Communication and Community Engagement (RCCE) Collective Service and the Global Outbreak Alert and Response Network (GOARN)'s Integrated Outbreak Analytics (IOA).

The donor community is engaged via the GLoPID-R Social Science Working Group.

Social science in outbreak response is a newer area in health emergency response and COVID-19 has seen progress in mainstreaming evidence production in this area, particularly in the use of socio-behavioural data.

Donors have also made significant investments in longer term research related to social dynamics and impacts of the pandemic to provide an emerging research portfolio that can guide response to current pandemic and to future events of this kind.

However, we need to move further, faster and with greater ambition to ensure evidence from social sciences can inform integrated and holistic understandings of pandemic challenges, steer effective and equitable public health responses, and mitigate pandemic and response impacts.

Big questions such as how to address global inequities, how to localize response actions, how to meaningfully engage civil society, and how to build resilience and readiness for future shocks need broad, ambitious, and sustained investment to respond to current challenges and to protect against future events of this kind.

## Aim

This thematic area brings technical expertise from a wide range of social sciences that integrate with biomedical approaches to strengthen the COVID-19 pandemic response at international, regional, national, and local levels. The research agenda aligns with the goals of strategic preparedness and response plans to stop the spread of COVID-19, save lives and livelihoods. It is a cross-cutting agenda to impact and strengthen inclusive, person and community-centred approaches across all pillars of operational response.

**There is a need to move further, faster and with greater ambition to ensure evidence from social sciences can inform integrated and holistic understandings of pandemic challenges, steer effective and equitable public health responses, and mitigate pandemic and response impacts.**

## Objectives

To date, the social science in outbreak response thematic areas has promoted evidence generation and uptake with the following objectives:

### Objective 1 To strengthen public health and clinical responses to the COVID-19 pandemic

Research to strengthen public health and clinical responses to COVID-19, including related to the uptake of public health and social measures (PHSMs) and medical countermeasures in the context of a protracted public health emergency.

#### Key achievements

Advanced primary evidence generation related to social and behavioural dynamics including, for example, on PHSMs, vaccine uptake, COVID-19 home care, psychosocial impacts, policy responses, evidence-informed policy, health workers, infection prevention and control, sexual and reproductive health and ethics of scarce resource allocation.

Informed WHO guidance through integration of evidence from social sciences.

Global consultation on community-centred approaches to health emergencies.

#### Contribution to our understanding of SARS- CoV2 transmission and control

Evidence from social sciences brings important perspectives related to social, behavioural, cultural, political and economic aspects of SARS-CoV2 transmissions and control, including those related to unintended impacts of response decisions, to inform holistic and integrated response actions.

Evidence to strengthen community-centred responses aims to learn lessons from this pandemic to build resilience and readiness for future events.

To date, work captured under the social science pillar has generated valuable evidence that is crucial for developing emergency response strategies that are robust and account for complex social, economic and political landscapes.

### Objective 2 To mitigate the uneven impact of COVID-19 on different social groups

Understanding the impacts of COVID-19 and giving attention to the uneven impacts of the pandemic and attendant public health interventions, with a focus on marginalized groups, contextual vulnerabilities, humanitarian and fragile settings.

#### Key achievements

Global and local level analyses and advocacy on the broader impacts of COVID-19.

Advanced research for inclusive, person-centred response actions and structural mechanisms for wider engagement

such as tools for rapid assessment of contextual vulnerability, community mapping, engagement of civil society organizations.

#### Contribution to our understanding of SARS- CoV2 transmission and control

Increases knowledge on needs and challenges to be addressed for vulnerable populations for more inclusive and people centred responses.

Fair and efficient allocation of resources and more equitable response.

### Objective 3 To develop and advance methods, research infrastructure and research capacity

3

Challenges and opportunities of researching in a pandemic, methodological innovations, interdisciplinary approaches, synthesizing large bodies of knowledge to inform policy, capacity-building, for example, via training and fellowship schemes, and engaging social science research networks.

#### Key achievements

Developed research protocols, tools, mechanisms and research infrastructure for standardized, systematic collection of data.

Training and capacity development, together with network development and formalization to collect and share data.

#### Contribution to our understanding of SARS- CoV2 transmission and control

Enables faster, more effective approaches to evidence generation and use for COVID-19 and for future events.

Research conducted under this thematic area has also advanced understanding of the variable socioeconomic and political contexts of the pandemic, thus enabling better insights into key issues, for example the impacts of the pandemic and control measures beyond direct health effects, the factors leading to reduced public trust, and the dynamics influencing vaccine confidence.

#### Key benefits

To date, work captured under the social science pillar has generated valuable evidence that is crucial for developing emergency response strategies that are robust and account for complex social, economic, and political landscapes.

It has provided frameworks and methodologies for data collection, synthesis and analysis that are tailored to community realities to advise evidence-informed decision-making at local, regional, and global levels.

This includes research related to a broad and inclusive definition of communities, including, for example, marginalized groups, contextual vulnerabilities, health workers, online communities, and policy makers.

Research conducted under this thematic area has also advanced understanding of the variable socioeconomic and political contexts of the pandemic, thus enabling better insights into key issues, for example the impacts of the pandemic and control measures beyond direct health effects, the factors leading to reduced public trust, and the dynamics influencing vaccine confidence.

#### Key outputs

##### Global consultation on community-centred approaches to health emergencies to define evidence gaps

A global consultation brought together researchers, practitioners, governmental representatives, representatives of multilateral agencies and donors to review progress and specify gaps and research priorities for advancing community-centred approaches across the health emergency cycle.

Meeting outcomes highlighted knowledge gaps and evidence needs that can be addressed through interdisciplinary or social science research. Subsequently, rapid evidence syntheses have highlighted key approaches to operationalize key concepts such as community resilience and community readiness to inform the work of a new unit in WHO, the Community Readiness and Resilience Unit.

##### Good Participatory Practices (GPP) resources for a global clinical trial of COVID-19 vaccines

For coordinated and standardized practices related to multi-stakeholder engagement for the global Solidarity Trial Vaccines (STV), a suite of engagement

and learning materials for standardized best practice was developed and implemented by national teams delivering the trial.

These include a handbook for GPP and crisis communications and an online learning programme. Additional materials include standardized communications tools (leaflets, FAQs etc), an animated explainer of the trial; and a FlipBook for standardized information exchange during recruitment to the trial.

- Landscape analysis and mapping of community structures at national and subnational level, including mapping of civil society organizations.
- Research on the challenges and constraints of science and policy advisers when accessing, interpreting, applying and communicating scientific evidence in the context of a public health emergency to inform responsive solutions.

**Mechanisms, tools and training for standardized and systematic data capture and use of evidence**

Examples include:

- **Research tools for health workers surveys to improve infection prevention and control practices:** A customizable research protocol and online data collection tool for rapid cross-sectional surveys to evaluate perceptions of health workers' individual and organizational preparedness to follow infection and control (IPC) measures in their place of work . An implementation guide assists health care administrators and other decision-makers to easily interpret findings and take action to improve IPC in health care settings at local, regional and/or national levels. A briefing document highlights key considerations for this work in humanitarian settings. Sixteen groups working across 12 countries piloted this package, capturing the views of 10,000+ health workers in different settings. Training is in development through WHO SocialNet.
- **Rapid access to large socio-behavioural datasets for COVID-19:** Developed by the RCCE Collective Service, a database and linked dashboard presents data covering 198 countries, with over 250,000 data points from 411 different data sources. This resource makes best use of available data, encourages data sharing, and provides an innovative framework and methodology for data analysis based on a framework of key variables essential for slowing COVID-19 transmission or measuring

**Evidence for holistic, inclusive, tailored and evidence-informed response**

An extensive portfolio of evidence production continues to be delivered across multiple partner organizations and WHO global regions.

Examples include:

- Rapid evidence syntheses and briefings that collate best practice approaches and key considerations, for example, related to use of masks, COVID-19 home care, immunity passports, and for working with community health workers, youth and faith-based organizations.
- Advocacy and mechanisms for integration of social science evidence for example, through the kinds of research questions to be addressed, structures for integration and integration for disease modelling.
- Evidence to strengthen RCCE practices, including among marginalized groups, to promote more standardized approaches to RCCE, approaches for measurement and uptake of RCCE interventions, and use of formative research to inform interventions.

Subsequently, rapid evidence syntheses have highlighted key approaches to operationalize key concepts such as community resilience and community readiness to inform the work of a new unit in WHO, the Community Readiness and Resilience Unit.



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the impacts of COVID-19 transmission on communities. A Social Data Tracker dashboard also tracks key socio-behavioural data on COVID-19 from multiple research projects conducted by partners and academic communities.

- **Behavioural insights tools for systematic collection of data on public knowledge, risk perception, behaviours and trust:** Capturing feedback from over 27,000 respondents from 23 Member States in the WHO Eastern Mediterranean Region (EMRO), UNICEF Middle East and North Africa (MENA) region, results of a time-series regional Knowledge, Attitudes and Practices Survey (KAP) have enabled WHO and UNICEF to support countries with implementing evidence-based interventions to increase public adherence to PHSMs, as well as build demand and address barriers affecting COVID-19 vaccine uptake. Behavioural insights data collected from approximately 120,000 participants in 18+ countries and territories in the region using the WHO Europe COVID-19 behavioural insights survey tool, in addition to multiple rounds of data collected independently in 11 other countries, has informed policy

approaches and response decisions at national level. A similar tool for use in Africa was developed and piloted in Nigeria and Zambia and key lessons related to implementation are also captured. From July 2021, in the Western Pacific Region (WPRO), four waves of behavioural insights data have been collected, with a fifth round in progress, together with focus group studies for rich exploration and contextualization of findings.

- **Standards for rapid qualitative methods for public health emergency events** Rapid evidence production at the start of COVID-19 has seen innovation in methods for social science research. Well-specified and robust methods are critical to address the full range of complex social, health, political, economic and structural dimensions of a pandemic. A rapid evaluation of 138 published and unpublished sources highlighted recommendations for best practices in conducting rapid qualitative assessments used in public health emergencies . All references and publications/further resources are available at the end of the report.





# 12 IPC research during the pandemic: Pointing to an opportunity for saving lives and money

## Overall summary

The WHO COVID-19 Infection Prevention and Control (IPC) Research and Development (R&D) Expert Group was established following the COVID-19 Global Research Forum in February 2020. It includes 48 experts.

In collaboration with the WHO Secretariat, this group convened regularly to identify and update on the research priorities for IPC in the context of the COVID-19 pandemic.

Group members ran 45 research projects directly supported through the WHO Secretariat. These included systematic reviews, laboratory studies, modelling, randomized control trials, longitudinal studies, qualitative surveys and a multicentric case-control study.

Through these partnerships, research gaps have been bridged, while the evolving pandemic has also highlighted new questions and priorities to be considered for COVID-19 and in preparation for future outbreaks.

## Aim

The aim of the WHO COVID-19 IPC R&D Expert Group is to better understand infection prevention and control (IPC) measures required to inform recommendations and to optimize the effectiveness of personal protective equipment (PPE) to minimize the risk of SARS-CoV-2 transmission in both health care workers (HCWs) and the community.

The work of the group is done in concert with the WHO Secretariat, other stakeholders, COVID-19 research pillars and working groups with the purpose of facilitating coordination and collaboration of R&D and empower synergies in the field of IPC research and response during the COVID-19 pandemic and beyond.

Group members ran 45 research projects directly supported through the WHO Secretariat. These included systematic reviews, laboratory studies, modelling, randomized control trials, longitudinal studies, qualitative surveys and a multicentric case-control study.

## Objective 1 Understand the effectiveness of public health and social measures (PHSMs) and IPC strategies to prevent secondary transmission in health care and community settings.

### Key achievements

**Estimating the cost-effectiveness of IPC interventions:** a global modelling study conducted by the Organisation for Economic Co-operation and Development (OECD) and WHO assessed the effectiveness and cost-effectiveness of IPC interventions aimed at reducing transmission of SARS-CoV-2 among HCWs.

These are: enhanced hand hygiene (HH); increased PPE access (PPE+); combined PPE+ and IPC education and training interventions.

The study results (not yet published) suggested that in the first 180 days of the pandemic:

- enhanced HH intervention could have averted about 1 million new infections in HCWs, globally
- PPP+ alone could have averted about 4.4 million new infections in HCWs resulting in estimated net savings of US\$ 1.5 billion, globally

- combined PPE+ and IPC education and training could have averted 9.8 million new infections in HCWs, resulting in estimated net savings of US\$ 7.23 billion circa, globally

- per capita, cost of enhancing HH was estimated to be around US\$ 0.27 adjusted for the differences in purchasing power, whereas the cost of PPE+ alone and combining PPE and IPC education and training are US\$ 0.63 and US\$ 1.15, respectively

### Contribution to our understanding of SARS CoV-2 transmission and control

In the first 180 days of the pandemic, increased access to PPE combined with IPC training could have averted new cases, admissions to hospital and intensive care and deaths among HCWs in all regions, worldwide.

HH was also found to be a cost-effective intervention in most regions. This study estimated that PPE and enhanced HH could have prevented millions of infections and billions of associated costs on a global scale.

Through these partnerships, research gaps have been bridged, while the evolving pandemic has also highlighted new questions and priorities to be considered for COVID-19 and in preparation for future outbreaks.

**Understanding HCW infections**

- Development of a standardized protocol for a case-control study assessing risk factors for COVID-19 infection in HCWs. This case-control study led by WHO was implemented in 97 health facilities across 19 countries, recruiting 2,285 HCWs. Preliminary results (unpublished) suggested that prolonged close contact (>15min within 1m) and inconsistent face masks (respirator or surgical masks) wearing during SARS-CoV-2 exposures were strongly associated with infection.

The findings of this study highlighted the gap in appropriate use of masks by HCWs and thus, IPC training during the pandemic, especially in low-to-middle income settings.

- Living rapid review on HCWs risk factors for infection regularly published in the Annals of Internal Medicine; evidence indicate that significant risk of SARS-CoV-2 infection among HCWs associated with certain exposures (e.g. involvement in intubations, more direct or intense patient contact, or contact with bodily secretions) and with black race, direct contact with infected co-worker or household member. No consistent association was found with age, sex or professional role (nurse vs physician). Implementation of universal masking, IPC training, appropriate PPE use and hand hygiene were associated with decreased risk of infection among HCWs.

The living rapid review highlighted wide-ranging HCWs SARS-CoV-2 infection (likely due to differences in local epidemiology of infections, exposures, PPE use, clinical settings) and key independent factors for infection risk among HCWs. The review also evidence gaps related to infection risk associated with PPE use and PPE reuse.

- Living rapid review on existing HOCl systems initially published in the Journal of Hospital Infection; 9 sets of definitions and surveillance systems identified. Proportion of HOCl

cases varied from 0% to 15.2%. A new definition was developed by the authors.

The review allowed understanding of different definitions and systems for HOCl and develop a standardised definition.

- Network analysis of COVID-19 transmission in healthcare settings using patient movement data and a risk prediction algorithm based on patient and specialty characteristics, and development of a real-time and automated HOCl surveillance and individual risk prediction system (not yet published).

The network analysis and algorithm development helped monitor patient pathway; informed local IPC practices by identifying the high-risk locations (surgical units and renal wards) and patient groups (elderly, male).

The methods can be translated to monitoring transmission of other pathogens.

**Understanding the impact of the pandemic on health care-associated infection:** A case-control study revealed that the pandemic and national responses had an impact on the patterns of community- and hospital-acquired bloodstream infections (BSIs) in patients (COVID-19 and not).

