How global research can end this pandemic and tackle future ones

Building a resilient research architecture and capability to protect us all

March 2022

World Health Organization

R&DBlueprint
Powering research
to prevent epidemics

Contents

Acronyms and abbreviations

CBPR	community-based participatory research
COVID-19	Coronavirus Disease 2019
COS	core outcome set
CRF	Case Record Form
C-TAP	COVID-19 Technology Access Pool
ECMO	Extracorporeal Membrane Oxygenation
EUL	Emergency Use Listing
KPI	Key Performance Indicator
HAI	health care-associated infection
HH	hand hygiene
HOCI	hospital-onset COVID-19 infection
HW	health care worker
ICMRA	International Coalition of Medicines Regulatory Authorities
IP	Intellectual Property
IPC	infection prevention and control
IS	International Standard
LMIC	low- and middle-income country
MIS-C	multisystem inflammatory syndrome in children
MPP	Medicines Patent Pool
mRNA	messenger RNA
NRA	national regulatory authority
PCR	Polymerase Chain Reaction
PHSM	public health and social measures
PRO	patient-reported outcome
RCT	randomized controlled trial
R&D	research and development
REACT	Rapid Evidence Appraisal for COVID-19 Therapies
RECOVERY	Randomised Evaluation of COVID-19 Therapy
RNA	Ribonucleic Acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
STV	Solidarity Trial Vaccines
TAG	Technical Advisory Group
TAG-VE	TAG on SARS-CoV-2 Virus Evolution
TRIPS	Trade-Related Aspects of Intellectual Property Rights
VA	virtual anthropology
VEWG	Virus Evolution Expert Working Group
VOC	variant of concern
VOI	variant of interest
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Introduction

The pandemic has shown the critical importance of research to the lives and livelihoods of people right across the world. Research in all its forms – from epidemiology and regulatory science to vaccines and therapeutics R&D – has played an integral role in the emergency response to COVID-19.

A multitude of working, coordination and exchange groups, operating at different scales, and involving researchers from across the globe, has enabled sustained, lightning-fast and unprecedented collaboration in research and innovation.

In the course of the pandemic, the World Health Organization (WHO) has hosted three critical forums of world experts on research and innovation that have helped shape the global research agenda for COVID-19 – including a coordinated R&D Roadmap at the very start of this emergency.

The most recent of these forums (24-25 February 2022) reviewed core thematic areas of research, highlighting knowledge gaps and research priorities in the next research phase.

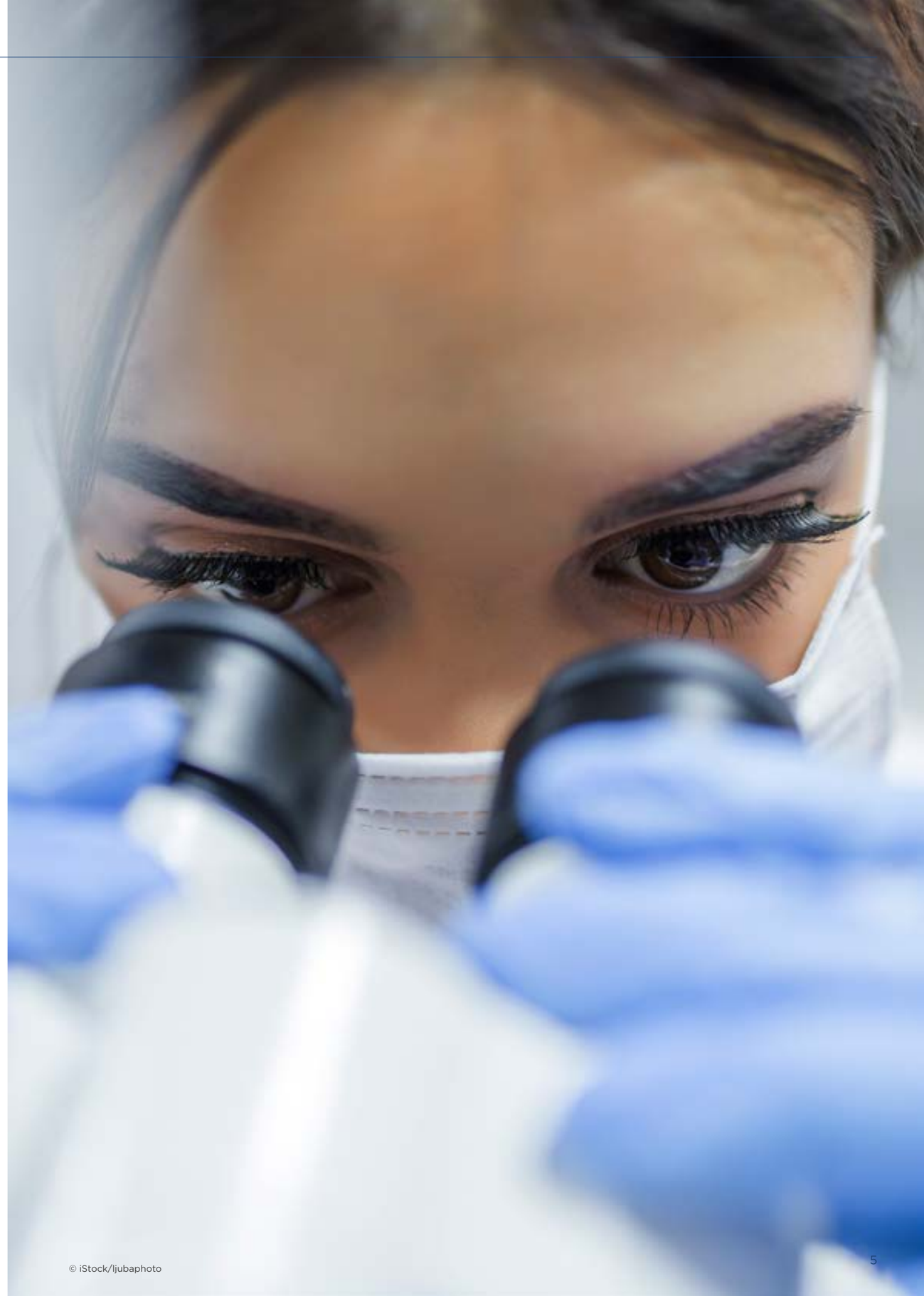
This report captures these areas and it highlights the need to:

- produce a global evidence base and world-class data for better outcomes
- build global trust for global research
- put equitable access at the centre of research
- strengthen global research capability and invest in pandemic preparedness in the long term

Research will continue to be a critical lever to end this pandemic. But this is a key moment in history. If we take the right action now, we can work to 'future proof' our global research architecture and capability to defend ourselves effectively against the new and deadly threats that lie ahead.

None of our work would be possible without the global research network, our funders and partners, and all research participants — and we thank them. We dedicate our efforts to the millions of people who have lost their lives to this devastating disease, their loved ones, and every community that has been affected.

This report should be considered in connection with COVID-19 Research and Innovation: Powering the world's pandemic response – now and in the future.



1. Strengthening global research capability for future pandemics

> **“The benefit-cost ratio of ensuring that everybody in the world has vaccines is enormous: it would cost us a few tens of billions of dollars to ensure that everybody has the vaccines. The benefit would be in the trillions of dollars.”**
>
> **Professor Joseph E. Stiglitz, Nobel Laureate. Columbia University**

1. Strengthening global research capability for future pandemics

The power of coordinating global research

The Constitution of the World Health Organization (WHO) defines that one of WHO's key roles is to promote, conduct and coordinate research in the field of health. The COVID-19 pandemic has seen this remit in the spotlight as never before.

Global research planning and coordination had started well before the pandemic hit. Evidence had already been discussed and collated on the globe's most dangerous pathogens, where the world has limited or no current medical defences. These preparations included analysing strategies for creating potential vaccines and clinical interventions that might work.

This allowed the world's research community to have a 'headstart' rather than a 'standing start' on beating the virus and COVID-19.

At the onset of the pandemic, expert working groups and global forums were rapidly convened to agree a Global Roadmap for COVID-19 Research and Innovation. This included immediate research actions and also priority areas to combat the new global threat. Thousands of researchers and scientists worldwide mobilized to implement COVID R&D, and contribute to building global research innovation and knowledge.

Many researchers are engaging in global platform trials and studies to develop life-saving vaccines medicines and continue to grow our understanding of SARS-CoV-2.