Main results: out of 1,047 BSIs, 38% were hospital-acquired. HAI, with bloodstream HAI rate increased to 132.3 per 100,000 patient-days during the first wave and to 190.9 during the second, compared to 100.4 across the pandemic (with significant increases in elective inpatients). Patients with HAI had longer hospital stays (≈20 days) and 26.7% higher mortality rates.

This retrospective analysis used data linkage to investigate possible changing patterns of BSIs during two COVID-19 waves; it seems that the pandemic and national responses had an impact on the aforementioned patterns.

However, the factors driving these patterns are complex and include changes in patient case mix and adjustments in health care access and practice, as well as the widening of patient-to-staff ratios, the increasing trend of proning COVID-19 patients, and the sub-optimal PPE use.

- Another study performed in Singapore investigated the impact of the pandemic on the incidence of infections

acquired in intensive care units and the incidence of carbapenem-resistant organisms. The results (unpublished), including whole genome sequencing, indicated decreasing trends in 2020 compared to previous years.

The Singapore study yielded different results from the Imperial London study, indicating a possible positive impact of enhanced IPC on health care-associated infection and AMR trends.

**Objective 2 Optimize the effectiveness of personal protective equipment (PPE) and its usefulness in reducing the risk of transmission in health care and community settings.**

**Key achievements**

Improving PPE effectiveness and addressing shortages:

- Protocols for evidence-based assessment of PPE effectiveness in nosocomial and community and PPE decontamination methods have been defined.
- The effectiveness and safety of different decontamination methods has been demonstrated; the effectiveness of methylene blue in inactivating SARS-CoV-2, MERS-CoV, Ebola, Lassa, and Nipah viruses on N95 and KN95 respirator material was demonstrated; a dedicated study, on methylene blue applied to N95 respirators and medical masks providing safety evidence for the use of MBL for SARS-CoV-2 decontamination.
- New actionable protocols for decontaminating PPE in the context of severe shortage are now under development.
- Existing methods for PPE antimicrobial treatments have been systematically reviewed, demonstrating their efficacy, while highlighting the heterogeneity of protocols adopted by different authors.

**Contribution to our understanding of SARS- CoV-2 transmission and control**

Several studies investigated the effectiveness of PPE (medical masks, face shields, respirators, face visors) and community masks in real settings, and combination of different PPE providing evidence on their efficacy in controlling virus transmission.

In the context of severe shortage, decontamination of single-use respirator seems a viable strategy as a logistical stop gap.

Discussion about existing evidence on methylene blue effectiveness in inactivating other viruses, including norovirus, was also fostered, together with the need to clarify that other IPC measures (e.g. HH) can be strengthened but not surrogated by PPE use and reuse alone.

Systematic analysis of existing methods and tools for antimicrobial treatment of PPE, suggested that this is a viable approach to increase the safety and effectiveness of PPE in the context of severe shortage, although further effort is required to standardize antimicrobial treatments' methods, tools, protocols and further assess their safety and effectiveness.

**Improving PPE design:** importance of mask and respirators comfort (combination of breathability and fit) in the context of continued and universal masking was highlighted, beyond traditional mask properties (i.e., filtering and breathability)

- Protocols for non-medical masks (aka community-masks) have been identified and disseminated.
- Protocols and tools for quantitative assessing properties of masks and respirators were developed.
- Protocols for characterization and selection of novel materials for masks and respirators were developed.

**Contribution to our understanding of SARS- CoV-2 transmission and control**

Protocols aiming to improve the fit, performance and comfort of non-medical, medical masks and respirators have been developed.

**Improving PPE and non-medical mask acceptability and availability:**

- Human factors affected adoption, effective and safe use of PPE in health care settings and non-medical masks in community; factors affecting the selection included feeling protected, while fatigue and communication were the most recurrent reasons hindering adherence to recommendations (mainly linked to breathability, fit and

comfort); inconsistent behaviours were documented in relation to PPE reuse and disinfection; concerns were raised on uncertainty on assessing PPE and community masks; regrading decontamination and reuse, users were worried about several aspects.

- Combinations of PPE, medical masks and visors have varying impact on HCW communication and fatigue.
- The feasibility of using novel technologies for improving PPE logistics (e.g. drones for PPE delivery in remote areas) was demonstrated.

**Contribution to our understanding of SARS- CoV-2 transmission and control**

These studies supported the understanding of HCW and public preferences in which PPE wear in different medical settings (i.e. ER, admission, ICU).

Combinations of PPE have different impact on HCW communication and fatigue. Several studies deepened the importance of comfort, as an important issue for prolonged use of PPE and non-medical masks, both in health care settings and in community, beyond filtering and breathability, which were well established features for respirators and medical masks.

Novel technologies such as drones for PPE delivery, for improving PPE access to marginalized communities demonstrated.

**Development of a standardized protocol for a case-control study assessing risk factors for COVID-19 infection in HCWs. This case-control study led by WHO was implemented in 97 health facilities across 19 countries, recruiting 2,285 HCWs.**

**Objective Identify the role of the environment in transmission**

**3**

**Key achievements Identifying the role of the environment in transmission:**

Infectious virus on fomites; high quantitative burdens of infectious virus were detected on fomites from almost 500 samples from 75 hospitalized and community cases. This study suggested that multiple modes of transmission could be exploited by SARS-CoV-2, including direct contact, large respiratory droplets, and fomite transmission.

Survival of coronavirus surrogates on different kinds of frozen meat and fish products was investigated: Phi 6 persisted over 60 days, compared 4C vs -20C on different meats, phage survived for all the time of the observation (4C at 2log10 vs -20C at 0.5log10); RNA viruses (i.e. MHV, TGEV) shown similar behaviour to phage; chicken and pork see slightly greater reduction than beef or salmon.

This study suggested that frozen meat contaminated with different surrogates could be still infectious after 60 days; temperature response is surrogate dependent, indicating that more than one surrogate is needed in order to understand the likely survival of SARS-CoV-2 in different conditions.

**Key benefits**

The WHO R&D IPC Secretariat worked synergistically and in collaboration with technical and scientific partners and relevant R&D stakeholders. It ran studies in all regions (Figure 1),<sup>1</sup> contributing to the global understanding of SARS-CoV-2 surveillance, prevention, and definition of effective and cost-effective IPC solutions.

The evidence generated by this research has supported and will further inform measures and guidance to reduce the risk of SARS-CoV-2 transmission and provide protection of HCWs and members of the general public.



**Figure 1: the WHO IPC Teams coordinated 45 research projects, which included 27 multicentre studies in 45 different states in order to generate evidence on the research priorities identified in February 2020**

<sup>1</sup>Details can be read here: [https://www.who.int/publications/m/item/who-covid-19-infection-prevention-and-control-\(ipc\)-pillar](https://www.who.int/publications/m/item/who-covid-19-infection-prevention-and-control-(ipc)-pillar)



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**Key outputs**

**Objective**

1

1) Addressing key questions on IPC in health care in the context of COVID-19:

- Research on the cost-effectiveness of IPC interventions has indicated that enhanced PPE use, IPC training and hand hygiene could have prevented millions of infections among health care workers and billions of associated costs on a global scale and provided an evidence base to inform the development and integration of programmatic support for IPC
- Priority research on health worker infections has yielded identification of risk factors for SARS-CoV-2 infection among health care workers, and capability to assess high-risk breaches in IPC practices
- Research on human factors has provided evidence on normative HCW preferences and behaviours in

simulated scenarios, along with study protocols enabling further research and evaluative approaches for introducing novel approaches and technologies to IPC programmes.

- Research on health care-associated infections and antimicrobial resistance among patients during the pandemic has indicated conflicting results (increase in some settings and decrease in others compared to pre-pandemic periods) which need to be further explored.

2) Addressing sanitation and waste management:

- Research on the use of hypochlorous acid has been explored as a rational non-toxic alternative for inactivation of SARS-CoV-2 and other common pathogens in health care settings.

**Objective**

2

1) Addressing intermittent global shortages and logistical constraints for procurement of PPE:

- Priority research on decontamination and reprocessing methods has yielded promising preliminary findings on the use of methylene blue + light and dry heat as filtering face piece respirator decontamination methods.
- Research to support fit testing of filtering face piece respirators has provided a prototype for a low-cost alternative to quantitative and qualitative fit testing methods.
- Research evaluating eye and face protection using a global sampling of face shields is expected to provide improved design guidance for manufactured and locally produced face shields.

- Research on persistent antimicrobial treatments for face coverings has provided an evidence base for further research and innovation in this area.
- Research on innovative delivery of PPE and other essential medical supplies has provided evidence for a promising strategy for distribution of supplies in remote communities.

2) Addressing mask use in the community:

- Priority research on the essential parameters of non-medical masks used in community settings has informed guidance on material combinations and design to optimize fit, filtration, and breathability.

Research on embedding PVA test strips to capture virus in exhaled breath has provided a multipurpose non-invasive surveillance strategy for SARS-CoV-2 congregate settings.

**This review highlighted wide-ranging HCW SARS-CoV-2 infection (likely due to differences in local epidemiology of infections, exposures, PPE use, clinical settings) and evidence gaps related to infection risk associated with PPE use and PPE reuse.**

**Objective**

3

- Research on fomites containing viable virus present in patient care environments has provided supporting evidence for IPC strategies to reduce environmental contamination of SARS-CoV-2.

Several journal papers have been published by the team members as reported in the IPC pillar achievements report<sup>1</sup> published in May 2021 (an update IPC report is under preparation), as a result of the projects mentioned above.

Currently, a dedicated special issue on the American Journal of Infection Control (AJIC) has been organized and from the 11 papers initially submitted, three have been accepted for publication and six are in an advanced stage of revision.



# 13 Ethics and research

## Overall summary

The response to the COVID-19 pandemic has repeatedly underlined the importance of ethics in R&D and response efforts in public health emergencies.

The Ethics and COVID-19 Working Group identifies ethics and governance issues raised by COVID-19. Convened under the WHO R&D Blueprint, the working group also covers broader issues emerging in transmission and control, given the ubiquity of ethical concerns in the pandemic.

Since the onset of the pandemic, the working group has developed several WHO guidance documents and policy briefs. These documents support WHO and Member States in attending to ethical issues in R&D, public health, and clinical response.

The working group has developed ethical standards for research in public health emergencies, rapid research ethics review, and controlled human infection studies. Further guidance addresses topics in the public health response, including but not limited to the allocation of scarce resources, the use of digital tools, and mandatory vaccination.

In order to respond to emerging developments and stakeholder needs, the group maintains close linkages with other relevant WHO working groups as well as external partners, particularly those operating within the R&D Blueprint workstreams and the ACT-Accelerator (ACT-A).

Through webinars, forums, and outreach activities, the group engages with more stakeholders. In the future, the group will intensify its work on integrating ethics and governance into R&D and public health decision-making and translating guidance into practice to better prepare for future public health emergencies.

## Aim

The Ethics and COVID-19 Working Group aims to examine and produce guidance with respect to the ethical considerations and dimensions associated with COVID-19 R&D and broader ethical issues raised by the pandemic response.

**The Ethics and COVID-19 Working Group identifies ethics and governance issues raised by COVID-19. Convened under the WHO R&D Blueprint, the working group also covers broader issues emerging in transmission and control, given the ubiquity of ethical concerns in the pandemic.**

### Objective 1 Build on pre-existing ethics guidance to develop guidance materials fit for purpose in COVID-19

# 1

#### Key achievement

Developing and contributing to WHO guidance documents and policy briefs on COVID-19

Specifying principles for research in public health emergencies

#### Contribution to our understanding of SARS-CoV-2 transmission and control

The working group has developed guidance documents and policy briefs on ethical issues raised by COVID-19.<sup>1-15</sup> It has also advised and collaborated with other WHO working groups on ethical considerations in their focus areas.

This achievement has also contributed to delivering objectives 2 and 3.

### Objective 2 Identify principles for research and their application (standard operating procedures – SOPs, Solidarity trials, human challenge studies)

# 2

#### Key achievement

Specifying principles for research in public health emergencies

#### Contribution to our understanding of SARS-CoV-2 transmission and control

The working group has developed ethical standards for research during public health emergencies,<sup>9</sup> rapid research ethics review,<sup>10</sup> and guidance to scientists, research ethics committees, funders, policy-makers and regulators on the design, conduct and governance of controlled human infection studies.<sup>6</sup>

**The Ethics and COVID-19 Working Group aims to examine and produce guidance with respect to the ethical considerations and dimensions associated with COVID-19 R&D and broader ethical issues raised by the pandemic response.**

**Objective 3 Develop allocation principles for clinical management, vaccines, diagnostics, and therapeutics**

3

**Key achievement**

Hosting the WHO Pandemic Ethics & Policy Summit (6 Dec 2021)

can interact more systematically with technical and policy work in current and future infectious disease outbreaks.<sup>7 8</sup>

**Contribution to our understanding of SARS-CoV-2 transmission and control**

The working group hosted a high-level global forum to explore how ethics

This achievement has also contributed to delivering objectives 2 and 4.

**Objective 4 Build ethical preparedness for the subsequent waves and future infectious disease threats**

4

**Key achievement**

Dissemination and outreach activities

through the Epidemic Ethics Platform. Working group members have advised their national governments and ethics committees, and published on ethics and governance issues raised by COVID-19 in peer-reviewed journals.<sup>18-34</sup>

**Contribution to our understanding of SARS-CoV-2 transmission and control**

The group has presented its work across multiple platforms, including at regional and global summits of national ethics committees. Nine additional seminars (since May 2021) were convened

This achievement has also contributed to delivering objectives 2 and 3.

**Key benefits**

The response to the COVID-19 pandemic has repeatedly underlined the importance of ethics in R&D and response efforts in public health emergencies.

researchers, policy-makers, and other stakeholders to integrate ethics and governance considerations into decision-making.

Examples include setting research priorities, facilitating rapid research ethics review, allocating vaccines and other scarce resources within and across countries, devising and implementing restrictions of movement, considering vaccination mandates, and COVID-19 vaccination in children. Sustainable and successful R&D and outbreak response strategies require an integrated consideration of ethical and governance issues.

Such guidance is vital towards the R&D Blueprint's aim to improve coordination between scientists and global health professionals, and to shape new norms and standards to enhance the global response.

The WHO Ethics & COVID-19 Working Group identifies ethical challenges in COVID-19 R&D and the ongoing pandemic response.

In addition, the working group has collaborated with various technical departments of WHO on specific ethical aspects of their work and advised the WHO Communications team on ethics-related messaging.

On this basis, the Group develops guidance for WHO Member States,

Learning from the ethical challenges at the centre of the ongoing pandemic will be essential to better prepare for the next unforeseen public health emergency.



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**Key outputs**

Since publication of the previous Achievements Report (2021),<sup>17</sup> the working group published the following key outputs:

- The Ethical Framework for WHO's Work in the ACT-Accelerator<sup>1</sup>

- Ethics sections in guidance documents led by the WHO Digital Health team on Digital Documentation of COVID-19 Certificates for:

- Vaccination status<sup>2</sup>

- Test results<sup>3</sup>

- Principles and key ethical considerations for COVID-19 Immunization in Refugees and Migrants<sup>4</sup>

- A Policy Brief on ethical considerations of COVID-19 Vaccine Trial Designs in the Context of Authorized COVID-19 Vaccines and Expanding Global Access<sup>5</sup>

- The new WHO Guidance on the Ethical Conduct of Controlled Human Infection Studies<sup>6</sup>

Further WHO publications prepared by the working group since the onset of the pandemic include:

- A Policy Brief on Ethical Standards for Research During Public Health Emergencies<sup>9</sup>

- Guidance for the Rapid Review of Research during Public Health Emergencies<sup>10</sup>

- Key Criteria for the Ethical Acceptability of COVID-19 Human Challenge Studies<sup>11</sup>

- An Interim guidance on Ethical Considerations to Guide the Use of Digital Proximity Tracking Technologies for COVID-19 Contact Tracing<sup>12</sup>

- A Policy Brief on Ethics and COVID-19: Resource Allocation and Priority-Setting<sup>13</sup>

- A Policy Brief on Emergency Use Designation of COVID-19 Candidate Vaccines: Ethical Considerations for Current and Future COVID-19 Placebo-Controlled Vaccine Trials and Trial Unblinding<sup>14</sup>

- A Policy Brief on COVID-19 and Mandatory Vaccination: Ethical Considerations and Caveats<sup>15</sup>

All references and publications/further resources are available at the end of the report.