This collaborating network is the powerhouse of the global research effort now and in the future. It has been instrumental in underpinning the extraordinary initiatives and breakthroughs in research innovation of the past two years.

> **"The research that is being done in Nigeria, in India, in Laos, in Barbados, in Fiji must all be considered, fully funded and seen as equally valid. This pandemic will not end and cannot end until the global north and the global south work together."**

Dr Ayoade Alakija, Africa Vaccine Delivery Alliance, Nigeria and, ACT-Accelerator, Switzerland

What are the central themes and drivers of the global coordination effort — past, present and future?

The Ebola outbreak in West Africa during the spring of 2014 highlighted how ill-prepared the global community was to cope with major disease outbreaks of this kind. There were no vaccines or effective treatments and few diagnostic tests.

The event taught the international community a difficult but valuable lesson that a global coalition was needed to make R&D outbreak-ready. There was an urgent need for a global R&D plan to identify emerging threats and accelerate the development of new medical products to detect and treat key priority diseases and to prevent epidemics.

At the request of its 194 Member States in May 2015, WHO convened a broad network of experts to develop an R&D Blueprint for Action to Prevent Epidemics.

The R&D Blueprint is a global strategy and preparedness plan to rapidly activate 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 a large- scale crisis, enhancing traditional epidemiology and public health responses with knowledge and skills from a number of areas.

Figure 1 overleaf displays a positive progress report on the delivery of key activities within the R&D Blueprint.

The work provides essential guidance, assets and support to the global research community - across COVID-19 and key priority diseases and pathogens.

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Figure 1. WHO R&D Blueprint for action to prevent epidemics progress across key disease/pathogen areas (as of March 2022)

DISEASE	Generic methodology	CCHF	Ebola & Marburg	Lassa fever	MERS-Cov & SARS	Nipah & henipavirviruses	Rift valley fever	Zika virus	Plague	Chikungunya	Pathogen X	COVID-19
R&D Roadmap	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Target Product Profile (TPP) vaccines	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	G	✓
Target Product Profile (TPP) therapeutics	✓		✓	✓								✓
Target Product Profile (TPP) diagnostics	✓	✓	✓	✓		✓		✓				✓
Regulatory pathways	✓	✓	✓	✓		✓		✓				✓
Vaccines trials design	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	G	LST
Therapeutics trials design	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Decision tree for trials design	✓											
Trial simulator	✓											
Innovative analysis	Accumulating evidence during outbreaks and hybrid trial designs											
Good Participatory Practice for Clinical Trials of emerging pathogens (GPP-EP)	✓		✓									✓

✓ In progress ✓ Done G Generic LST Large Simple Trials

Recently and more widely, there have also been a number of high-level multilateral discussions centred on how the world might prepare for future outbreaks, epidemics and pandemics.

Most notably:

- The UN Research Roadmap for the COVID-19 Recovery has provided a global framework for leveraging the power of research in support of a better socioeconomic recovery and a more equitable, resilient and sustainable future.

  Designed to complement the UN framework for the immediate socioeconomic response to COVID-19, it identifies 25 research priorities and key scientific strategies to support a recovery that benefits everyone, as well as actions that researchers, research funding agencies, governments, civil society organizations and UN entities can act upon.

  It is a commitment and a guide to make use of research to determine how COVID-19 socioeconomic recovery efforts can be purposefully designed to stimulate equity, resilience, sustainability and progress towards the Sustainable Development Goals (SDGs).

- The World Trade Organization (WTO) is working with global partners such as WHO and the World Organization on Intellectual Property (WIPO) to address barriers to equity and explore ways to share the benefits of research with everyone and particularly those at highest risk through patent and IP waivers and the exemption from certain provisions of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement.

  Moreover, it is looking at various long-term investment avenues, for example a dedicated financing mechanism for pandemic preparedness as one of several financing options.

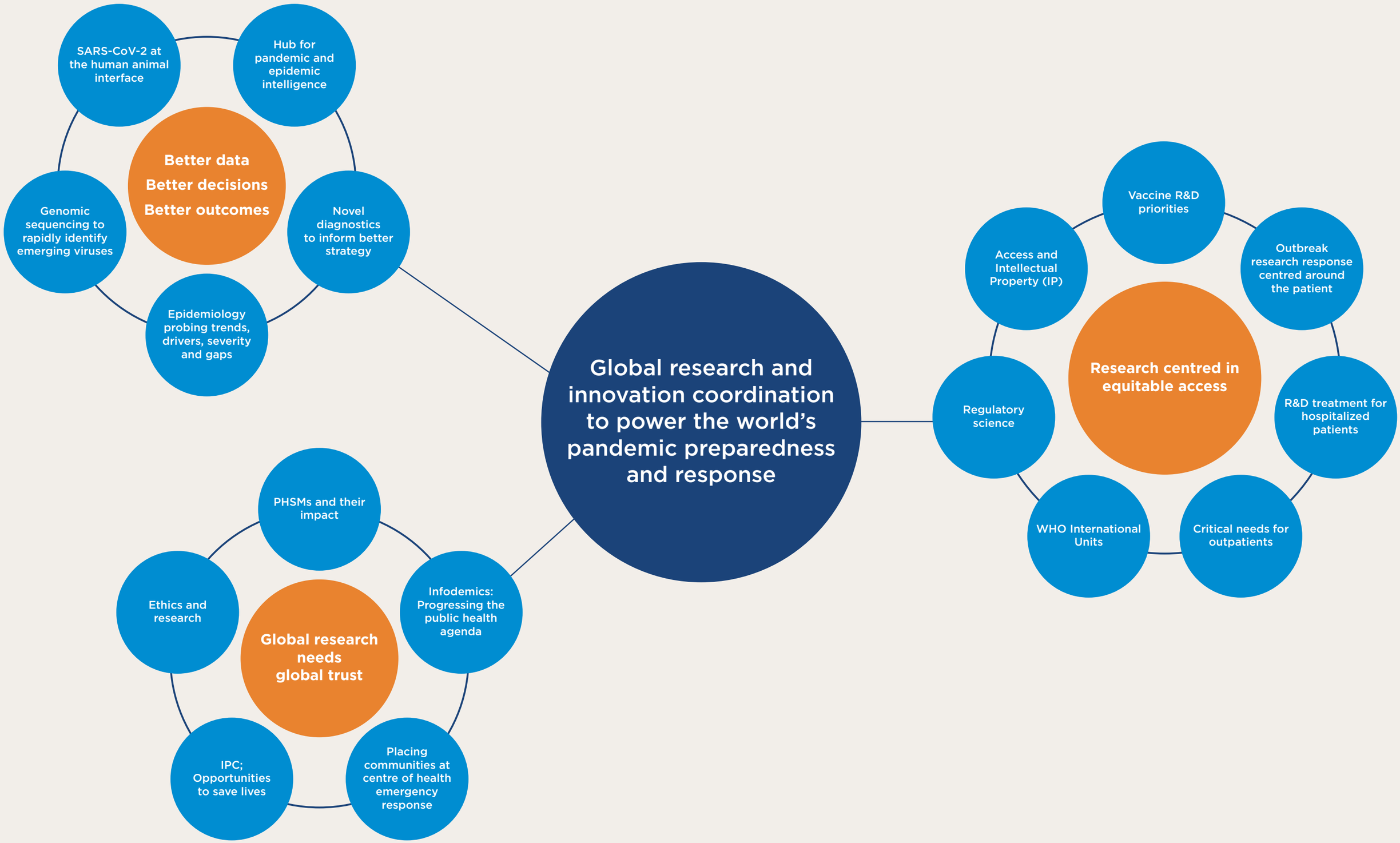
- The World Health Assembly agreed on December 2021 to launch negotiations for an agreement to fight pandemics. The 194 Member States of the World Health (WHO) Organization reached a consensus to kickstart the process to draft and negotiate a convention, agreement or other international instrument under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

These discussions will continue and we will return to the issue of research preparedness and investment in the final chapter of this report. What we know now is this that research is playing a key role in helping communities around the world fight, and also recover from, COVID-19. And it is providing hope for a better future.

However we must be vigilant and global research and innovation must always strive to stay ahead of the virus. Learning is a key part of the iterative research process, so this report highlights, across all R&D areas, our current knowledge and gaps in understanding, and also what we do next as critical research priorities.

The global co-ordination of R&D has a strong, fast and flexible architecture. It is now grouped into three major areas bringing together the wide range of research being delivered. This architecture is reflected in Figures 2-5 on the coming pages.

Figure 2. WHO R&D Blueprint for action to prevent epidemics global coordination that powers pandemic preparedness and response



2. Better data, better decisions, better outcomes

Many different forms of research data and evidence have been important in tracking and countering the pandemic. But we must build on successes to create a global evidence base and world-class data.

This chapter assesses four key R&D areas, highlighting knowledge gaps and research priorities for the future.

> **“Pandemic preparedness ... [needs]... to address key research gaps in top viral families to accelerate the development of vaccines, therapeutics and diagnostics for both priority pathogens and prototype pathogens.”**
>
> **Dr Anthony S. Fauci, Director National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)**

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

Summary

The mission of the WHO Hub for Pandemic and Epidemic Intelligence 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. To better address pandemic and epidemic risks, the WHO Hub will strengthen intelligence specifically for pandemics and epidemics by striving for better data, better analytics, and better decisions across all aspects of public health emergencies at national and local levels.

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.

Several knowledge gaps remain

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.

There are gaps in knowledge about context, occurrences and predictors of epidemic and pandemic risks. These encompass disease, environmental, social, health and risk, cultural, and economic factors, as well as contributing factors in agriculture and nature.

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Critical research priorities

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 and insights for pandemic and epidemic intelligence to improve policies and decision-making for pandemics and epidemics preparedness. 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. As a global collaboration of partners from multiple sectors, the WHO Hub will enable innovators to co-create tools and used linked data that all countries need to prepare, detect and respond to pandemic and epidemic risks.

The WHO Hub 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.

It will:

- → enhance access and linkages 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
- → 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.

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

Summary

Many of the most pressing research priorities in the outbreak of a novel high-threat pathogen are to clarify the mode of transmission, infectious dose, incubation period, duration and degree of viral shedding, and other features of the natural history of pathogen infection. Understanding these features depends on the existence of diagnostic testing which has of course been the case with COVID-19.

There was early success developing and validating a SARS-CoV-2 PCR assay within days of the sequence of the viral genome being published. This is attributed to a strong understanding already of coronaviruses and the sharing of genetic sequence information. Experts underlined the importance of developing the capacity to analyse genetic data to understand the phenotypic consequences of viral mutations to enable future prediction. While there have been tremendous strides in rapid scale-up of sequencing capacity, the analytical capacity to interpret and then potentially predict the impact of genotypic changes on the phenotype of the virus needs to be strengthened.

Through sequencing, the evolution of SARS-CoV-2 has been tracked, starting with the emergence of the 614G mutation and the first five variants of concern (VOCs) — alpha, beta, gamma, delta, Omicron — and we have begun to understand the genetic determinants of the virus's adaptation to be more transmissible. The use of sequencing has been important to inform the response of the pandemic. However more important than the number of sequences is how they are used. The early sharing of these has enabled real-time analyses. Finally, it was noted that the COVID-19 response has shown how collaboration can facilitate rapid response and highlighted the importance of maintaining readiness. Early sharing of sequences has allowed critical breakthroughs such as first diagnostics and vaccines.

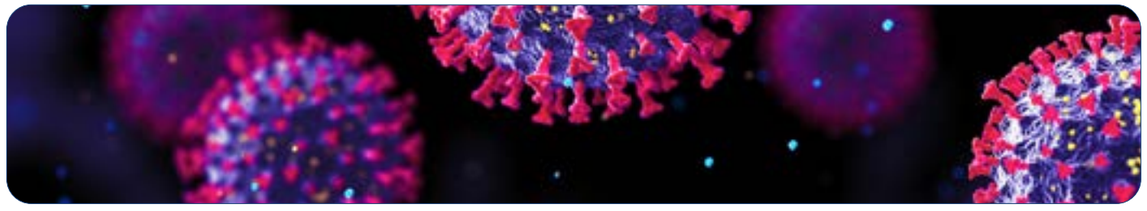
A global effort with 210 countries and territories that contributed to various global platforms (e.g. GISAID) and improvements was made in the last six months, and 114 countries and territories were able to share sequences within a month from sample collection (and 31 within two weeks).

This has also been critical for the development of tools for early warning of variants, the first step of the multidisciplinary approach to the characterization of newly emerging variants that pose a threat to public health.

Several knowledge gaps remain

- Improved understanding and monitoring viral genotypic diversity is critical to assays design. Early publication of a standardized assay design was important to distribution and uptake as was collaboration with a commercial PCR assay partner manufacturing under stringent quality systems. Our overall knowledge of coronaviruses and SARS-CoV-2 in particular is still limited.

- Diagnostics, both in endemic and epidemic disease, and substantial progress made in point-of-care diagnostic systems, including multiplexed and quantitative assays, have been remarkable. These tools have opened up novel options for testing. What remains unaddressed is equity of access. Availability of high-performance tests in high-income countries allows accurate pathogen identification.



Critical research priorities

- Addressing how to continue to track virus evolution when there may be less testing and sequencing data available, as well as how to understand viral characteristics more deeply, e.g. its immune escape properties, recombination, and circulation in animal reservoirs.

- Enabling timely analyses is even more important than just accumulating sequences. Building new tools and resources, and sharing/collaboration is essential, especially now that the volume of data has become unprecedented and can easily overwhelm the software previously in use.

- Empowering people builds on different strengths and perspectives and is therefore a great asset to the research community. In the same way that the range of pathogens we examine is so diverse, so the range of tools and approaches to enable analysis of their distribution and spread should be.

- Democratizing research when it comes to sequencing means ensuring better access at a global scale but also empowering through better and more diverse analytical tools.

- Regarding diagnostics, one potential solution is the development and evaluation of high-speed manufacturing plants established in low- and middle-income countries. Early diagnostic test development and commercial manufacture will support global research preparedness efforts.

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

Summary

Despite the repeated waves of infection, the global epidemiological picture of COVID-19 remains dynamic. The Omicron variant has led to substantially larger peaks of infection putting considerable strain on surveillance and health care systems worldwide.

There remain limitations in the quality of surveillance data due to availability of testing, and level-off monitoring mortality. Nonetheless, the epidemiological patterns seen are consistent globally; that is repeated waves of infections.

Key factors driving transmission include: the evolution of SARS-CoV-2 variants with higher transmissibility and greater immune evasion; the remaining susceptible population due to lack of vaccines, vaccine hesitancy, waning immunity; seasonal variation affecting social mixing; and changes and levels of adherence to public health and social measures (PHSMs) in the context of social mixing.

The severity of disease is modified by the emergence of variants of concern (VOCs) with increased or decreased virulence and immune escape; age (and different levels of immunization coverage); co-morbidities and non-communicable diseases, obesity and immunosuppression.

Moreover, variant levels of immunity and of vaccine coverage especially in vulnerable populations; access to effective medical interventions (e.g. antivirals, steroids); and aspects associated with human genetic susceptibility, are all contributing factors.

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Several knowledge gaps remain

- Need for enhanced global surveillance systems and improve capabilities in every country for the detection of VOCs including rapid access to epidemiological early signals of transmissibility and severity
- Predicting viral evolution (and consequences of combinations of mutations and/or deletions) and trends in infection and severe disease
- Assessing the levels of population immunity and waning (vaccines and infection derived) against infection and severe disease
- Understanding the distribution, determinants, prevention and treatment of post COVID-19 condition

Critical research priorities

- Better understanding of the implications of viral evolution on key epidemiological parameters, vaccine-induced and natural immunity on transmission and disease severity
- This highlights the need to strengthen surveillance and sequencing capabilities and the conduct of studies on variants of interest (VOIs) and VOCs.
- Lastly, there is a need to further assess the most effective and efficient combination of PHSMs to prevent transmission of SARS-CoV-2, its variants and future respiratory pathogens.
- Additional understanding of post-COVID-19 condition (or long COVID) in different populations and the value of current and future vaccines is needed together with the development and evaluation of novel, cheaper treatments that will prevent progression to severe disease.

Genomic sequencing to rapidly identify emerging viruses and develop tools

Summary

Sequencing enabled the world to rapidly identify SARS-CoV-2 and develop diagnostic tests and other tools for outbreak management in the very early stages of the pandemic.

Continued work in this area supports the monitoring of the disease's spread and evolution of the virus. Accelerated integration of genome sequencing into the global health architecture and pandemic preparedness is essential if we want to be better prepared for future threats.