# 14 Regulatory science and convergence between national regulatory authorities

## Overall summary

Regulatory science plays a critical role in enabling and facilitating access to quality assured, safe and effective vaccines and treatments which provide a basis for good health.

**In 2021, WHO assessed and recommended nine additional COVID-19 vaccines for Emergency Use Listing (EUL) with approval of 25 drug substance and 41 drug product manufacturing sites and evaluation of over 200 post-EUL changes.**

WHO also shared 470 EUL dossiers and reports with 100 national regulatory authorities (NRAs) and assisted over 150 low- and middle-income country (LMIC) NRAs to issue nearly 3,300 regulatory authorizations of ten EUL COVID-19 vaccines.

Working closely with NRAs and regulatory networks, WHO has been helping to promote regulatory alignment and convergence in the COVID-19 pandemic response and providing support to NRAs to strengthen regulatory systems and increase regulatory capacities.

## Aim

A key aim of the regulatory science thematic area has been to develop and implement efficient and effective product assessment mechanisms to evaluate quality, safety and efficacy of urgently needed investigational diagnostics, therapeutics and vaccines for COVID-19 based on WHO clinical guidelines and Target Product Profiles (TPPs).

In parallel, the regulatory preparedness work aims to assist COVAX-supported countries to efficiently authorize COVID-19 vaccines and to provide technical assistance to collect adverse events, identify key safety signals and take appropriate actions in coordination with regulatory agencies around the world.

**Updating EUL and prequalification evaluation guidance is also critical for accelerated assessment of COVID-19-related products.**

## Key achievements by objective

**Regulatory science plays a critical role in enabling and facilitating access to quality assured, safe and effective vaccines and treatments which provide a basis for good health.**

**In 2021, together with regulatory experts around the world, WHO recommended nine additional COVID-19 vaccines for EUL, approved 25 drug substance and 41 drug product manufacturing sites and evaluated over 170 post-EUL changes.**

A total of 470 EUL dossiers and reports were shared with 100 NRAs and we assisted over 150 LMIC NRAs to issue nearly 3,300 regulatory authorizations of ten EUL COVID-19 vaccines.

## Objective

# 1

**Conduct risk-based assessment to ensure quality, safety, efficacy and user-suitability of COVID-19 diagnostics, treatments and vaccines, including investigational products that are under clinical trials**

### Key achievements

- Listed nine additional COVID-19 vaccines for EUL with 17 NRA of records for vaccines manufactured and/or authorized in Australia, Argentina, Belgium, Canada, China, France, Germany, India, Italy, Japan, Mexico, Rep Korea, South Africa, the Netherlands, Spain, Switzerland, Thailand, UK and the USA
- Approved 25 drug substance and 41 drug product vaccine manufacturing sites
- Evaluated over 200 post-EUL changes
- Prequalified nine 0.3ml-auto-disabled (AD) syringes and four other AD syringes
- Prequalified four FPPs, two APIs, two injectable dexamethasone
- Prequalified three formulations of tocilizumab
- Four applications for API of Molnupiravir under assessment
- Developed the first Expert Review Panel mechanism for biotherapeutics
- One hundred and sixty eight applications received for EUL of COVID-19 diagnostics with listing of 29 products and rejection of 53 products
- Conducted over 40 onsite inspections, including COVID-19 vaccines manufacturing sites in China and Russia despite the unprecedented travel restrictions and quarantine requirements in place

## Objective 2 Implement a reliance mechanism for resource-limited countries to efficiently and effectively authorize vaccines that are listed for EUL for procurement

### Key achievements

- Under confidentiality agreement, shared 470 EUL dossiers and reports with 100 national NRAs and provided technical support
- Assisted over 150 LMIC NRAs to issue nearly 3,300 regulatory authorizations of ten EUL COVID-19 vaccines
- Held weekly meeting with WHO regions, UNICEF and GAVI to provide technical support and to ensure timely regulatory authorization of donated COVID-19 vaccines
- Organized technical webinars for NRAs in each WHO region on each of the ten EUL COVID-19 vaccines
- Held EUL workshops on COVID-19 diagnostics in three regions

## Objective 3 Promote information sharing, reliance and regulatory alignment and convergence in the COVID-19 pandemic response and engage in dialogues with regulatory agencies around the world

### Key achievements

- Actively participated in weekly meetings organized by the International Coalition of Medicines Regulatory Authorities (ICMRA) and its subject specific-working groups.
- Contributed to the ICMRA workshops on:
  - [Vx safety collaboration](#) (13 Jan 2021)
  - [COVID-19 Virus Variants](#) (10 Feb 2021)
  - [COVID-19 Virus Variants](#) (24 Jun 2021)
  - [Enabling manufacturing capacity in the COVID-19 pandemic](#) (07-08 Jul 2021)
  - [Global public health emergencies and regulatory systems – moving forward](#) (01-02 Dec 2021)
  - [Omicron variants](#) (12 Jan 2022)
- Issued WHO-ICMRA joint statements on:
  - [Transparency and data integrity](#)
  - [How COVID-19 vaccines are regulated for safety and effectiveness](#)
- Took a lead in developing the ICMRA report on:
  - [Review of regulatory flexibilities/agilities as implemented by NRAs during pandemic](#)
  - [Deep dive report on the review of provisions and procedures for emergency authorization of medical products for COVID-19 among ICMRA members](#)
- Co-chaired monthly COVAX Regulatory Advisory Group (RAG) meetings and published technical brief on:
  - [Synopsis from Aug-Oct 2020 COVAX RAG meetings](#)
  - [Synopsis from Apr 2021 COVAX RAG meeting](#)
  - [Synopsis from May 2021 COVAX RAG meeting](#)
- Issued 38 regulatory updates on COVID-19

## Objective 4 Continue strengthening national and regional regulatory procedures for risk-based evaluations during public health emergencies and increase the number of national regulatory authorities to implement the reliance concept to expedite regulatory authorizations

### Key achievements

- Published WHO guidelines on Good Regulatory and Reliance Practices and implementation of quality management system
- Over 300 regulators trained on assessment of CTD-based dossiers, bioequivalence studies, regulatory preparedness during public health emergencies
- Conducted quality assessment training for 70 regulators from over 40 countries
- Published WHO guidelines on Good Regulatory and Reliance Practices and implementation of quality management system and a list of potential adverse events of special interest (AESIs), to monitor and ensure the safety of these new vaccines
- Published Emergency Interim Guideline on the detection and management of thrombosis with thrombocytopenia syndrome (TTS) associated with the adenovirus vector COVID-19 vaccines
- Though subcommittee of the WHO Global Advisory Committee on Vaccine Safety, adverse events were closely monitored and relevant advice was issued

### Assisted 40 self-benchmarking and completed five formal benchmarking (GBT) of regulatory systems, with follow up of 11 NRAs on the implementation status of institutional development plans and provided technical support to over 15 NRAs

- Use of virtual platforms developed for benchmarking methodology
- Launched training of GBT assessors
- Assessed 24 substandard and falsified reports on COVID-19 vaccines
  - 15 falsified vaccines
  - 4 substandard vaccines
- Supported countries to implement national strategies and develop plans of action for pharmaceutical manufacturing:
  - 4 manufacturers in Ethiopia achieved national GMP certification
  - advanced GMP and CAPA implementation virtual training workshop (Mar 2020) in Ethiopia

### Issued four global medical products alerts

- Issued four global medical products alerts
  - 2 unauthorized vaccines
- Published a COVID-19 vaccines safety surveillance manual and training aids, together with relevant study protocols
- Conducted feasibility assessments and situational analyses for sustainable local production:
  - Ethiopia with feasibility assessments for local vaccine production and Virtual benchmarking of Kilinto Pharmaceutical Industrial Park



- Egypt for assessment of cGMP compliance readiness of a vaccine manufacturer and local production of COVID-19 Vxs
- Sri Lanka, etc: Holistic situational analyses for sustainable local production
- Successful execution of:
  - 1st World Local Production Forum ‘Enhancing access to medicines and other health technologies’ in Jun 2021
  - 2 cGMP training marathons, each with 12 topics (6 weeks in 2021, 13 weeks in 2020) and high participations from >60 country
  - Holistic training workshops on key enabling factors for successful LP, tailored for each region (EMRO)
  - Virtual training workshop on LP of Quality and Safe Essential IVDs, WHO PQ, EUL and ERPD processes (Feb 2021)
  - Virtual workshop on strengthening collaboration as one WHO in supporting Member States towards sustainable quality LP (Sep 2020)
- Conducted a joint UNICEF-UNFPA-WHO meeting with manufacturers and suppliers (Dec 2020)
- Global resources on local production and technology transfer:
  - Situational analysis tool and its e-version for sustainable local production of quality health products (refining and piloting)
  - Updated WHO guideline on technology transfer for pharmaceutical manufacturing
- Partnerships and collaborations in local production to improve access:
  - Joint WHO-UNCTAD webinars on ‘Pandemic Preparedness beyond COVID-19: Investing in vaccine production and supply in LMICs’ (Apr 2020, Mar 2021, Oct 2021)
- Co-organization WHO-CEPI Vaccine Manufacturing Workshop for WHO EMRO (Sep 2021)



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## Objective 5 Continue developing product evaluation guidance for variants

### Key achievements

- Published a points-to-consider guidance for evaluation of modified COVID-19 vaccines to ensure scientifically sound, ethically acceptable, efficient, prompt and reliable evaluation of modified versions of monovalent vaccines
- Provided technical input to the WHO ACT-A Ethics Advisory Group in developing policy brief on ‘COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: ethical considerations’

### Key benefits

The COVID-19 pandemic has created unprecedented demand on health care systems in all countries with an urgent need for access to quality assured health products.

Over 70% of countries have weak regulatory systems with inadequate capacity, especially to cope with pandemic.

**Thus, sharing of WHO EUL dossiers and reports with NRAs under confidentiality agreement and implementing reliance concept-facilitated timely regulatory decision-making without compromising the independent evaluation of quality, safety and efficacy of COVID-19 vaccines has been essential.**

In a rapidly changing environment, the COVID-19 pandemic has brought together informal groups of regulatory leaders, including WHO regulatory teams, to explore and provide strategic directions for enhanced collaboration to address common challenges.

These frequent open dialogues have not only resulted in considerable regulatory alignment and convergence in the COVID-19 pandemic response, but they have also created opportunities to reflect on lessons learned and explore more effective and efficient approaches.

The outputs and their associated references can be found at the end of the report.



# 15 WHO International Units: A common language in evaluation of the immune response to vaccines

## Overall summary

### Regulatory Science Vaccines R&D

International written standards and measurement standards have been developed, through global collaborative effort, to facilitate the development and regulatory convergence of COVID-19 vaccines, diagnostics and therapeutics.

WHO standards are referred to by the WHO Emergency Use Listing Procedure (EUL) for COVID-19 products.

Measurement standards help with assay validation and quality assessment and enable the comparison of results from different assays and vaccine clinical trials.

The use of the WHO International Standard (IS) of SARS-CoV-2 antisera is important for interpreting the results from vaccine clinical trials by providing the basis for the expression of the antibody titres in International Units (IUs).

In particular, this allows results from efficacy trials for different vaccine candidates to be defined with a single, common unitage (IU/mL), which in turn aids in establishing correlates of protection.

Following the establishment of WHO standards, continuous support has been provided to users, for example through organizing trainings and webinars on their implementation and utilization.

In addition, a WHO manual to create national and other secondary standards for antibodies against infectious agents focusing on SARS-CoV-2 is being developed to further assist with this.

In response to the rapid development of messenger RNA (mRNA) vaccines, a WHO document 'Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations' was developed in broad consultation with stakeholders worldwide.

This document provides guidance and establishes international specifications on the manufacture, quality control, nonclinical and clinical evaluation, of preventive mRNA vaccines against infectious disease for human use.

Although applicable to all mRNA vaccines, it has provided special considerations for COVID-19 mRNA vaccines.

## Aim

To provide international standards and relevant technical support to manufacturers and regulators, and to facilitate regulatory convergence in the evaluation of COVID-19 vaccines, diagnostics and therapeutics.

**International written standards and measurement standards have been developed, through global collaborative effort, to facilitate the development and regulatory convergence of COVID-19 vaccines, diagnostics and therapeutics.**

## Objective 1 Develop, standardize, and evaluate assays for SARS-CoV-2, its variants of concern, and confirming the continual applicability of the International Standard (IS)

### Key achievements

- 1st WHO International Standard and Reference Panel for the anti-SARS-CoV-2 antibody were established by the WHO Expert Committee on Biological Standardization (ECBS)
- 1st WHO International Standard for SARS-CoV-2 RNA was established by the WHO ECBS

### Contribution to our understanding of SARS-CoV2 transmission and control

- Facilitate and harmonize the evaluation of COVID-19 diagnostics, vaccines and therapeutics

The use of the WHO International Standard (IS) of SARS-CoV-2 antisera is important for interpreting the results from vaccine clinical trials by providing the basis for the expression of the antibody titres in International Units (IUs).

### Key benefits

WHO standards provide guidance and establish international specifications for manufacturers and regulators on the development, regulatory evaluation and approval of vaccines.

These efforts facilitate regulatory convergence and ensure the availability of safe and efficacious vaccines internationally and through the WHO prequalification programme.

- Additional pertinent guidance documents are available at: <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/vaccine-standardization/>

These include:

- Guidelines on nonclinical evaluation of vaccines
- Guidelines on nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines
- Guidelines on clinical evaluation of vaccines: regulatory expectations
- Human challenge trials for vaccine development: regulatory considerations

- WHO manual for the establishment of national and other secondary standards for antibodies against infectious agents focusing on SARS-CoV-2 (To be reviewed at WHO ECBS in April 2022) [https://www.who.int/health-topics/biologicals#tab=tab\\_1](https://www.who.int/health-topics/biologicals#tab=tab_1)
- WHO Guideline for the safe production and quality control of monoclonal antibodies and related products for use in humans are being developed (To be reviewed at WHO ECBS in April 2022) [https://www.who.int/health-topics/biologicals#tab=tab\\_1](https://www.who.int/health-topics/biologicals#tab=tab_1)

2. Measurement standards for SARS-CoV-2 to facilitate and harmonize the evaluation of COVID-19 diagnostics, vaccines and therapeutics, developed by WHO Collaborating Centre, the National Institute for Biological Standards and Control (NIBSC) in the UK, and established by WHO ECBS:

In addition, a WHO manual to create national and other secondary standards for antibodies against infectious agents focusing on SARS-CoV-2 is being developed to further assist with this.

### Key outputs

1. Relevant WHO technical documents for COVID-19 vaccines and other biologicals have been made available: <https://www.who.int/publications/m/item/relevant-who-tech-docs-for-covid-19-vaccines-and-other-biologicals-v2>. In particular, the following guidance documents are most pertinent to vaccines for SARS-CoV-2:

- Guidelines on the quality, safety and efficacy of plasmid DNA vaccines, ECBS 2020: <https://www.who.int/publications/m/item/plasmid-dna-vaccines-annex-2-trs-no-1028>
- Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations, ECBS 2021: <https://www.who.int/publications/m/item/evaluation-of-the-quality-safety-and-efficacy-of-messenger-rna-vaccines-for-the-prevention-of-infectious-diseases-regulatory-considerations>



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- 1st WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody (established and made available in Dec 2020 and distributed to the users worldwide in 2021 (Figure 2))
- 1st WHO International Standard for SARS-CoV-2 RNA (established and made available in Dec 2020)

- WHO Reference Panel for antibodies for SARS-CoV-2 Variants of Concern (ongoing with the aim for submission to the WHO ECBS in October 2022)
- 2nd WHO IS for anti-SARS-CoV-2 immunoglobulin (ongoing with the aim for submission to the WHO ECBS in October 2022)

To provide international standards and relevant technical support to manufacturers and regulators, and to facilitate regulatory convergence in the evaluation of COVID-19 vaccines, diagnostics and therapeutics.

- International standard for SARS-CoV-2 antigens to support the development, assessment and comparability of antigen-based rapid diagnostic tests (ongoing with the aim for submission to the WHO ECBS in October 2022)

3. Training activities and technical support have been provided on the standardization of immune assays and calibration using WHO ISs through webinars organized in collaboration with CEPI, COVAX Enabling Sciences SWAT, the Bill and Melinda Gates Foundation (BMGF), and other partners in January, March, May, August, October and November 2021.

These activities were attended by members of the vaccine industry, regulatory authorities, national control

laboratories, academia and other participants worldwide. One aspect of the implementation of the WHO IS into practice is illustrated by Figure 3.

4. In light of the rapid development of COVID-19 vaccines which utilize SARS-CoV-2 viral stocks for their development, as well as animal studies and human clinical trials, an investigation of the serial propagation of the virus in Vero cells was organized by NSB/HPS/MHP team.

This was to explore the potential impact of cell substrates on the genetic stability of the SARS-CoV-2 virus.

Studies conducted at Public Health England (PHE), NIBSC, University of Wisconsin-Madison and BEI Resources all concluded that when SARS-CoV-2 is

propagated in Vero E6 cells there is a risk that deletions may arise in critical virulence components of the virus, including the FCS, during the sequential passage of the virus for the production working stock.

Such deletions appear to result in the stock virus being less virulent in animal models (as measured by clinical observations and/or viral titration in mucosal secretions).

The results were published (Reference 3). They may have an impact on the interpretation of the data from both animal studies and clinical trials and may help to improve the quality and control of viral working stocks used in vaccine development, production and evaluation.



**Figure 2.** Distribution of the WHO International Standard for anti-SARS-CoV-2 immunoglobulin.

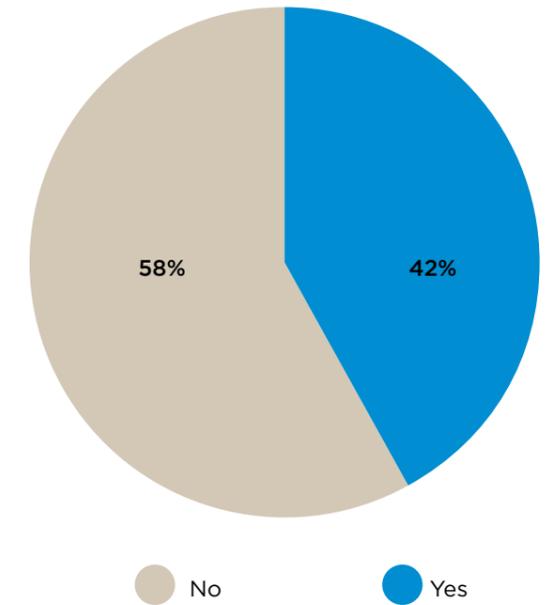
The map shows the geographical distribution of end users who have acquired the WHO International Standard (IS), NIBSC code 20/136 from December 2020 until July 2021.

The size of the circle corresponds to the relative number of units shipped per country. The location of the circle within a country is arbitrary and is not pinned to the end user.

Overall, more than 2,400 units were shipped to 581 individual customers in 46 different countries worldwide.

The graph has been produced using Microsoft Power BI.

**Figure 3.** Use of the WHO International Standard for Anti-SARS-COV-2 Immunoglobulin by 26 vaccine manufacturers



**Figure 3.** Use of First WHO International Standard (IS) for anti-SARS-CoV-2 immunoglobulin by the vaccine manufacturers

### 3. Pandemic preparedness is a constant, long-term investment

We cannot completely prevent outbreaks or pandemic, but we can be much better prepared and better coordinated in responding to possible future outbreaks and ensuring that they are detected and prevented at an early stage. This session provides insights on how the scientists in the different research areas are reflecting on the lessons learned from the COVID-19 pandemic and applying them to propose future priorities.

The underlying principle is that a comprehensive research and innovation effort should continue to be at the core of pandemic response and of any efforts to be better prepared.

By embedding research at the centre heart of the pandemic response, we pursue and achieve two goals: helping fight this pandemic while it is still underway; and protecting us in the future.

The Constitution of WHO defines as part of its functions a role to promote and conduct research in the field of health. It states that one of the functions of the World Health Assembly shall be to promote and conduct research in the field of health by the personnel of the Organization, by the establishment of its own institutions or by cooperation with official or non-official institutions of any Member with the consent of its Government. Moreover, the functions of the Executive Board include ... “to undertake studies and research the urgency of which has been drawn to the attention of the Board by any Member or by the Director-General”.

[https://www.who.int/governance/eb/who\\_constitution\\_en.pdf](https://www.who.int/governance/eb/who_constitution_en.pdf)

The global research network has been instrumental in delivering the COVID-19 pandemic response and platform trials have been very important.

This collaborating network is the powerhouse of the global research effort now and in the future.

Three examples demonstrate how collaborations are powering the global research and innovation response to COVID-19:

Figure 4 on the opposite page shows the core WHO R&D themes/teams and their satellite expert groups for COVID-19 intersecting to build global research innovation and knowledge.

Figure 5 on page 100 shows the extent of global collaboration: 5,000 researchers now registered from 171 countries to implement COVID-19 R&D; a network that can be activated for future outbreaks and pandemic.

Figure 6 also on page 100 shows Solidarity II – a global platform trial and global serologic study engaging 442 research representatives from 65 countries to better understand how SARS-CoV-2 affects different populations across the world.

There is emerging consensus for global platform trials – established as working during pandemic in COVID-19 -- to become a preferred future approach; their adaptive design and master protocol meaning results are rapid, robust and comparable across multiple sites.

**Figure 4. Co-ordinated research work in key R&D thematic areas is powering the global response to COVID-19**

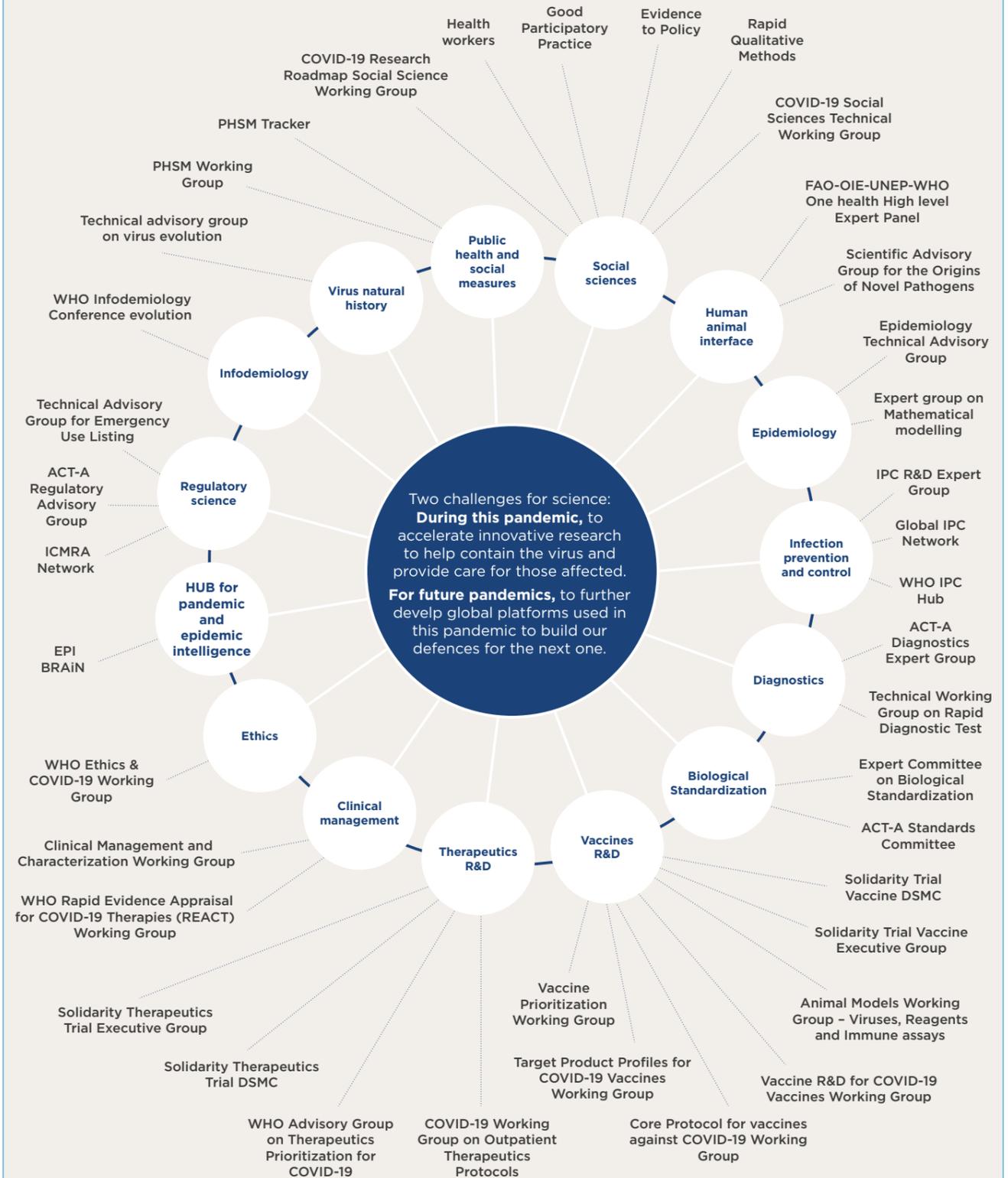


FIGURE 5

**Registered researchers across the globe working to combat COVID-19**

Over 5,000 researchers from 171 countries are now registered / collaborating to implement COVID-19 R&D.

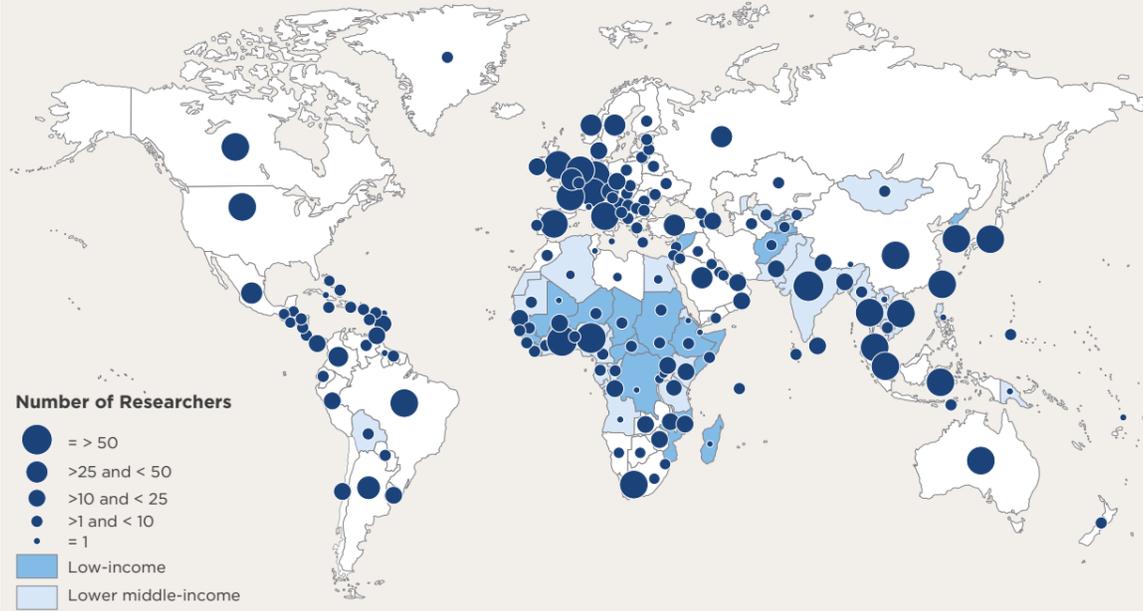


FIGURE 6

**Solidarity II - a global serologic study for COVID-19**

442 research representatives from 65 countries are co-ordinating globally to better understand how the virus affects different populations across the world



Solidarity II is a global collaboration led by the World Health Organization that promotes the implementation of serological surveys of SARS-CoV-2.

The collaboration will provide key data to help the world understand many key issues:

- how frequently SARS-CoV-2 infection occurs among different populations
- how many people have had mild or asymptomatic infection

- how many people have been infected but may not have been identified
- what proportion of the population may be immune from infection by SARS-CoV-2

This map shows there are over 442 research representatives from 65 countries taking part in this global data effort to better understand how the virus is affecting different populations across the world

**Building our research capacity and defences against old and new threats**

We must complement our research pandemic activities with longer-term investments in research capabilities globally that better prepare us for the emergence of any future virus. Now we risk focusing only on the current variants of concern. Instead, our long-term research investments should be selected to be effective now and in the future.

The greatest priority should be empowering existing research institutions and researchers in LMICs, and building research capacity where it is lower than in higher-income countries.

Below is a preliminary list of research questions that will be complemented and finalized with the deliberations during the forthcoming Global Research and Innovation Forum.



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## 1. SARS-CoV-2 at the human-animal interface

The three major research priorities going forward are:

1. Susceptibility studies in potential animal hosts
2. Surveillance of SARS-CoV-2 infections in susceptible animal species, including genetic sequencing
3. Virus evolution predictions in susceptible animal species

This research agenda is designed to lay the scientific foundation to:

- limit the risk of viral circulation in animals and transmission of SARS-CoV-2 and related variants from established animal reservoir to human
- reduce selection pressure associated with spillover and genomic variations of the circulating viruses. A better understanding of the dynamics of the COVID-19 outbreak together with improved biosafety and monitoring at the human-animal interface will be essential to reduce the risk of future spillover of zoonotic pathogens between humans and domestic and/or wild animals.

In addition, the partnership platform with OIE, FAO, UNEP, other partners in national institutes of animal and public health as well as academics is being strengthened and expanded. This will enable us to be better prepared for future events at the human-animal interface during the current pandemic and future ones, working together through a One Health approach.

## 2. Virus natural history, transmission, and diagnostics

Outbreaks of viruses, known and unknown, are a fact of nature. Part of being prepared for the next pandemic is planning what steps we will take to assess its origins. There has been an increasing number of high threat pathogens emerging and re-emerging in recent years with, for example, SARS-CoV, MERS-CoV, Lassa, Marburg, Ebola, Nipah, avian influenza, the latest being SARS-CoV-2.