The continued circulation of SARS-CoV-2 and the emergence of variants requires constant vigilance and a global mechanism to track, monitor, and evaluate the evolving situation.

WHO has taken the lead in coordinating R&D action in this critical area:

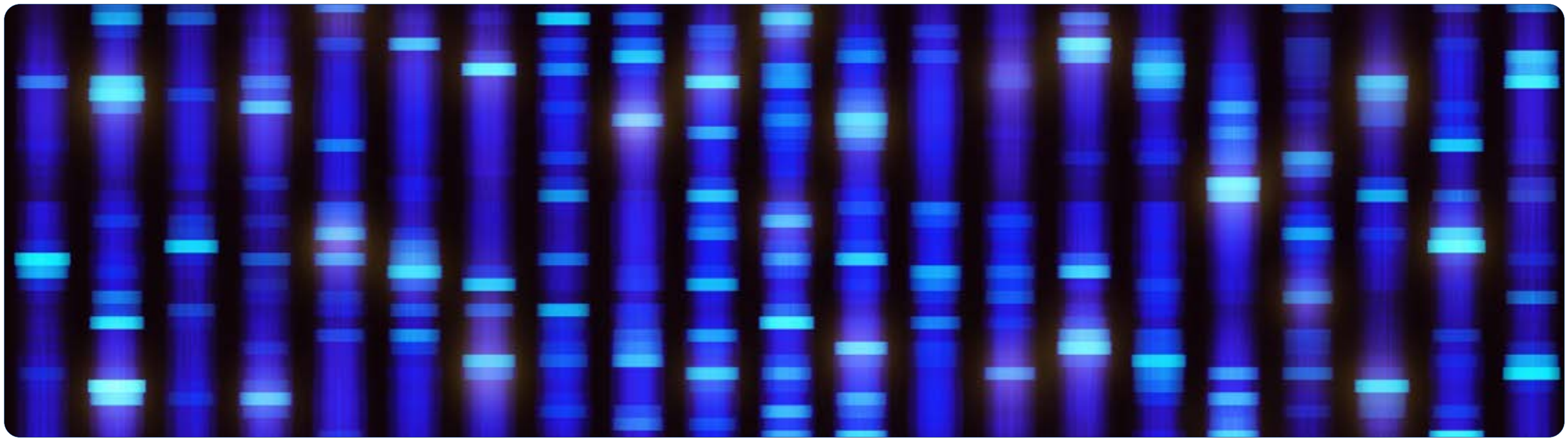
- WHO guidance has been produced for laboratories to maximize the impact of SARS-CoV-2 sequencing now and of other emerging pathogens in the future
- In June 2020, WHO established an informal Virus Evolution Expert Working Group (VEWG) to specifically assess SARS-CoV-2 evolution, mutations and variants

The Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) is the expert group that analyses the impact of SARS-CoV-2 variants on transmissibility, clinical presentation, disease severity, diagnostics, and therapeutics and determine whether a given variant constitutes a variant of interest (VOI) or a variant of concern (VOC).

Research and data collection are currently underway to determine how the Omicron variant affects transmissibility, severity of illness, and reinfection risk.

The TAG-VE is also collecting data on how effective current vaccines and previous infection are against Omicron (its immune escape potential).

With WHO and the TAG-VE, this kind of global cooperation and rapid information exchange is possible.



SARS-CoV-2 at the human-animal interface

Summary

Seventy per cent of emerging pathogens are of zoonotic nature. Progress towards global health security requires a greater focus on the interface between humans and animals and a strong collaboration between the human health and the animal health sectors.

WHO is working together with international organizations and national institutions in charge of animal health to improve the rapid detection of emerging pathogens and to ensure coordination of rapid control measures.

The next pandemic is likely to be caused by a virus of zoonotic origin, which usually emerges in two stages: first sporadic acquisition form animal-to-human, then human adaptation of the virus. When a spillover between species occurs, emergence of genetic adaptations and novel variants is likely. Preparedness will include (i) understanding pathogen diversity in animal reservoirs (genetic and functional); (ii) the ecology of reservoirs and intermediate hosts (drivers, hotspots and frequency of spillover); (iii) evolutionary biology of viruses in early transmission chains (e.g. adaptive versus neutral evolution).

Several knowledge gaps remain

- Identification of coronavirus related to SARS-CoV-2 in potential hotspots of emergence
  - Which are the coronaviruses of possible public health interest circulating in areas known to be prone to the emergence of these viruses?
  - Susceptibility studies in animals
  - What species are susceptible to SARS-CoV-2 and can transmit the virus and what are the determinants of susceptibility in animals and spillover?

- Surveillance in animal populations
  - What is the prevalence and what are the epidemiological consequences of SARS-CoV-2 infections in farmed, captive, and free-living animal species?
  - What animal species have or could become a SARS-CoV-2 maintenance or reservoir host?

- Virus evolution predictions in susceptible species
  - How might we predict and detect novel SARS-CoV-2 variants or recombination of coronaviruses which have a spillover risk to humans and/or animals?

- Risks linked to trade and consumption of potentially infected animal species
  - What are the risks linked to trade and consumption of potentially infected animal species?
  - What are the communities or occupational groups at increased risk?

Critical research priorities

- More targeted surveillance of pathogens in animals is needed, calling for low-cost, easily accessible methods and common protocols. Since animal studies are notoriously underfunded, an international funding consortium is needed.

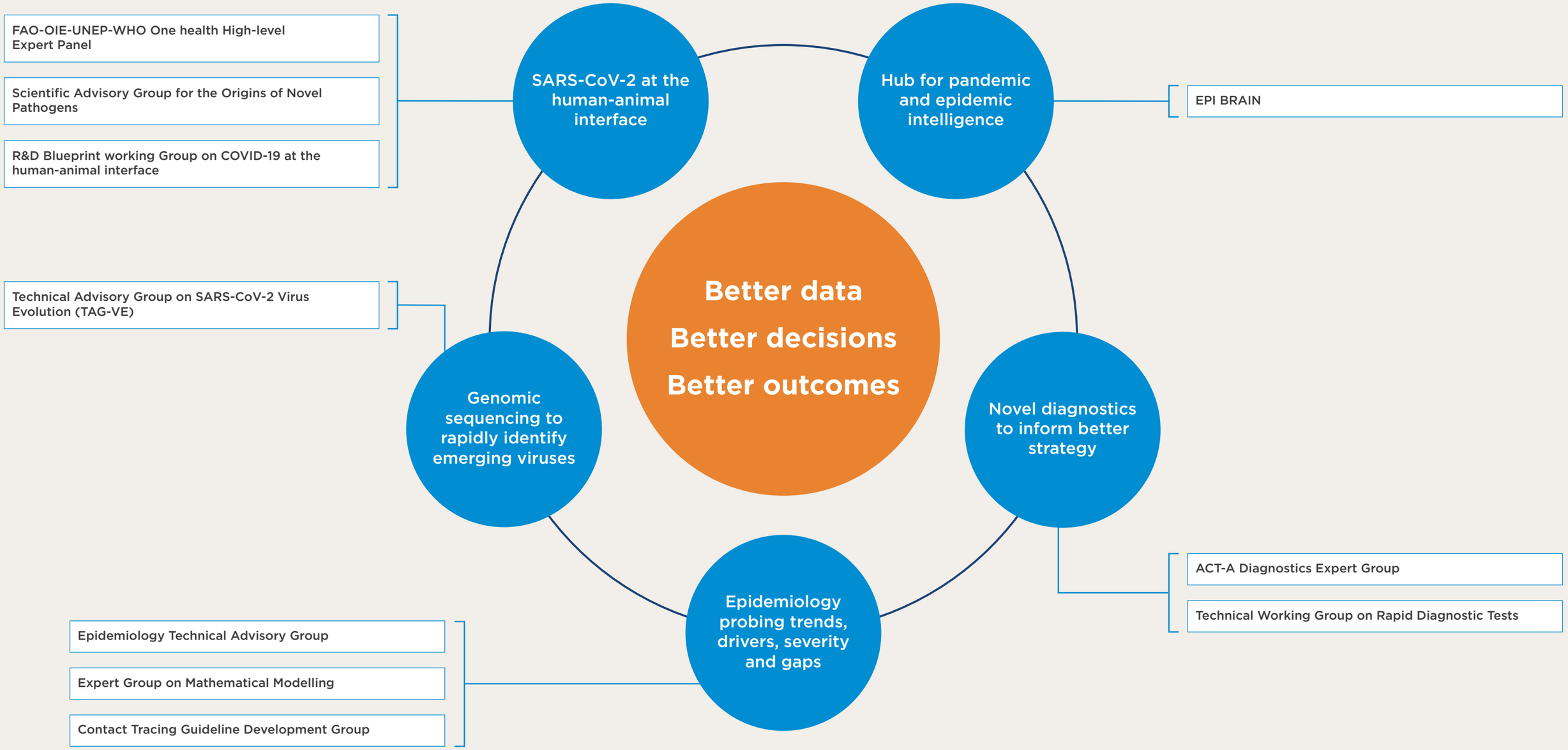
- We need to take into account the complexity of zoonotic diseases, calling for more than one counterstrategy, and to adapt to the country context (including cultural aspects) and ownership by countries. The drivers of pandemics are at the human-animal-environment interface, and impacted by land use change, urbanization, social inequality and climate change.