1. There is now a need for robust surveillance and early actions for rapid detection and mitigation efforts.
2. There is also a need for robust and systematic processes to establish the study around the emergence of these pathogens and routes of transmission from their natural reservoirs to humans.

This is essential for putting in place risk reduction measures, targeting surveillance and designing control measures for outbreak response.

It is why WHO has formed the Scientific Advisory Group for the Origins of Novel Pathogens (SAGO). This committee will provide a robust framework outlining the range of studies that are needed in animals, humans, the environment, and biosafety and biosecurity. [https://www.who.int/groups/scientific-advisory-group-on-the-origins-of-novel-pathogens-\(sago\)](https://www.who.int/groups/scientific-advisory-group-on-the-origins-of-novel-pathogens-(sago))

#### 4. Epidemiology of COVID-19, focusing on past and current trends, drivers of transmission and severity, and epidemiological research gaps

Globally we need a system to promptly detect new SARS-CoV-2 variants and other emerging pathogens. We have several data collection systems and analytic initiatives that could be more efficient if they contribute to global coordinated efforts to answer key questions.

The following research activities have been identified:

1. Research into the most effective surveillance strategies, in various contexts, to monitor burden and hospitalizations, detect early trends and detect and monitor new variants
2. Continued use of serological studies in the context of new variants and vaccination – to better understand transmission dynamics, waning of immunity, and use of serotyping
3. Scenario planning and forecasting for the short- and long-term, including the role of waning immunity, seasonality, and prior infection/ vaccination in outlining future actions
4. Addressing unknown factors of emerging SARS-CoV-2 variants and lessons learned from epidemiology and PHSMs in how to tackle the next variant.

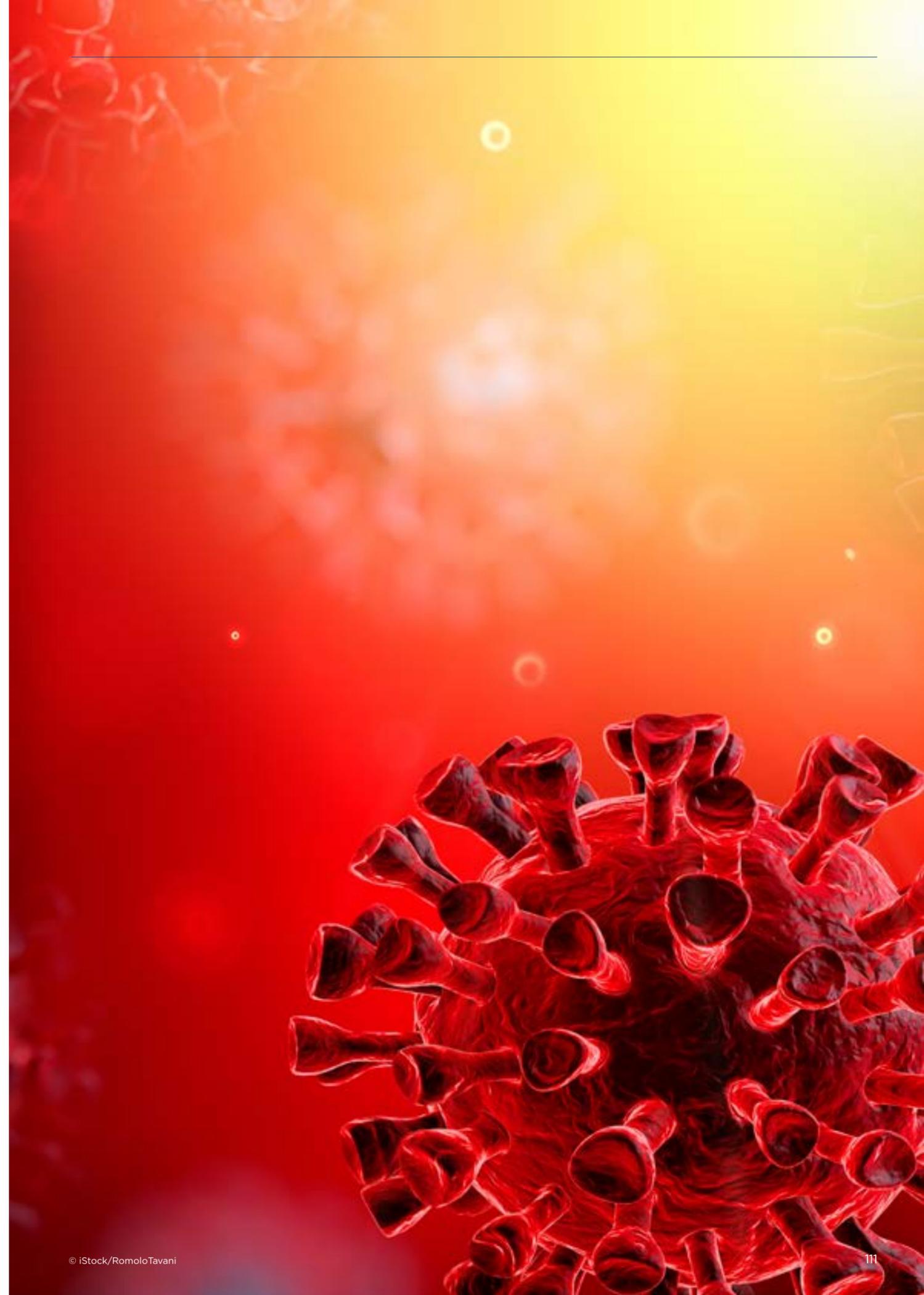
#### 5. Outbreaks should be detected and prevented at an early stage: A hub for Pandemic and Epidemic Intelligence

Researchers plan to use artificial intelligence to identify possible pandemics at an early stage. The mission of the WHO Hub is to build a system of collaborative intelligence enabling better decisions to avert and manage pandemic and epidemic risks.

The WHO Hub will foster collaborations across the world to use the best technology and data to detect and understand risks about future epidemics and pandemics. The WHO Hub will work to:

1. enhance access and linkage across multiple data sources necessary to generate signals and insights on disease emergence, risks, evolution, and impact
2. develop state-of-the-art tools to process, analyse and model data for prediction, detection, assessment and response
3. connect and catalyse institutions and existing networks developing disease outbreak solutions for the present and future; and
4. provide WHO, our Member States, and partners with collaborative tools to underpin better and faster decisions on how to address outbreak signals and events.

All aspects of pandemic and epidemic intelligence will be developed and adapted continuously through the hub's collaborative intelligence approach, including technical, governance, ethical and other dimensions.







## 6. Research on public health and social measures and their impact

The scale and duration of the implementation of public health and social measures (PHSMs) has been unprecedented for the COVID-19 pandemic to reduce the risk of spread of COVID-19 and the impact of the disease globally, including in low capacity and humanitarian settings with some adaptation for use.

Given the significant impact of PHSMs at individual, social and economic levels, evidence-based decision-making is critical to ensure that the benefit/burden ratio of these measures is well understood.

The following research themes have been identified:

1. Mapping existing research to identify knowledge gaps
2. Measuring the direct effectiveness and impact of PHSMs on transmission, morbidity and mortality
3. Assessing the impact of PHSMs on health, social and economic outcomes
4. Building preparedness for future health emergencies: resilience and response capacity
5. Promoting uptake of and adherence to PHSMs
6. Methodological research to advance implementation and evaluation of PHSMs

## 7. Infodemiology: Progressing on the public health research agenda for managing infodemics

Developing infodemiology and translating practice into the field will be key to limiting the harms that the infodemic accompanying the COVID-19 pandemic continues to perpetuate. Evidence generated today can inform management of infodemics that will accompany future emergencies, particularly related to building and maintaining trust in health systems and emergency response to support adherence to PHSMs and uptake of treatments, diagnostics and vaccines.

The following research priorities have been outlined:

1. Measuring and monitoring the impact of infodemics during health emergencies
2. Detecting and understanding the spread and impact of infodemics
3. Responding and deploying interventions that protect against the infodemic and mitigate its harmful effects
4. Evaluating infodemic interventions and strengthening resilience of individuals and communities to infodemics
5. Promoting the development, adaptation and application of tools for managing infodemics

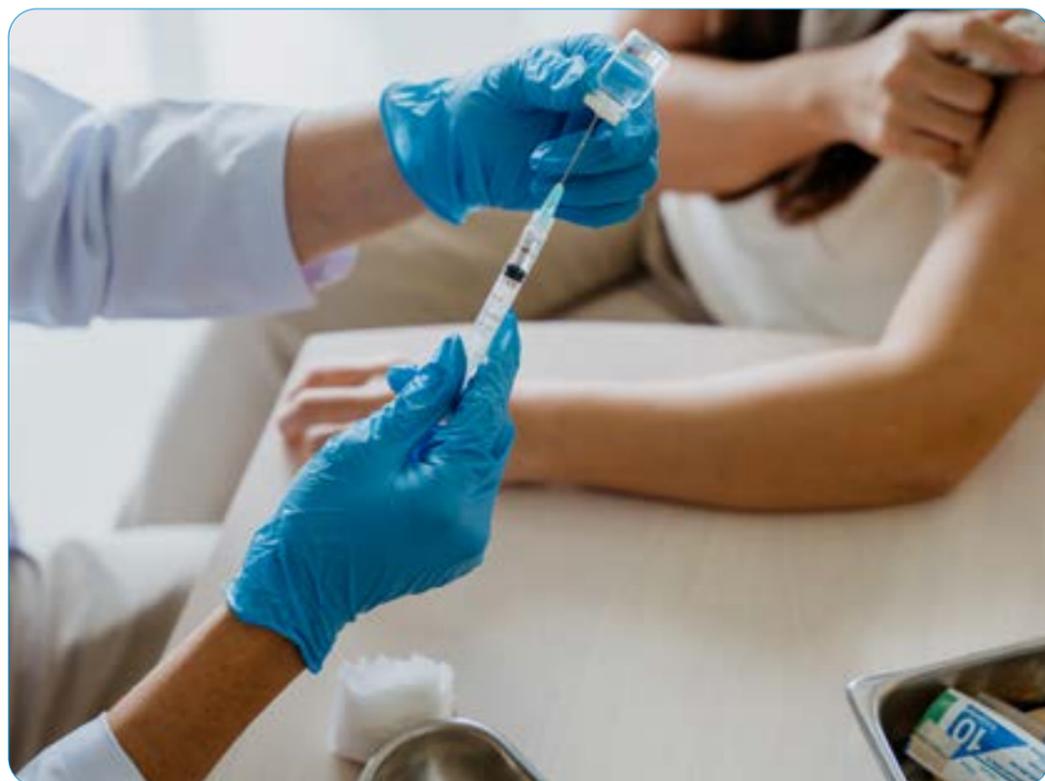
## 8. Vaccines: Research and development priorities

Additional vaccines are urgently needed. Many current approaches are highly promising and feasible; however, the speed at which they are further developed will depend on resource availability. Novel platforms may also require support for significant manufacturing development.

Selected priority research topics include:

1. A framework that could be used for variant-specific modifications of current vaccines, new variant-specific vaccines, or pan-sarbecovirus vaccines is thus needed
2. Increased standardization of assays and readouts: more information about mechanisms of protection (e.g. CMI, non-neutralizing responses, mucosal immunity especially against severe disease; larger sample size studies; animal studies
3. Enhanced sharing of reagents, particularly the need for convalescent Omicron and VOC serum

4. Improved understanding about the source of VOCs, in order to be better prepared for future variants
5. Assessment of Omicron-specific responses to more vaccines including variant-specific vaccines
6. Generation of data that permits the connection of laboratory results on variants and immune evasion to clinical outcomes
7. Additional epidemiological data regarding vaccine effectiveness against Omicron and other VOCs
8. Additional evidence on the severity of Omicron disease (and other VOCs) in different groups (vaccinated, not vaccinated, previously infected, hybrid immunity)
9. Improved understanding on the spread and transmissibility of Omicron
10. Future research that should support research on a range of sarbecoviruses that may protect against emerging variants and other coronaviruses



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## 9. Advancing the COVID-19 clinical care pathway: Outbreak research response centred around the patient

The global clinical characterization and management working group has brought together clinician researchers who are actively engaged in the care of patients with COVID-19 around the world. Its strength lies in its ability to provide a forum for clinicians, clinical researchers, and policy-makers to respond to the rapidly changing profile of the pandemic, and to build robust international collaborations.

There is a valuable role for such a forum in the ongoing pandemic, in preparing for future pandemic needs, and in using the knowledge gained and partnerships formed over the past two years to accelerate knowledge generation and dissemination within the global health care system. This points inexorably to a future where the generation of new knowledge through research is a core health care right, and where that research is integrated and championed by the health care system.

The core research priority themes have been identified as follows:

1. Conducting rigorous research, as the most powerful tool the health care system has to improve care, through large-scale collaboration as the most efficient means of using that tool, and through the use of new research models such as platform trials
2. Shaping a research agenda through patient leadership, promoting and providing research education, particularly in LMICs and the global south, regions currently under-represented in knowledge generation

3. Recognizing the importance of a global forum for clinician-scientists to share thoughts and perspectives on addressing common clinical challenges, and a role for the WHO in forging a dialogue amongst research groups to harmonize activities, minimize duplication of efforts, and expedite the consolidation and release of new knowledge

### 10a. Research and development for treatments of hospitalized patients

Global collaboration is needed to rapidly identify new and repurposed treatments, for hospitalized patients in this and future pandemics. The current pandemic has seen several initiatives of unprecedented levels of collaboration prove invaluable in generating evidence on hospital-based treatments through the conduct of large-scale and robust clinical trials, as flexible and adaptive platforms supporting therapeutic candidates for clinical evaluation in hospitalized patients.

Research priorities include the following:

1. Accelerating the identification of promising compounds, repurposed and new, for evaluation in the treatment of hospitalized patients, through sustained collaborations involving the public and private sectors
2. Promoting the rapid generation of large scale randomized evidence on promising therapeutic candidates, through broad collaborations and with equity and accessibility as guiding principles

## 10b. Critical needs for outpatients and for the design of outpatient therapeutic trials

The availability of effective outpatient treatment is essential to control this and future pandemics, and outpatient clinical trials with the clinical goals of limiting progression, limiting hospitalization and improving symptoms have emerged as essential for many communities in this pandemic.

The following priority research activities have been proposed:

1. Consolidating the experience and knowledge gained from the conduct of outpatient treatment platform trials and how to better generate evidence to guide treatment in a pandemic; including but not limited to the choice of outcomes measures and endpoints, design and analysis, dynamics, sample size and number of events, reproducibility and robustness of results, implementation challenges and mitigating factors
2. Promoting the development and sustainability of research centres around the world to conduct outpatient trials as an integral part of the health care system, as part of regional and global collaborations across the clinical development spectrum

## 11. Moving from rhetoric to reality: Placing communities at the centre of health emergency readiness and response

The social science in outbreak response thematic area will continue to advocate for integration and inclusion of evidence from a wide range of social sciences to strengthen strategic preparedness and response to COVID-19. Going forward, a key focus will be on evidence for localized solutions and to underpin systems and structures for resilient communities.

This knowledge is critical for refining governance systems, informing resource allocations, and shaping RCCE approaches. Efforts to build networks and infrastructure to systematically collect and manage data are ongoing.

This knowledge must be contextualized, produced in an equitable way and integrated across policy-making platforms, so that no community is left behind.

To prepare for future public health emergency events, key lessons from the COVID-19 pandemic need to be incorporated across the health emergency cycle.