- It will be key to better join research forces from all areas of society: public health, veterinary medicine, social science, environmental health.

- Research funding must be diversified from mostly funding response to cover all aspects, including prevention, detection and recovery.

We must leverage existing surveillance and information sources from all relevant sectors (including veterinary and ecology sectors) for predictions and early detection of zoonotic outbreaks. Upstream prevention at the human-animal-environment interface, especially at the community level, is crucial to prevent zoonotic outbreaks in the future.

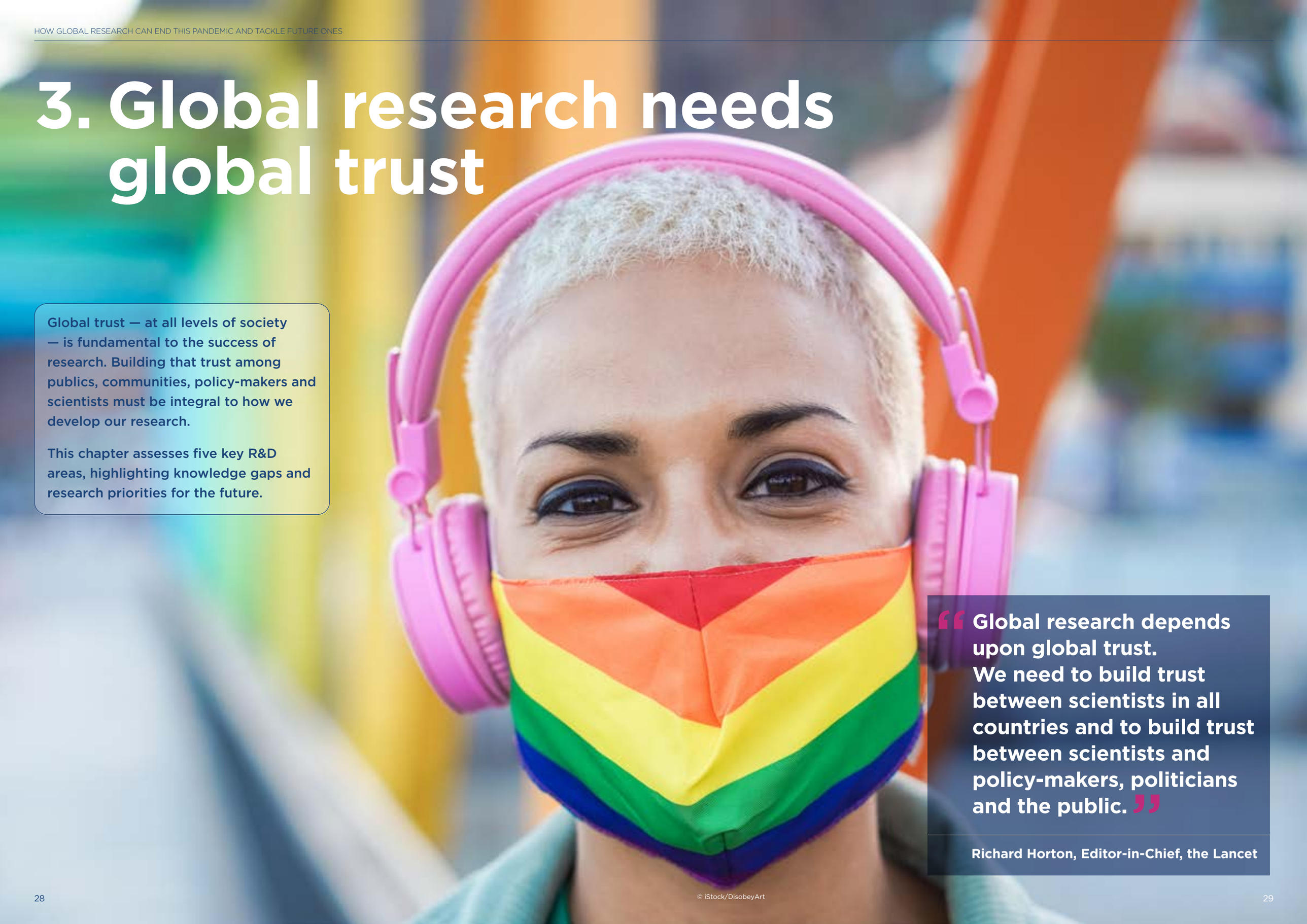
Figure 3. WHO R&D Blueprint for action to prevent epidemics: coordinated and flexible global architecture that underpins R&D delivery: Expert groups and committees guiding the policies



3. Global research needs global trust

Global trust — at all levels of society — is fundamental to the success of research. Building that trust among publics, communities, policy-makers and scientists must be integral to how we develop our research.

This chapter assesses five key R&D areas, highlighting knowledge gaps and research priorities for the future.



> **“Global research depends upon global trust. We need to build trust between scientists in all countries and to build trust between scientists and policy-makers, politicians and the public.”**
>
> **Richard Horton, Editor-in-Chief, the Lancet**

Research on public health and social measures and their impact

Summary

Evaluation of the effectiveness and health, social and economic impact of public health and social measures (PHSMs) is accompanied by several methodological challenges. There are conceptual challenges ("complex interventions in complex systems") related to interactions between measures, levels of governance, with context and implementation. Moreover, there is a multitude of health and non-health outcomes to consider.

In addition, the design challenges are considerable ("assessing effectiveness"). These include whether randomization is feasible or appropriate. It is challenging to conduct a randomized controlled trial (RCT) in a real-life context that potentially affects people's level of protection during a pandemic. Effects of individual measures are difficult to disentangle. PHSMs were often implemented as "packages". Hence, hardly any data on the effectiveness and impact of individual interventions is available.

Ethical, legal and logistical challenges determine data collection options. RCTs have often not been possible as approval by ethical review boards could not be obtained in a timely manner or at all due to concerns about conducting RCTs in a real-life emergency context. Furthermore, it has been difficult to set up studies quickly enough and to collect data on a large scale.

Several knowledge gaps remain

Because of the unresolved issues detailed above, there is hardly any high-quality data from RCTs available to assess the effectiveness and health, social and economic impact of PHSMs. The current evidence base mostly relies on modelling studies but their significance can be questionable due to low quality of imputed primary data. Furthermore, there are methodological challenges associated with the integration of social and behavioral sciences data into PHSM guidance.

In summary, the evidence base is not strong enough to guide decision-making about PHSM implementation.

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Critical research priorities

A strong conceptual basis is needed to strengthen research on PHSMs. WHO and the Ludwig Maximilian University of Munich are currently developing a logic model to promote a more systematic approach towards PHSM research and decision-making.

High-quality study designs and timely data collection during emergencies are required to produce a meaningful evidence base for PHSM decision-making. WHO will develop blueprints for studies similar to the Unity studies approach for seroprevalence surveys.

Key questions to be answered with future research (to be adjusted through an iterative global research agenda development process led by WHO):

- → Which PHSMs are the most effective at reducing transmission during a health emergency?
- → Which unintended consequences — health, social and economic impacts — are associated with PHSMs?
- → Which implementation approaches ("degree of intrusiveness") are most successful during different stages of a health emergency?
- → How do contextual factors (e.g. geographical, sociocultural) influence the benefit-harm balance of different PHSMs?
- → How to address the methodological and design challenges in measuring the effectiveness and impact of PHSMs?