Priorities for action related to research, research infrastructure (such as global platforms) and policy in the following areas include:

1. Learn from COVID-19 to be ready for future shocks: Key lessons from the COVID-19 pandemic, including related to its impacts and secondary impacts to inform planning for community readiness and resilience for future health shocks. This includes driving evidence to advance community-centred approaches across the health emergency cycle, for example, to disease surveillance, and building the case for sustained investment in social sciences evidence.

2. Build fit-for-purpose structures for social research to inform action in a future public emergency: Invest in systems and structures for rapid evidence production, including mechanisms for localized research agenda setting, rapid funding mechanisms linked with pre-positioned, partially approved research protocols; building and strengthening networks and capacity-building of local and national social scientists and best practice approaches for integrated, robust, rapid social science research, including innovations related to data collection, analysis and dissemination; sensitizing emergency response and policy leaders to the benefits and methods of including social science into readiness and response.

3. Promote systematic, institutional inclusion of social evidence for readiness and response: Promote mechanisms and structures for intersectoral dialogue (private sector, government, NGOs, etc.) and transdisciplinary initiatives to address the complexity of problems experienced by marginalized groups; and the need for adaptive responses. Systematic inclusion and embedding of social scientists in national policy and/or advisory groups and government response teams.



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## 12. IPC research during the pandemic: Pointing to an opportunity for saving lives and money

Significant progress has been made in critical areas of IPC highlighted during the pandemic. However, several questions remain open. The following research priorities were identified.

### Regarding the effectiveness of PHSMs and IPC strategies

1. Understanding infection (and reinfection) of HCWs: epidemiology and risk factors, case definitions and surveillance methods
2. Continually assessing new strains, their impact and consequential need to re-evaluate strategies related to epi/surveillance in HCF settings
3. Understanding the impact of vaccination on HCW behaviour/compliance that may impact the dynamics of infection transmission, including the impact of mandatory vaccination, and the impact of vaccination on required PPE and IPC measures (de-escalation)
4. Understanding the impact of the pandemic on antimicrobial resistance and hospital-acquired infections (HAIs), also in the context of a protracted emergency; impact on device-associated infections, risk of HAIs due to resistant pathogens; assessing the impact on antibiotic use and access; and understanding emerging and re-emerging pathogens associated with surges in disease cases

### Regarding PPEs

1. Generating high-quality evidence on the comparative effectiveness and safety of medical masks and respirators, in the context of prolonged use, repeated use and in combination with other PPE. Role of fit testing in respirator effectiveness and the need for novel technologies

2. Comparing the effectiveness of different decontamination methods of medical masks, respirators and other PPE; developing standardized protocols for implementation of decontamination methods and antimicrobial treatments
3. Defining standards for the manufacturing, mass production, optimal use, performance assessment and decontamination of community masks (also known as non-medical masks), as well as associated public communication strategies
4. Assessing human factors affecting the effective and safe use of PPE; investigating if PPE use affects compliance with other IPC measures
5. Investigating benefits, costs and risks related to the use of PPE, medical and community masks in persons with specific needs (such as children, elderly people; people with hearing, cognitive, or respiratory impairment; people with autistic spectrum disorders, people with mental health conditions)
6. Improving international standards, design processes of PPE, medical and community masks, taking into consideration physical differences, including gender and/or ethnicity
7. Optimizing the life cycle of PPE, medical and community masks: logistics, management, surveillance, and waste management, minimizing the impact on environment, including through innovative solutions and decontamination
8. Defining exit strategy for PPE use in the context of the epidemic: when can PPE measures be relaxed?

### In relation to the role of the environment in transmission

1. Understanding further the presence of viable SARS-CoV-2 in different WASH environments; the role of fomites (through PPE, contaminated hands) in infection transmission in health care and community settings, and related

- mitigation measures, including the cost-effectiveness of novel approaches and technologies for environmental decontamination
- 2. Documenting the role of contaminated water and sanitation in transmission
- 3. Evaluating the utility of wastewater surveillance in the evaluation and implementation of PHSMs in community settings, and for detection of unsuspected cases in health care settings
- 4. Understanding modes of transmission in different settings, including the role of ventilation, humidity, temperature and pressure, the role of contaminated fomites and whether the virus can infect through water and food in poor hygiene environments

### 13. Ethics and research

The WHO Ethics and COVID-19 Working Group was recently merged with the WHO ACTA Ethics and Governance Working Group. The newly constituted WHO COVID-19 Ethics and Governance Working Group is currently drafting a specific workplan, based on WHO priorities that will be identified and updated in ongoing road mapping. The working group will continue to integrate ethics into R&D and public health decision-making and to translate guidance into practice to better prepare for future public health emergencies.

Its specific objectives include:

- Develop WHO guidance on ethics and governance matters and related tools for COVID-19, including on research, public health measures, and equitable allocation of COVID-19-related resources
- Discuss and advise on ethical and governance aspects of preparedness for subsequent waves and other public health emergencies

- Facilitate the implementation of the ethical framework developed for the ACT-Accelerator
- Support WHO and Member States in responding to ethical and governance issues as they arise in the ACT-Accelerator

Specific priority research areas include but are not limited to:

1. ethics review, prioritization, and ethical oversight of COVID-19 research R&D governance, funding, and policy-making for global health justice and equitable access in future public health emergencies
2. monitored emergency use of unregistered and investigational interventions (MEURI), emergency use of unproven interventions outside research, expanded access ('compassionate use'), and off-label use
3. ethics of public health response to COVID-19 and future public health emergencies, including ethics of vaccination mandates, vaccination certification, and adjusting PHSMs in light of increasing rates of vaccination
4. ethics of digitally mediated outbreak countermeasures
5. ethics of transitioning out of the acute phase of the pandemic and of the implications of post-COVID-19 conditions (i.e. 'long COVID')
6. evaluating whether and how ethics guidance was used in the development of COVID-19 pandemic policies by subnational and national governments, regional and global organizations, non-profits, etc. to provide an empirical basis for improving the practical contribution that ethics can make going forward.
7. outreach, dissemination, and knowledge translation of research findings by the Epidemic Ethics network

8. focus areas identified at the WHO Pandemic Ethics & Policy Summit:<sup>7,8</sup> integrating ethics advice into policy-making and further societal sectors, systematic updating of existent ethics and infectious disease guidance documents in light of the pandemic, and addressing standards of quality and rigour of ethics guidance documents

The new expert group will further intensify its linkages with other relevant WHO working groups as well as external partners, particularly those operating within the R&D Blueprint workstreams.

The working group is continuously revisiting its roadmap. This includes updating its guidance in the light of new developments. For example, the group is currently finalizing an update of the WHO Policy Brief on COVID-19 and mandatory vaccination.<sup>15</sup> The update reflects new evidence and changed circumstances since the first version of the document was published.

### 14. Regulatory science convergence in response to a global public health emergency

Regulatory science plays a critical role in enabling and facilitating access to quality assured, safe and effective vaccines and treatments which provide a basis for good health. The COVID-19 pandemic has confronted the robustness of regulatory

systems and revealed the exacerbated challenges from having weak regulatory systems and inadequate regulatory capacities around the world.

On the other hand, the COVID-19 pandemic has brought together NRAs, research communities and other stakeholders worldwide to collaborate and focus on regulatory alignment and convergence in the COVID-19 pandemic response.

1. WHO, together with NRAs and regulatory networks, will continue to collaborate with countries to strengthen regulatory systems in particular in LMICs so that they are fit for purpose and agile. This is essential to facilitate access to medicines and vaccines for a world where everyone has access to quality assured medicines, vaccines and other essential health products.
2. WHO will continue to closely collaborate with the International Coalition of Medicines Regulatory Authorities (ICMRA). This is acting as a forum to support strategic coordination and international cooperation among global medicine regulatory authorities.
3. As part of ACT-A efforts and recognized as one of the critical enablers for further accelerating equitable access efforts, WHO will continue to support accelerated regulatory processes.

## 15. WHO International Units: A common language in evaluation of the immune response to vaccines for pandemics

The development, establishment and use of international measurement standards is essential for communicating information on the clinical performance of vaccines and involves elaborate collaborative studies in many laboratories around the world. The following research priorities have been identified:

1. Research capacity in WHO Collaborating Centres and other Institutions that collaborate with WHO to be expanded
2. A framework for the rapid response and collection of source bulk materials needs to be established
3. Tools for education on the calibration of secondary reference standards for serological assays should be developed and made available to regulators, vaccine developers, and contract laboratories involved in clinical trials as well as for other users of WHO standards
4. Training centres for serological assays with a mandatory use of WHO International Standards (ISs) to be established and become operational

## 16. Working to increase access to, and facilitate the development of, COVID life-saving medicines and vaccines in the LMICs

WHO and partners established the mRNA technology transfer hub in South Africa to boost vaccine production on the continent. And more than 100 Member States co-sponsored a World Health Assembly resolution on strengthening

local production. The first six countries that will receive the technology needed to produce mRNA vaccines on the African continent have been identified. Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia all applied and have been selected as recipients.

<https://www.who.int/news/item/18-02-2022-who-announces-first-technology-recipients-of-mrna-vaccine-hub-with-strong-support-from-african-and-european-partners>

1. To ensure that all countries build the necessary capacity to produce their own vaccines and other health technologies, WHO has been working to establish a biomanufacturing workforce training hub that will train people from all interested countries in scientific and clinical research and production capacity. The training hub will be announced in the coming weeks.
2. In addition, WHO's current regulatory strengthening activities in LMICs will expand through a global benchmarking tool that assesses countries' ability to ensure the quality, safety and efficacy of health products and provides training where improvements are needed to build regulatory authorities that are agile and fit for purpose for the future.
3. The WHO mRNA technology transfer hub is part of a larger effort aimed at empowering LMICs to produce their own vaccines, medicines and diagnostics to address health emergencies and reach UHC. The initial effort is centred on mRNA technologies and biologicals, which are important for vaccine manufacturing and can also be used for other products, such as insulin to treat diabetes, cancer medicines and, potentially, vaccines for other priority diseases such as malaria, tuberculosis and HIV. The ultimate goal is to extend capacity-building for national and regional production to all health technologies.

The COVID-19 Technology Access Pool (C-TAP) and the Medicines Patent Pool finalized its first licensing agreement for a COVID-19 serological antibody test. <https://www.who.int/initiatives/covid-19-technology-access-pool>

1. C-TAP will continue to provide platform for developers of COVID-19 therapeutics, diagnostics, vaccines and other health products to voluntarily share their intellectual property, knowledge, and data, with multiple quality-assured manufacturers.
2. C-TAP will continue to work through its implementing partners, the Medicines Patent Pool, Open COVID Pledge, UN Technology Bank and Unitaid to facilitate timely, equitable and affordable access to COVID-19 health technologies.
3. Developers of COVID-19 health technologies and holders of related knowledge, intellectual property and/or data are invited to voluntarily share with C-TAP by joining the Solidarity Call to Action.

## 17. Health system resilience during the pandemic: Priority research areas for preparedness

COVID-19 has had a wide-ranging impact on all areas of society, leading to setbacks in health gains and efforts to achieve universal health coverage (UHC). The diversion of health system resources to address COVID-19 care led to a protracted disruption of essential health services.

WHO's position paper on building health systems' resilience towards UHC and health security during COVID-19 and beyond underlines the urgent need for renewed and heightened national and global commitment to make countries better prepared and health systems resilient against all forms of public health threats for sustained progress towards both UHC and health security. <https://www.who.int/news/item/19-10-2021-who-s-7-policy-recommendations-on-building-resilient-health-systems>

This position paper emphasizes the need to create and promote enabling environments for research, innovation and learning, this includes:

1. enabling regulatory environments
2. maintaining and adapting innovative models implemented during the pandemic encompassing infodemics
3. providing regulatory support to facilitate intercountry and intra-country information management, data-sharing and coordination
4. promoting research, innovation and learning in all-hazards emergency risk management and health system resilience

It is a priority to support a radical reorientation of health systems towards primary health care, as the foundation of UHC. That means restoring, expanding, and sustaining access to essential health services, especially for health promotion and disease prevention, and reducing out-of-pocket spending.

# 4. Publications and further resources

## Key WHO research related documents and guidance

### 1. SARS-CoV-2 at the human-animal interface

1. Reducing public health risks associated with the sale of live wild animals of mammalian species in traditional food markets; Interim guidance, 12 April 2021. <https://www.who.int/publications/i/item/WHO-2019-nCoV-Food-safety-traditional-markets-2021.1>
2. SARS-CoV-2 in animals used for fur farming; GLEWS+ Risk assessment, 20 January 2021. <https://www.who.int/publications/i/item/WHO-2019-nCoV-fur-farming-risk-assessment-2021.1>
3. COVID-19 and Food Safety: Guidance for competent authorities responsible for national food safety control systems Interim guidance 22 April 2020. [https://www.who.int/publications/i/item/WHO-2019-nCoV-Food\\_Safety\\_authorities-2020.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-Food_Safety_authorities-2020.1)
4. COVID-19 and food safety: guidance for food businesses Interim guidance 7 April 2020. <https://www.who.int/publications/i/item/covid-19-and-food-safety-guidance-for-food-businesses>
5. WHO recommendations to reduce risk of transmission of emerging pathogens from animals to humans in live animal markets or animal product markets 26 March 2020. <https://www.who.int/publications/i/item/10665332217>

### 2. Virus natural history, transmission and diagnostics

- <https://www.who.int/publications/i/item/9789240018440>
- <https://apps.who.int/iris/handle/10665/338483>
- <https://apps.who.int/iris/handle/10665/341241?locale-attribute=fr>
- <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>
- [https://www.who.int/news/item/26-11-2021-classification-of-omicron-\(b.1.1.529\)-sars-cov-2-variant-of-concern](https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern)
- <https://www.who.int/news/item/22-02-2022-statement-on-omicron-sublineage-ba.2>

### 4. Epidemiology of COVID-19 focusing on past and current trends, drivers of transmission and severity, and epidemiological research gaps

- WHO website
- COVID-19 epidemiological dashboard <https://covid19.who.int/>
  - <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/early-investigations>
- Scientific publications
- <https://pubmed.ncbi.nlm.nih.gov/34173715/>
  - <https://pubmed.ncbi.nlm.nih.gov/34611986/>
  - <https://pubmed.ncbi.nlm.nih.gov/34142653/>
  - <https://onlinelibrary.wiley.com/doi/full/10.1111/irv.12915>
  - <https://www.medrxiv.org/content/10.1101/2021.12.14.21267791v2>
  - <https://www.medrxiv.org/content/10.1101/2022.02.14.22270934v1>
  - <https://www.medrxiv.org/content/10.1101/2021.12.02.21266897v1>
  - <https://onlinelibrary.wiley.com/doi/full/10.1111/irv.12915>

### 6. Research on public health and social measures and their impact

- Meeting report of the global technical consultation on measuring the effectiveness and impact of PHSM during health emergencies (forthcoming, to be published on PHSM website)
- Background paper on the draft global research agenda for PHSM (published as annex in the meeting report)
- Enria et al. (2021). Strengthening the evidence base for decisions on public health and social measures. WHO Bulletin, 99(9) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8381089/>

### 7. Infodemiology

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- WHO public health research agenda for managing infodemics: <https://www.who.int/publications/i/item/9789240019508>

- WHO 3rd infodemic management conference: whole-of-society challenges and approaches to respond to infodemics: <https://www.who.int/publications/i/item/9789240034501>
- Meeting report of the 4th WHO infodemic management conference on advances in social listening, May 2021 (forthcoming, to be published on infodemic health topic website)
- Meeting report of the 5th WHO infodemic management conference on measurement of the burden of infodemics, November 2021 (forthcoming, to be published on infodemic health topic website)
- WHO competency framework: Building a response workforce to manage infodemics: <https://www.who.int/publications/i/item/9789240035287>

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2. Purnat T, Vacca P, Czerniak C, Ball S, Burzo S, Zecchin T, Wright A, Bezbaruah S, Tanggol F, Dubé È, Labbé F, Dionne M, Lamichhane J, Mahajan A, Briand S, Nguyen T Infodemic Signal Detection During the COVID-19 Pandemic: Development of a Methodology for Identifying Potential Information Voids in Online Conversations JMIR Infodemiology 2021;1(1):e30971; URL: <https://infodemiology.jmir.org/2021/1/e30971>, DOI: 10.2196/30971
3. Calleja N, AbdAllah A, Abad N, Ahmed N, Albarracin D, Altieri E, Anoko J, Arcos R, Azlan A, Bayer J, Bechmann A, Bezbaruah S, Briand S, Brooks I, Bucci L, Burzo S, Czerniak C, De Domenico M, Dunn A, Ecker U, Espinosa L, Francois C, Gradon K, Gruzd A, Gülgün B, Haydarov R, Hurley C, Astuti S, Ishizumi A, Johnson N, Johnson Restrepo D, Kajimoto M, Koyuncu A, Kulkarni S, Lamichhane J, Lewis R, Mahajan A, Mandil A, McAweeney E, Messer M, Moy W, Ndumbi Ngamala P, Nguyen T, Nunn M, Omer S, Pagliari C, Patel P, Phuong L, Prybylski D, Rashidian A, Rempel E, Rubinelli S, Sacco P, Schneider A, Shu K, Smith M, Sufehmi H, Tangcharoensathien V, Terry R, Thacker N, Trewinnard T, Turner S, Tworek H, Uakkas S, Vraga E, Wardle

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5. Purnat TD, Wilson H, Nguyen T, Briand S. EARS - A WHO Platform for AI-Supported Real-Time Online Social Listening of COVID-19 Conversations. Stud Health Technol Inform. 2021 May 27;281:1009-1010. doi: 10.3233/SHTI210330. PMID: 34042825. <https://pubmed.ncbi.nlm.nih.gov/34042825/>; <https://ebooks.iospress.nl/volumearticle/57037>
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1. Health Security <https://www.liebertpub.com/toc/hs/19/1>
  2. Big data and Society <https://journals.sagepub.com/page/bds/collections/studyinginfodemicatscale>
  3. Pan American Journal of Public Health <https://www.paho.org/journal/en/special-issues/infodemiology>
  4. The International Journal of Intelligence, Security, and Public Affairs <https://www.tandfonline.com/doi/full/10.1080/23800992.2021.1956777?src=>

### 8. Vaccines: research and development priorities

WHO ad hoc consultation: COVID-19 New variants – Knowledge gaps and research priorities, <https://www.who.int/publications/m/item/covid-19-new-variants-knowledge-gaps-and-research> COVID-19 vaccines

Knowledge gaps and research priorities, <https://www.who.int/publications/m/item/covid-19-vaccines-knowledge-gaps-and-research-priorities---who-ad-hoc-consultation>

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

Consultation on the use of trained dogs for screening COVID-19 cases, <https://www.who.int/publications/m/item/consultation-on-the-use-of-trained-dogs-for-screening-covid-19-cases>

WHO Webinar meeting on Community-centred responses to health emergencies: progress, gaps and research priorities, <https://www.who.int/news-room/events/detail/2021/03/31/default-calendar/global-consultation-on-community-centred-responses>

COVID-19 Global Research & Innovation Forum, <https://www.who.int/news-room/events/detail/2021/05/13/default-calendar/covid-19-global-research-innovation-forum-meeting-announcement>

WHO Meeting on correlates of protection, <https://www.who.int/news-room/events/detail/2021/06/01/default-calendar/covid-19-vaccine-swho-meeting-on-correlates-of-protection>

Can booster doses contribute to control this pandemic: what research is needed?, <https://www.who.int/news-room/events/detail/2021/08/13/default-calendar/who-consultation-on-covid-19-vaccines-research-13-august-2021>

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Emerging evidence on additional doses of COVID-19 vaccines and their safety, <https://www.who.int/news-room/events/detail/2021/10/25/default-calendar/who-consultation-on-covid-19-vaccines-research-emerging-evidence-on-safety-and-the-need-for-additional-doses-of-covid-19-vaccines>

WHO COVID-19 vaccines research. How can vaccine research further contribute to achieve the control of the pandemic everywhere?, <https://www.who.int/news-room/events/detail/2021/12/06/default-calendar/who-consultation-on-covid-19-vaccines-research-how-can-vaccine-research-further-contribute-to-achieve-the-control-of-the-pandemic-everywhere>

WHO Global Consultation - What evidence do we have that omicron is evading immunity and what are the implications?, <https://www.who.int/news-room/events/detail/2021/12/15/default-calendar/who-global-consultation---what-evidence-do-we-have-that-omicron-is-evading-immunity-and-what-are-the-implications>

WHO consultation on COVID vaccines research: Why do we need a pan-sarbecovirus vaccine? <https://www.who.int/news-room/events/detail/2022/01/28/default-calendar/who-consultation-on-covid-vaccines-research-why-do-we-need-a-pan-sarbecovirus-vaccine>

What recent evidence do we have that omicron is evading immunity and what are the implications? <https://www.who.int/news-room/events/detail/2022/02/14/default-calendar/save-the-date---what-recent-evidence-do-we-have-that-omicron-is-evading-immunity-and-what-are-the-implications>

WHO Target Product Profiles for COVID-19 Vaccines - preferred characteristics of a COVID-19 vaccine- <https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines>

The COVID-NMA initiative: Living Mapping of Trials - a living mapping of all registered vaccine trials <https://covid-nma.com/vaccines/mapping/>

The COVID-NMA initiative: Living Synthesis of Published Trials - a living synthesis of vaccine trial results <https://covid-nma.com/vaccines/>

The COVID-19 candidate vaccine landscape and tracker - a living compilation on vaccine candidates in development <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

The landscape of observational study designs on the effectiveness of COVID-19 vaccination - a living compilation- <https://www.who.int/publications/m/item/draft-landscape-of-observational-study-designs-on-the-effectiveness-of-covid-19-vaccination>

Report of the WHO AG on human challenge studies <https://www.who.int/publications/m/item/report-of-the-who-ag-on-human-challenge-studies>

Assays & Animal Models - Outline of research priorities related to the Omicron variant <https://www.who.int/publications/m/item/assays-animal-models---outline-of-research-priorities-related-to-the-omicron-variant>

### Peer-reviewed articles

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Fleming TR, Krause PR, Nason M, Longini IM, Henao-Restrepo A-MM. COVID-19 vaccine trials: The use of active controls and non-inferiority studies. Clinical Trials. 2021;18(3):335-342. doi:10.1177/1740774520988244

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Krause PR, Fleming TR, Longini IM, et al. SARS-CoV2 Variants and Vaccines. N Engl J Med 2021; 385:179-186. DOI: 10.1056/NEJMs2105280.

Fleming TR, Krause PR, Nason M, Longini IM, Henao-Restrepo A-MM. COVID-19 vaccine tri-

als: The use of active controls and non-inferiority studies. Clinical Trials. 2021;18(3):335-342. doi:10.1177/1740774520988244

### 9. Advancing the COVID-19 clinical care pathway: outbreak research response centered around the patient

References are embedded in the text of the chapter.

#### 10a/ Research and development for treatments of hospitalized patients.

WHO Solidarity Trial Consortium (2021). Repurposed Antiviral Drugs for Covid-19 – Interim WHO Solidarity Trial Results. N Engl J Med 2021; 384:497-511. doi: 10.1056/NEJMoa2023184

WHO Solidarity PLUS Therapeutics Trial

WHO Advisory Group on Therapeutics Prioritization for COVID-19

#### 10b/ Critical needs for outpatients and for the design of outpatient therapeutic trials

Outpatient treatment platform trials

[ACTIV2](#)  
[ACTIV6](#)  
[AGILE](#)  
[ANTICOV](#)  
[COVERAGE](#)  
[OTAC](#)  
[PANORAMIC](#)  
[PRINCIPLE](#)  
[TOGETHER](#)

### 11. Moving from rhetoric to reality: Placing communities at the centre of health emergency readiness and response

<sup>1</sup>The Collective Service is a collaborative partnership between WHO, IFRC, UNICEF and supported by GOARN, that brings together a wide range of organizations engaged in policy, practice, and research for RCCE to ensure expert driven, collaborative, consistent and localized RCCE support reaches governments and partners involved in the national response to COVID-19 and beyond - <https://www.rcce-collective.net/>

<sup>2</sup> Integrated Outbreak Analytics (IOA) was developed during the 10th (2018-20) Ebola outbreak in the Democratic Republic of Congo (DRC). It is an approach that brings together multiple data types, disciplines, and sources to better understand and explain outbreak dynamics and their impacts on communities. It is focused on collaborative partnership across operational and academic actors in support of outbreak response and on rapid, operational analytics to support decision-making.

<sup>3</sup> COVID-19 Research Project Tracker by UKCDR & GloPID-R | UKCDR



<sup>4</sup> Hrynick TA, Ripoll et al COVID-19 response: mitigating negative impacts on other areas of health BMJ Global Health 2021; 6:e004110.

<sup>5</sup> Community-centred approaches to health emergencies: progress, gaps and research priorities – meeting report of an international consultation (October 2021).

<sup>6</sup> Milanese, van Kessel et al (under review) What is community resilience to public health emergencies? How can it be strengthened and measured? a rapid scoping review.

<sup>7</sup> English, Geduld et al (under review) Defining and identifying critical elements of and lessons learnt from addressing 'operational readiness' for public health emergency events, including COVID-19: a rapid scoping review.

<sup>8</sup> Solidarity Trial Vaccines (who.int)

<sup>9</sup> COVID-19 Research Roadmap Social Science working group (internal briefing) Public face covering as source control during the COVID-19 pandemic: key considerations from social science; May 2020.

<sup>10</sup> COVID-19 Research Roadmap Social Science working group (under review) Scoping document: considerations for providing care to COVID-19 individuals at home: May 2020.

<sup>11</sup> COVID-19 Research Roadmap Social Science working group (internal document) Rapid background brief: Social, behavioural and economic considerations of immunity passport policies – to inform ethics working group: May 2020.

<sup>12</sup> Dada, S., Battles, H., et al (2021) Learning from the past and present: social science implications for COVID-19 immunity-based documentation. Humanit Soc Sci Commun 8, 219. <https://doi.org/10.1057/s41599-021-00898-4>

<sup>13</sup> Voo TC., Reis AA., et al. (2021) Immunity certification for COVID-19: Ethical considerations Bull World Health Organ 2021;99:155–161 | doi: <http://dx.doi.org/10.2471/BLT.20.280701>

<sup>14</sup> Carter SE., Gobat N etc (2020) What questions we should be asking about COVID-19 in humanitarian settings: perspectives from the Social Sciences Analysis Cell in the Democratic Republic of the Congo BMJ Global Health, 5

<sup>15</sup> Carter, S. E., S. Ahuka-Mundeke, et al (2021) 'How to improve outbreak response: a case study of integrated outbreak analytics from Ebola in Eastern Democratic Republic of the Congo', BMJ Glob Health, 6.

<sup>16</sup> Bedson, J., L. A. Skrip, D. et al (2021). 'A review and agenda for integrated disease models including social and behavioural factors', Nat Hum Behav, 5: 834-46.

<sup>17</sup> Tam, W.J., Gobat, N., et al. (2021). Risk communication and community engagement (RCCE) during the migrant worker COVID-19 outbreak in Singapore. Science Communications Journal. December 2021. doi:10.1177/10755470211061513.

<sup>18</sup> Guide to Effective RCCE among large, closed communities” <https://www.rcce-collective.net/case-study/a-national-risk-communication-and-community-engagement-campaign-for-large-closed-communities-in-singapore/>

<sup>19</sup> For example, coaching and support to countries on social listening, including customised set up of FB CrowdTangle tool in 6 countries in the WHO European Region and 9 Facebook Brand lift studies.

<sup>20</sup> For example, direct support by WHO Regional Office for Europe to surveys in 18+ Member States and indirect support by the Regional Offices of WHO and UNICEF via the HealthBuddy+ tool.

<sup>21</sup> For example, WHO EURO conducted landscape analysis to understand impacts of COVID\_19 on Roma populations in North Macedonia

<sup>22</sup> Perceptions of Health workers regarding health facility infection prevention and control procedures for COVID-19: A Research Template (who.int)

<sup>23</sup> Guidance for Health Care Worker surveys in humanitarian contexts in LMICs <https://extranet.who.int/goarn/guidance-health-care-worker-hcw-surveys-humanitarian-contexts-lmics-0>

<sup>24</sup> Van Hout, Hutchinson et al (2022) The experience of European hospital-based health care workers on following infection prevention and control procedures and their wellbeing during the first wave of the COVID-19 pandemic PlosOne 17(2): e0245182. <https://doi.org/10.1371/journal.pone.0245182>

<sup>25</sup> Sharma, L., Thapa, A., Chand, H., Pant, S., & Neopane, A. (2020). Perception of doctors and nurses regarding prevention of COVID-19 infection at a Teaching Hospital, Nepal. Journal of Patan Academy of Health Sciences, 7(3), 13–21. <https://doi.org/10.3126/jpahs.v7i3.33820>

<sup>26</sup> Silverberg, Puchalski Ritchie, et al. (2021). 'COVID-19 infection prevention and control procedures and institutional trust: Perceptions of Canadian intensive care and emergency department nurses', Can J Anaesth, 68: 1165-75.

<sup>27</sup> COVID-19 Behavioural Indicators - Collective Service for Risk Communication and Community Engagement (RCCE) (rcce-collective.net)

<sup>28</sup> COVID-19 Behaviour Change Framework - Collective Service for Risk Communication and Community Engagement (RCCE) (rcce-collective.net)

<sup>29</sup> Data Source Tracker - Collective Service for Risk Communication and Community Engagement (RCCE) (rcce-collective.net)

<sup>30</sup> Betsch C, Wieler LH, Habersaat K, on behalf of the COSMO group. Monitoring behavioural insights related to COVID-19. Lancet 2020; published online April 2. [http://dx.doi.org/10.1016/S0140-6736\(20\)30729-7](http://dx.doi.org/10.1016/S0140-6736(20)30729-7)

<sup>31</sup> WHO Regional Office for Europe COVID-19 Behavioural Insights Survey Tool

<sup>32</sup> <https://www.afro.who.int/publications/social-and-behavioural-insights-covid-19-data-collection-tool-africa>

<sup>33</sup> Social and behavioural insights COVID-19 data collection tool for Africa - Case study: Pilot implementation in Nigeria and Zambia | WHO | Regional Office for Africa

<sup>34</sup> Giles Vernick, Yeoh et al (in development) Rapid Review of Rapid Qualitative Research Tools in Urgent Epidemic Settings, including COVID-19.

## 12 IPC research during the pandemic: pointing to an opportunity for saving lives and money

World Health Organization. "A coordinated global research roadmap: 2019 novel coronavirus." Geneva: World Health Organization (2020). Available at: <https://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1>

World Health Organization. "Infection Prevention and Control (IPC) Pillar Achievements, February 2020 – April 2021". Available at: [https://www.who.int/publications/m/item/who-covid-19-infection-prevention-and-control-\(ipc\)-pillar](https://www.who.int/publications/m/item/who-covid-19-infection-prevention-and-control-(ipc)-pillar)

This report is under revision and will provide full references for the studies mentioned above.