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

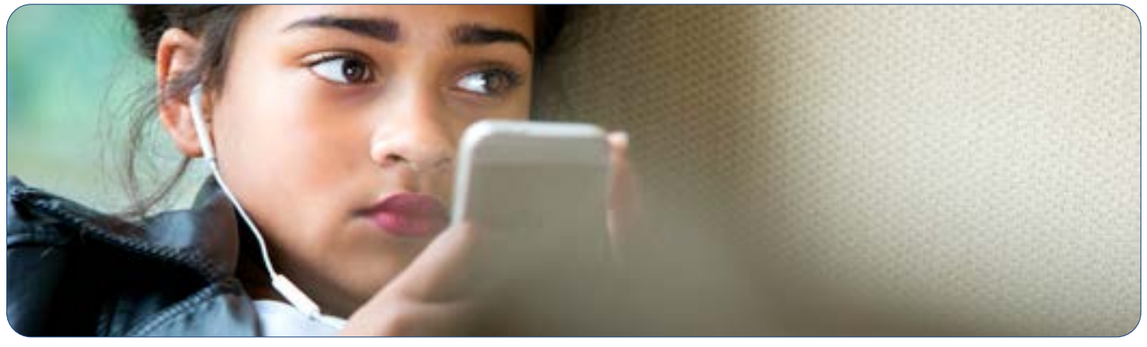
Summary

The phenomenon of an 'infodemic' has escalated in the context of the COVID-19 pandemic to a level that requires a far more coordinated response. An infodemic is an overabundance of information — some accurate and some not — occurring during an epidemic. It can make it very hard for people to find trustworthy sources of information and reliable guidance when they need it.

Even when people have access to high-quality information, there are still barriers they must overcome to take the recommended action. Like pathogens in epidemics, misinformation spreads further and faster and adds to the complexity of the health emergency response. An infodemic cannot be eliminated, but it can be managed. To respond effectively to infodemics, WHO and experts call for adaptation, development, validation and evaluation of new evidence-based measures and practices to prevent, detect and respond to mis- and disinformation.

Several knowledge gaps remain

- Most data-driven research is focused on individual social media platforms, which means it is not generalizable and most research makes the flawed assumption that the volume of misinformation that can be found on social media platforms is associated with concentration of exposure to that misinformation.
- Even when researchers measure exposure, they often do not calculate what proportion makes up of a person's overall information diet. Most importantly, the majority of research is disconnected from any measure of health attitudes, knowledge, or behavioural outcomes and simply concludes that the presence of misinformation has an impact, without knowing how much of an impact.
- Other knowledge gaps include the need for ethical frameworks for infodemiology; the assessment of the impact of infodemics on trust in health authorities; and evidence connecting research to practice through initiatives such as infodemic management training.



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Critical research priorities

- Measuring and monitoring the impact of infodemics during health emergencies
- Detecting and understanding the spread and impact of infodemics
- Responding and deploying interventions that protect against the infodemic and mitigate its harmful effects
- Evaluating infodemic interventions and strengthening resilience of individuals and communities to infodemics
- Promoting the development, adaptation and application of tools for managing infodemics
- There is a need to move beyond testing interventions in individuals in artificial scenarios that are removed from the real-world context; and to stop thinking about social media as the only way that infodemics spread.
- Infodemiology researchers also need to consider the relationships between the information ecosystem, individuals who interact with the information they are exposed to, and social and health system impacts of infodemics.
- Tools and protocols for measuring the burden of infodemics need to be standardized globally so that infodemiology researchers can contribute to a global surveillance initiative.

Social science in outbreak response: Placing communities at the centre of health emergency readiness and response

Summary

Since the beginning of the pandemic, this thematic area has produced contextual evidence, innovative methods while establishing policy pathways and supporting the development of equitable solutions. This expertise has strengthened the public health and clinical response, mitigated the uneven impact of COVID-19 on different social groups, and developed research infrastructure and capacity.

The new phase of the pandemic is likely to push 49 million people into extreme poverty: the 'new poor' will be concentrated in countries that are already struggling with high poverty rates, but middle-income countries will also be significantly affected.

When it comes to disease control measures, working households are making trade-offs between non-COVID-related economic impacts and COVID-related impacts. It is critical to understand those and take them seriously. Our frameworks must enable people to choose healthy behaviours, and not think only in terms of compliance and information. In this context, enabling means returning to the social determinants: the pandemic cannot be overcome without social protection. The message for social protection must come as much from public health, medicine and science as from economists, workers, and activism.

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Several knowledge gaps remain

- Understanding the pandemic, and controlling and reducing its human costs, requires a dynamic and in-depth knowledge of social, economic, cultural and political processes, including social drivers of vulnerability and risks during pandemic and its impacts on different populations/communities across and within countries.
- To advance the field, best practice approaches and evidence to underpin inclusive, appropriate, tailored and responsive interventions and programmes that address the realities and needs of specific community groups are needed.

Critical research priorities

- Tools and best practice approaches for nuanced and realistic assessments of how marginalized groups and those who are most vulnerable are affected socially, economically and health-wise by epidemics need to be implemented at scale to drive change.
- Evidence is needed to articulate and address structural barriers and enablers to community-centred approaches for readiness and response to public health crises, for COVID-19 and beyond.
- Investment in research readiness and response is needed to build the systems and structures for sustainable integration of evidence from social sciences for the current pandemic and future emergency events. This includes critical review and capacity development for use of innovative methods that are fit for purpose in public heath crises, such as rapid assessments, longitudinal ethnography, virtual anthropology (VA), photo narratives, and community-based participatory research (CBPR) methods.

Infection prevention and control research during the pandemic: Pointing to an opportunity for saving lives and money

Summary

The effectiveness and cost-effectivness of infection prevention and control (IPC) measures are well demonstrated. Increased access to personal protective equipment (PPE), IPC training in preventing infections among health workers (HWs) can save lives and also costs.

Thus, the development of budgeted IPC plans for better preparedness to respiratory diseases epidemics and pandemics, both in high- and low- and middle-income countries, is pivotal.

Several knowledge gaps remain

- A reliable estimation of COVID-19 cases and deaths among HWs is still not available globally and in most countries, and there is limited data on identification of occupational vs community acquisition and exposure settings. There is a need to understand the role of working conditions as factors influencing infection and re-infection among HWs, and HWs' adherence to IPC measures, such as hand hygiene (HH) and PPE use, following vaccination.

- As for the impact of the COVID-19 pandemic on health care-associated infections (HAIs) and antimicrobial resistance in COVID-19 and other patients, conflicting evidence is emerging about increasing or decreasing trends of HAIs and antimicrobial resistance during the pandemic. There is a need to study these in depth and with standardized methods, including secular trends from established national and international HAI and antimicrobial resistance surveillance networks, prevalence studies, and prospective incidence studies.

- Gaps remain in implementation of real-time point-of-care surveillance to promptly detect hospital-onset COVID-19 infections (HOCIs) among patients, and connect it to prompt implementation of tailored IPC measures.

- It is important to leverage research outputs on innovative PPE, decontamination methods for surgical and non-medical masks, and to deploy actionable guidance and protocols for nosocomial and community settings, suitable for high- and low- and middle-income countries.

Critical research priorities

To better understand, prevent and control HWs' infections, it is critical to implement the following activities:

- Develop and implement surveillance with standardized methods for reliable estimation of HW cases and outcomes, identification of occupational vs community acquisition and exposure settings
- Perform surveys and qualitative studies on the role of working conditions, such as overload, excess working hours, variations in post-infection return-to-work criteria, on the epidemiology of reinfection
- Conduct observational studies about vaccinated HWs' compliance with IPC measures

Critical research priorities to help protect HWs, patients and the wider community include the following:

- It is essential to assess the impact of enhanced IPC measures and antibiotic use on antimicrobial resistance in COVID-19 and other patients, identifying and monitoring the epidemiology of emerging and re-emerging pathogens associated with surges of COVID-19 cases and applying innovative methods of real-time surveillance.
- Innovative real-time surveillance methods and tools should include whole genome sequencing to detect SARS-CoV-2 transmission in HWs and in community, and understand its dynamics and to assess the impact of tailored IPC measures implemented according to real-time HOCI surveillance data and the applicability of these methods to other pathogens.
- To inform evidence-based and cost-effective global IPC measures and interventions, it is important to promote the development of standardized protocols to generate high-quality evidence on the efficacy and safety of PPE, including the risks of antimicrobial treatments for PPE.
- It is necessary to improve PPE international standards, design processes, with a user-centric approach, taking into consideration physical differences, gender and users living with disabilities, and to focus on the lifecycle of PPE and non-medical masks, optimizing logistics, waste management, degradable materials, decontamination and reuse, recyclability, minimizing the environmental impact and promoting innovation.
- There is also a need to generate high-quality evidence on medical masks vs respirators effectiveness and adverse events in the context of prolonged use, repeated use and in combination with other PPE. Moreover, it is essential to increase the quality of non-medical masks, including adequate standards for manufacturing, mass production, optimal use, standard sizing, performance assessment, decontamination, and communication strategies to the public.
- Human factors, such as those that drive users' preferences (e.g. which PPE to use, where and when), reasons hindering PPE adherence (e.g. comfort, communication, breathing), users' acceptability of decontamination methods also in relation to different environments, are important to consider and understand.
- Finally it is critical to define strategies for IPC/PPE de-escalation in relation to COVID-19 pandemic scaling back.