## 13. Ethics and research

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1. World Health Organization. (2021). Ethical Framework for WHO's work in the ACT-Accelerator (WHO-2019-nCoV-ACT-Accelerator-Ethical-framework-2021.1). <https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-ACT-Accelerator-Ethical-framework-2021.1>
2. World Health Organization. (2021). Digital Documentation of COVID-19 Certificates: Vaccination Status—Technical Specifications and Implementation Guidance (WHO/2019-nCoV/Digital\_certificates/vaccination/2021.1). [https://www.who.int/publications/i/item/WHO-2019-nCoV-Digital\\_certificates-vaccination-2021.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-Digital_certificates-vaccination-2021.1)

3. World Health Organization. (2021). Digital Documentation of COVID-19 Certificates: Test Result: Interim guidance. <https://www.who.int/publications/m/item/digital-documentation-of-covid-19-certificates-test-result>
4. World Health Organization. (2021). COVID-19 Immunization in Refugees and Migrants: Principles and Key Considerations (WHO/2019-nCoV/immunization/refugees\_and\_migrants/2021.1). <https://www.who.int/publications/i/item/covid-19-immunization-in-refugees-and-migrants-principles-and-key-considerations-interim-guidance-31-august-2021>
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12. World Health Organization. (2020). Ethical Considerations to Guide the Use of Digital Proximity Tracking Technologies for COVID-19 Contact Tracing (WHO/2019-nCoV/Ethics\_contact\_tracing\_apps/2020.1). [https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Ethics\\_contact\\_tracing\\_apps-2020.1](https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Ethics_contact_tracing_apps-2020.1)

13. World Health Organization. (2020). Ethics and COVID-19: Resource Allocation and Priority-Setting (WHO/RFH/20.2). <https://www.who.int/ethics/publications/ethics-covid-19-resource-allocation.pdf>
14. World Health Organization. (2020). Emergency Use Designation of COVID-19 Candidate Vaccines: Ethical Considerations for Current and Future COVID-19 Placebo-Controlled Vaccine Trials and Trial Unblinding (WHO/2019-nCoV/Policy\_Brief/EUD\_placebo-controlled\_vaccine\_trials/2020.1). [https://www.who.int/publications/i/item/WHO-2019-nCoV-Policy\\_Brief-EUD\\_placebo-controlled\\_vaccine\\_trials-2020.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-Policy_Brief-EUD_placebo-controlled_vaccine_trials-2020.1)
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17. WHO Ethics & COVID-19 Working Group. (2021). Achievements. WHO R&D Blueprint. [https://cdn.who.int/media/docs/default-source/documents/r-d-blueprint-meetings/09\\_ethics\\_full-achievements-reportpdf.pdf?sfvrsn=313fe4cc\\_5&download=true](https://cdn.who.int/media/docs/default-source/documents/r-d-blueprint-meetings/09_ethics_full-achievements-reportpdf.pdf?sfvrsn=313fe4cc_5&download=true) **Selected new peer reviewed articles since the previous Achievements report17 (May 2021):**
18. Aliyu, M. H., et al. (2021). The V-RAMP program: Building research administration and management capacity in Nigeria. *Journal of Global Health Reports*. <https://doi.org/10.29392/001c.24355>
19. Asghari, F., et al. (2021). Priority Setting of Ventilators in the COVID-19 Pandemic from the Public's Perspective. *AJOB Empirical Bioethics*, 12(3), 155-163. <https://doi.org/10.1080/23294515.2021.1907474>
20. Emanuel, E. J., et al. (2021). What are the obligations of pharmaceutical companies in a global health emergency? *The Lancet*, 398(10304), 1015-1020. [https://doi.org/10.1016/S0140-6736\(21\)01378-7](https://doi.org/10.1016/S0140-6736(21)01378-7)
21. Emanuel, E. J., et al. (2021) On the Ethics of Vaccine Nationalism: The Case for the Fair Priority for Residents Framework. *Ethics & International Affairs*, 35(4), 543-562. <https://doi.org/10.1017/S0892679421000514>
22. Ho, C., Craals, K. (2022). The International Pandemic Preparedness Treaty and an Emerging Digital Divide. *AsiaGlobal Online*. <https://www.asiaglobalonline.hku.hk/international-pandemic-preparedness-treaty-and-emerging-digital-divide>
23. Iliyasu, Z., et al. (2021). 'Why Should I Take the COVID-19 Vaccine after Recovering from the Disease?' A Mixed-methods Study of Correlates of COVID-19 Vaccine Acceptability among Health Workers in Northern Nigeria. *Pathogens and Global Health*, 1-9. <https://doi.org/10.1080/20477724.2021.2011674>
24. Iliyasu, Z., et al. (2021). Predictors of COVID-19 vaccine acceptability among patients living with HIV in northern Nigeria: A mixed methods study. *Current HIV Research*, 19. <https://doi.org/10.2174/1570162X19666211217093223>
25. Iliyasu, Z., et al. (2021). "They have produced a vaccine, but we doubt if COVID-19 exists": Correlates of COVID-19 vaccine acceptability among adults in Kano, Nigeria. *Human Vaccines & Immunotherapeutics*, 17(11), 4057-4064. <https://doi.org/10.1080/21645515.2021.1974796>

#### 14. Regulatory science and convergence between national regulatory authorities

- The Food and Drug Administration's Emergency Use Authorization: Lessons Learned from the Past to Guide the Future: Proceedings of a Workshop in Brief (2021) Workshop proceedings: [Download: The Food and Drug Administration's Emergency Use Authorization: Lessons Learned from the Past to Guide the Future: Proceedings of a Workshop in Brief | The National Academies Press \(nap.edu\)](https://www.nationalacademies.org/event/10-04-2021/the-food-and-drug-administrations-emergency-use-authorization-lessons-learned-from-the-past-to-guide-the-future-a-workshop) Workshop materials: <https://www.nationalacademies.org/event/10-04-2021/the-food-and-drug-administrations-emergency-use-authorization-lessons-learned-from-the-past-to-guide-the-future-a-workshop>.
- [Considerations in boosting COVID-19 vaccine immune responses.](https://www.who.int/publications/i/item/WHO-2019-nCoV-TTS-2021.1) Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, Cravioto A, Rees H, Higgins JPT, Boutron I, Pan H, Gruber MF, Arora N, Kazi F, Gaspar R, Swaminathan S, Ryan MJ, Henao-Restrepo AM. *Lancet*. 2021 Oct 9;398(10308):1377-1380. doi: 10.1016/S0140-6736(21)02046-8. Epub 2021 Sep 14. PMID: 34534516.

- [SARS-CoV-2 Variants and Vaccines.](https://www.who.int/publications/i/item/10665348966_9789240036963) Krause PR, Fleming TR, Longini IM, Peto R, Briand S, Heymann DL, Beral V, Snape MD, Rees H, Ropero AM, Balicer RD, Cramer JP, Muñoz-Fontela C, Gruber M, Gaspar R, Singh JA, Subbarao K, Van Kerkhove MD, Swaminathan S, Ryan MJ, Henao-Restrepo AM. *N Engl J Med*. 2021 Jul 8;385(2):179-186. doi: 10.1056/NEJMs2105280. Epub 2021 Jun 23. PMID: 34161052
- WHO Pharmacovigilance workshop on Unmasking safety signals in an 'Infodemic' [https://worldhealthorg-my.sharepoint.com/personal/lamprianous\\_who\\_int/\\_layouts/15/onedrive.aspx?id=%2Fpersonal%2Flamprianous%5Fwho%5Fint%2FDocuments%2FFPV%2DUnmasking%20safety%20signals%20in%20an%20infodemic](https://worldhealthorg-my.sharepoint.com/personal/lamprianous_who_int/_layouts/15/onedrive.aspx?id=%2Fpersonal%2Flamprianous%5Fwho%5Fint%2FDocuments%2FFPV%2DUnmasking%20safety%20signals%20in%20an%20infodemic)
- Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification, 2nd ed., 2019 update <https://www.who.int/publications/i/item/causality-assessment-aefi-user-manual-2019>
- Brief overview of anaphylaxis as an adverse event following immunization (AEFI) and practical guidance on its identification, case management and response in a primary care setting <https://www.who.int/publications/i/item/anaphylaxis-aefi-management-and-response>
- Protocol template to be used as template for observational study protocols for sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines. <https://www.who.int/publications/i/item/9789240029507>
- Protocol template to be used as template for observational study protocols for cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines. <https://www.who.int/publications/i/item/9789240027398>
- COVID-19 Vaccines: safety surveillance manual. Module on safety surveillance of COVID-19 vaccines in pregnant and breastfeeding women <https://www.who.int/publications/i/item/WHO-MHP-RPQ-PVG-2021.1>
- Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19) <https://www.who.int/publications/i/item/WHO-2019-nCoV-TTS-2021.1>
- Global vaccine safety blueprint 2.0 (GVSB2.0) 2021-2023 [https://www.who.int/publications/i/item/10665348966\\_9789240036963](https://www.who.int/publications/i/item/10665348966_9789240036963)
- COVID-19 vaccines: safety surveillance manual and training materials developed together with e-training materials and conducted webinars and trainings for countries and health care professions to collect and identify key safety signals and take appropriate actions in coordination with regulatory agencies around the world. Covid-19 vaccines: safety surveillance manual and training materials <https://www.who.int/publications/i/item/10665338400>
- The Global Advisory Committee on Vaccine Safety on COVID-19 vaccines reviewed concerned safety signals and provided its analytical statements. <https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/>
- Guidance on Good Reliance Practices finalized and encourage all national regulatory authorities to apply its concept to streamline approvals of urgently needed COVID-19 vaccines. <https://www.who.int/news/item/29-04-2021-who-publishes-new-guidance-to-promote-strong-efficient-and-sustainable-regulatory-systems>
- Technical support provided to regions and countries for efficient authorization of COVID-19 vaccines through reliance concept, follow-up safety assessments and mitigating risks from substandard and falsified products Sharing of WHO EUL assessment reports with NRAs under confidentiality agreement
- Surveillance, detection and protective actions strengthened to mitigate health impact from substandard and falsified COVID-19 related products in the market. [https://www.who.int/health-topics/substandard-and-falsified-medical-products#tab=tab\\_1](https://www.who.int/health-topics/substandard-and-falsified-medical-products#tab=tab_1)
- WHO Quality Management System Guidance Launch Webinar [https://who.zoom.us/webinar/register/WN\\_46rg5YqRQ36StnqPb7sAfA](https://who.zoom.us/webinar/register/WN_46rg5YqRQ36StnqPb7sAfA)
- Implementing quality management systems in national regulatory authorities: Examples and practices <https://www.who.int/publications/i/item/9789240022379>
- Addendum to EUL for modified Vx (Mar 2021)
- Consent for manufacturer to agree on sharing info with NRAs (Feb 2021)
- Confidentiality undertaking by NRA (Feb 2021)

- WHO guidance on rolling review (Jan 2021)
- Operational tool for efficient & effective lot re-release (Jan 2021)
- WHO model for NRA/NCL lot release certificate (Jan 2021)
- Product eligibility for COVAX Facility (Dec 2020)
- Model product information (Dec 2020)
- EUL TAG ToR (Dec 2020)
- about EUL TAG (Dec 2020)
- EUL Evaluation guidance (Nov 2020)
- Associated guidance (Nov 2020)
- Model packaging labels for carton (Nov 2020)
- Model packaging labels for vial(Nov 2020)
- Guidance on bar-code, QR code, Vx vial monitor (Oct 2020)
- Q&A: Vx EUL procedure (Jul 2020)
- Regulatory preparedness to address PHEIC (May 2017)
- EUAL Vx procedure (Jul 2015)

#### EUL Covid-19 Vaccines

- Pfizer–BioNTech COMIRNATY (31 Dec 2020 – Ref NRA: EMA)
- AstraZeneca/SKBio VAXZEVRIA (15 Feb 2021 – Ref NRA: MFDS)
- SII\*: COVISHIELD (15 Feb 2021 – Ref NRA: DCGI)
- Janssen COVID-19 Vx (12 Mar 2021 – Ref NRA: EMA)
- AstraZeneca VAXZEVRIA (15 Apr 2021 – Ref NRA: EMA)
- Moderna: SPIKEVAX (30 Apr 2021 – Ref NRA: EMA)
- Sinopharm: BIBP Vx (07 May 2021 – Ref NRA: NMPA)
- Sinovac: CoronaVac (01 Jun 2021 – Ref NRA: NMPA)
- AstraZeneca VAXZEVRIA (09 Jul 2021 – Ref NRA: MHLW)
- AstraZeneca VAXZEVRIA (09 Jul 2021 – Ref NRA: TGA)
- Pfizer–BioNTech: COMIRNATY (16 Jul 2021 – Ref NRA: US FDA)
- Moderna: SPIKEVAX (06 Aug 2021 – Ref NRA: US FDA)
- AstraZeneca VAXZEVRIA (21 Aug 2021 – Ref NRA: Health Canada)
- Bharat: Covaxin (03 Nov 2021 – Ref NRA: DCGI)
- SII\*: Covovax (17 Dec 2021 –Ref NRA: DCGI)
- Novavax: Nuvaxovid (20 Dec 2021 – Ref NRA: EMA)
- DP: AstraZeneca VAXZEVRIA (23 Dec 2021 – Ref NRA: COFEPRIS)
- DS: AstraZeneca VAXZEVRIA (23 Dec 2021 – Ref NRA: ANMAT)
- Moderna: SPIKEVAX (23 Dec 2021 – Ref NRA: MFDS)

#### 15. WHO International Units: a common language in evaluation of the immune response to vaccines

Knezevic I, Liu MA, Peden K, Zhou T, Kang H-N. (2021) Development of mRNA Vaccines: Scientific and Regulatory Issues. *Vaccines* 9, no. 2: 81. <https://doi.org/10.3390/vaccines9020081>.

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Funnell SGP, Afrough B, Baczenas JJ, Berry N, Bewley KR, Bradford R, Florence C, le Duff Y, Lewis M, Moryarty RV, O’Conor SL, Osman KL, Pullan S, Rashid S, Richards KS, Stemple KJ, Knezevic I. A cautionary perspective regarding the isolation and serial propagation of SARS-CoV-2 in Vero cells. *npj Vaccines* (2021) 6:83; <https://doi.org/10.1038/s41541-021-00346-z> (<https://rdcu.be/cmlhQ>).

Knezevic I, Mattiuzzo G, Page M, Minor P, Griffiths E, Nuebling M, Moorthy V. WHO International Standard for evaluation of the antibody response to COVID-19 vaccines: call for urgent action by the scientific community. *The Lancet Microbe* (2021); [https://doi.org/10.1016/S2666-5247\(21\)00266-4](https://doi.org/10.1016/S2666-5247(21)00266-4). (<https://www.sciencedirect.com/science/article/pii/S2666524721002664>).

Liu MA, Zhou T, Sheets R, Meyer H and Knezevic I. WHO informal consultation on regulatory considerations for evaluation of the quality, safety and efficacy of RNA-based prophylactic vaccines for infectious diseases, 20–22 April 2021, *Emerging Microbes & Infections* (2022), 11:1, 384–391, DOI: 10.1080/22221751.2022.2026742.

Sheets R, Kang H-N, Meyer H, Knezevic I et al. WHO informal consultation on the guidelines for evaluation of the quality, safety, and efficacy of DNA vaccines, Geneva, Switzerland, December 2019. *npj Vaccines* 5:52 (2020). <https://doi.org/10.1038/s41541-020-0197-2>.

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