Ethics and research

Summary

The WHO COVID-19 Ethics and Governance Working Group has highlighted how ethics is integral to every decision taken in this pandemic.

The WHO Director-General has repeatedly referred to ethical concepts to frame developments, for example when cautioning of a “catastrophic moral failure” in connection with global vaccine inequity.

Further key issues such as setting research priorities, facilitating rapid research ethics review, considering vaccination mandates, and navigating different kinds and degrees of uncertainty swiftly and while responding to rapidly emerging evidence are fundamentally ethical issues.

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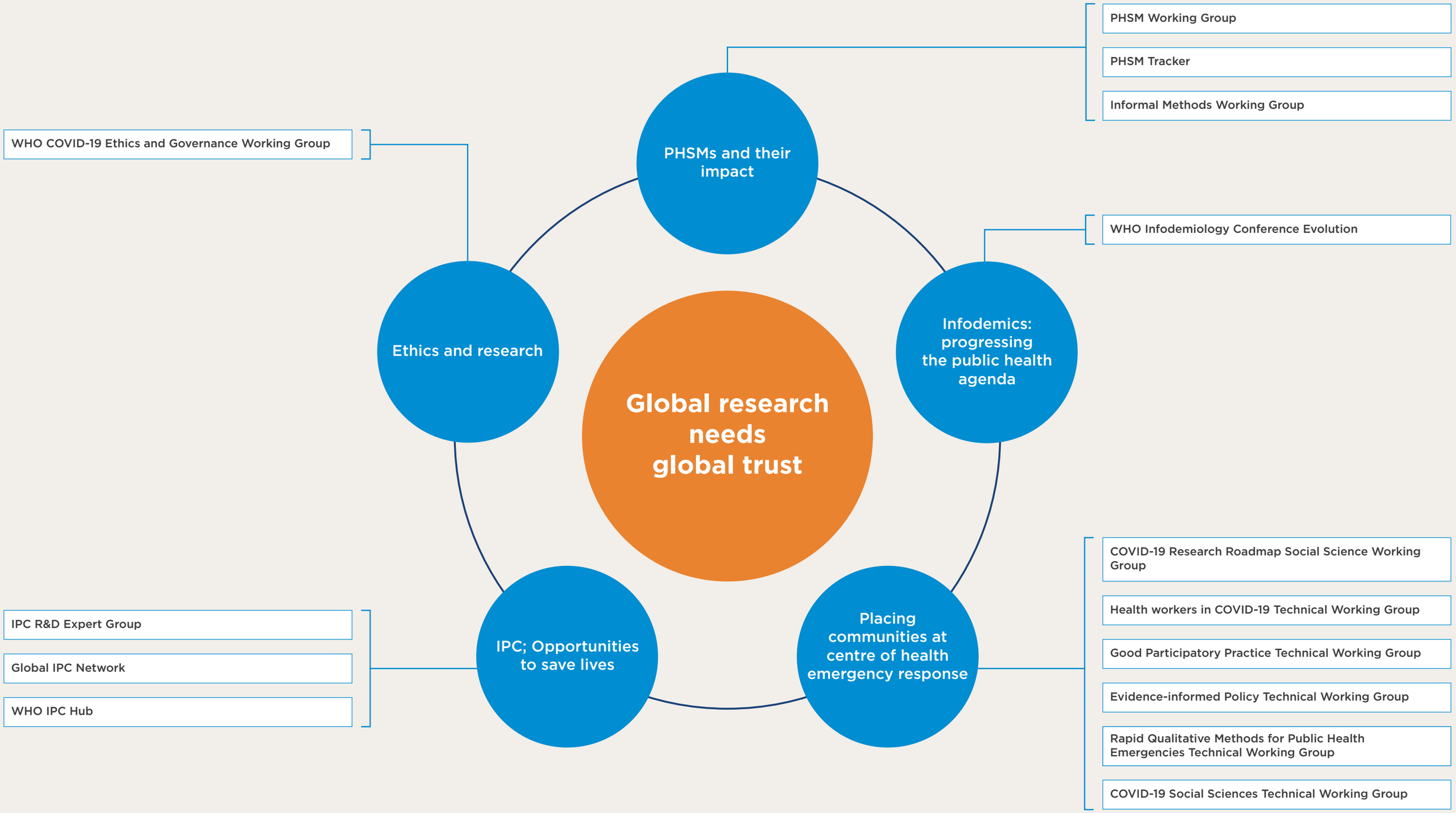
Several knowledge gaps remain

- Besides highlighting the centrality of ethics to the most pressing challenges of the pandemic, it is recognized that decisions on ethical challenges in public health emergencies need not be taken in a vacuum, but should be guided by existing and ongoing work of the ethics community that can clarify relevant concepts and their application.
- Experts argued that there is a need to focus not just on the ethical conduct of R&D, but also to consider the outcomes of R&D processes, for example whether or not they meet global needs or result in scarcity and inequitable distribution.
- In R&D and the pandemic response, moving fast can mean that some people get left behind. It is crucial to attend to and protect the most at-risk populations, and to be aware that the short- and medium-term impact of the pandemic has been particularly severe for the most disadvantaged and has worsened existing socio economic divides.
- While many of these insights appear familiar from previous public health emergencies such as SARS, H1N1, and Ebola, the world was not well prepared to apply these lessons learnt in the COVID-19 pandemic. 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.

Critical research priorities

- It is proposed to cultivate a spirit of ethical humility as we continue to face the uncertainty and under-determination of science that has been a key feature of this pandemic.
- The WHO Ethics Experts Group will continue to devote attention to issues related to research ethics, particularly with respect to methodology, design, and oversight.
- It is highlighted that current calls to “live with the virus” raise a host of further ethical issues which have yet to be explored, including but not limited to issues of inclusion, exclusion, and marginalization.
- The WHO Ethics Experts Group has recently proposed a set of high-level governance principles and will continue its efforts to specify how these principles can be implemented in practice and through robust, yet flexible oversight mechanisms.
- In order to respond to emerging developments, stakeholder needs, and ethical issues in different settings, the working group continues to maintain 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.

Figure 4. WHO R&D Blueprint for action to prevent epidemics coordinated and flexible global architecture that underpins R&D delivery: Expert groups and committees guiding the policies



4. Research centred in equitable access

The pandemic response has been a moment for research but the benefits have not been available to everyone. Equity — and access for those at highest risk — must be central in the next research phase.

This chapter assesses six key R&D areas, highlighting knowledge gaps and research priorities for the future.

> “All pandemics start within communities and with people and that is where we must refocus our attention and demonstrate by our actions that we are not just going to do the science but we are going to make sure that science is available to everybody.”

Sir Jeremy Farrar, Director, Wellcome Trust

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> “Aside from warfare the greatest threat to the human race is pandemic disease. These last two years in vaccinology have been the best since the polio days because we have multiple strategies for developing vaccines. A universal coronavirus vaccine that will broadly protect against all beta coronaviruses ... is not simply a dream.”

Stanley Plotkin, Emeritus Professor of Paediatrics, University of Pennsylvania

Vaccines: Research and development priorities

Summary

Important and critical research carried out by WHO and the global research community has helped advance our understanding about safe and effective COVID-19 vaccines with a significant number of vaccines having been approved in record time. This has become possible thanks to coordinated efforts in global research and development including evaluation of candidate vaccines and their potential efficacy, effectiveness and safety.

To date there are 33 approved vaccines and 197 countries and territories with access to these vaccines. Ten vaccines have received an Emergency Use Listing (EUL) approval by WHO, with an additional 184 candidate vaccines in development and more than 600 clinical trials conducted in over 70 countries.

Many trials are occurring in places where the Omicron variant wave has reached its peak. Animal model research played a significant role in the characterization of the pathogenesis, transmission and immunology of SARS-CoV-2 variants of concern (VOCs). Global effort has been directed to engineer animal models that would mimic these important disease drivers and research groups have shared their experiences and data on the development of immune assays, including the International Standard (IS) for neutralizing assays.

Although it is possible that additional doses of currently approved vaccines may raise antibody titres temporarily against the Omicron and other variants, it may take months to protect large numbers of unvaccinated people.

Several knowledge gaps remain

- → To improve our understanding of the source of VOCs in order to be better prepared for future variants
- → To better understand how the Omicron variants are transmitted
- → To collect additional epidemiological data on vaccine effectiveness against Omicron and other VOCs
- → To collect additional evidence on the severity of Omicron disease (and other VOCs) in different population groups (vaccinated, unvaccinated, previously infected, hybrid immunity)

Critical research priorities

- → There is an urgent need for additional vaccines. Many current approaches are highly promising and feasible; however, the speed at which they are developed depends on resource availability. Novel platforms may also require support for significant manufacturing development.
- → A framework that could be used for variant-specific modifications of current vaccines, new variant-specific vaccines or pan-sarbecovirus vaccines is needed. WHO is developing such a framework to contribute to increased supply of vaccines that meet WHO TPP criteria for effectiveness against severe disease. This may also help guide researchers and developers with the additional data needed for the assessment of new vaccines.
- → Increased standardization of assays and readouts is essential: more information about mechanisms of protection (e.g. cell-mediated immunity - CMI, non-neutralizing responses, mucosal immunity especially against severe disease; larger sample size studies; animal studies).
- → There is a need for the enhanced sharing of reagents, particularly convalescent Omicron and VOC serum.
- → Assessment of Omicron-specific responses to more vaccines including variant-specific vaccines is critical.
- → Generation of data that permits connecting laboratory results on variants and immune evasion to clinical outcomes is needed.
- → Optimizing vaccine schedules is critical.
- → Research on a range of sarbecoviruses that may protect against emerging variants and other coronaviruses must be supported.

To help deliver these research priorities WHO and its partners will:

- → update the TPP for COVID-19 vaccines and continue to facilitate strategic research collaboration.
- → coordinate large simple platform trials – such as the Solidarity Trial Vaccines (STV). The STV will continue to contribute to evaluating additional new candidate vaccines. The proposed framework for evaluating new vaccines will be published and novel approaches to evaluate vaccines will be explored.
- → Map all pre-clinical and clinical COVID-19 vaccines candidates. This process is in development worldwide through the COVID-19 candidate vaccine tracker and landscape. This tool which provides an overview of vaccine technologies in development can potentially benefit specific populations, improve access and availability, and target specific VOCs.

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

Summary

Bringing evidence generation to global clinical management guidelines in real time to save lives is critical.

Corticosteroids were prioritized in early 2020, tested in multiple trials, including large platform trial such as the Randomised Evaluation of COVID-19 Therapy (RECOVERY). Simultaneous prospective meta-analysis (WHO Rapid Evidence Appraisal for COVID-19 Therapies - REACT) led to the first WHO Living guideline: Therapeutics and COVID-19 in September 2020. The guideline contains the WHO's most up-to-date recommendations for the use of therapeutics in the treatment of COVID-19. To date eight versions of the living guideline have been produced.

Corticosteroids, IL6 RB, baricitinib, casirivimab/imdevimab, sotrovimab are to be included in the toolbox for effective COVID-19 treatments and the guidelines will be updated within 8-10 weeks of data availability.

Several knowledge gaps remain

A better understanding of the natural history and full spectrum of disease remains an essential need. The following research tools and activities aim to further accelerate this understanding:

- The rapid publication of tools to support standard patient data collection, such as: Case Record Forms (CRFs) for acute COVID-19, multisystem inflammatory syndrome in children (MIS-C), pregnant women and post-COVID-19 condition; minimal common data set; core outcome set (COS); and COVID-19 severity classification system (published in May 2020)
- The simultaneous availability of large data registries to consolidate individual patient level data, such as the WHO Global Clinical Data Platform and Dashboard (launched in April 2020), now including 570,172 individual patient records and the ISARIC platform, now including > 500 000 entries
- The ongoing and coordinated prospective data collection for disease severity in children with COVID-19; post-COVID-19 condition; and maternal, pregnancy and neonatal outcomes for women and neonates infected with SARS-CoV-2

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Critical research priorities

- Improving access to oxygen therapy is a top priority. Indeed, there are still global inequalities in oxygen delivery, as well as access to advanced respiratory support devices and access to basic emergency and critical care. WHO launched the O2CoV2 study in September 2021 to assess the availability and use of oxygen for COVID-19 and will also launch a platform study to assess non-invasive interventions for those with severe or critical COVID-19. We are currently onboarding 36 study sites across 24 LMICs.
- WHO is also leading the development of Global Oxygen Investment Key Performance Indicators (KPIs) that capture oxygen from procurement to patient care to inform research, clinical operations and advocacy, using the Delphi methodology.
- Post-COVID-19 condition (long COVID): burden of disease, symptoms, natural history, recognition, pathophysiology, clinical management, therapeutics and service delivery are all areas that need to be further understood.
- There needs to be an evaluation of supportive care and clinical management interventions to improve outcomes in severe or critical COVID-19 in LMICs.
- It is also important to develop and validate prognostic models to better describe high-risk patients and to establish reliable approaches to update severity classification and define disease severity with VOCs.
- Finally, prospective monitoring of the resistance and safety of antivirals must be set up with the introduction of new therapeutics.

Research and development for treatments of hospitalized patients

Summary

Severity of COVID-19 illness is not simply a marker of how likely one is to die or have a long recovery; not all COVID patients are the same (e.g. different vaccination status, different virus; different genetics; age; gender; environment; etc.).

Moreover, we need to acknowledge that with COVID-19 there are pros and cons to a one-size-fits-all research agenda regarding patient enrolment; and that there is a role in targeting the virus (and understanding its mutations) in hospitalized patients who are less sick.

Several knowledge gaps remain

- Understanding that different approaches are not mutually exclusive (e.g. lumpers vs splitters or both?)

- **Lumpers: the simplest and most pragmatic approach to enrolment for large collaborative trials such as Solidarity**
  It is however unclear how differences in disease severity/patient characteristics translate to biology; this can lead to questions such as, “What are the new pathways that can be targeted that we have not yet targeted?”; “What existing drugs can we repurpose?”; and, more importantly, “What is affordable and can be distributed worldwide?”.

- **Splitters: drugs used in outpatient settings do not work in hospitalized patients**
  Moreover, drugs used on inpatients are contraindicated in outpatients and less sick patients due to side-effects; we can make an argument that we are far enough into the pandemic that we can target individual groups of patients in certain settings; a patient on mechanical ventilation or on ECMO is likely having a remarkably different host response than someone on 2-4 litres nasal-canula; an unvaccinated patient or an immunosuppressed transplant who does not respond to a vaccine will not respond in the same way as a vaccinated immunocompetent patient. Therefore, why should we examine them in the same trials?

- **Conducting research when the news is good**
  There are fewer hospitalized patients when rates go down, however this means there are fewer patients that can be enrolled in clinical trials, and many of them may be resistant for the same reasons that many choose not to get vaccinated.

- Having hundreds of simultaneous trials may not provide the outcome we want. Research aimed at the virus should continue. The host response does not look the same in patients with different disease severity or in different patients’ populations. Research aimed at a precision medicine approach will likely be more fruitful than simply enrolling all patients as we initially did when we had no agents to treat COVID-19.

- There is a role both for landmark pragmatic trials such as Solidarity with global research that can touch the largest numbers of patients, and precision medicine approaches: a balance is needed.

Critical research priorities

- Ensure that the enhanced collaboration ecosystems and networks are sustained at the same unprecedented speed and scale and repurposed to target other high priorities

- Maintain a continued acceleration of product research and development, with sustained investments of financial and human capital, as well as long-term investments in platform technologies and infrastructures. The importance of research not only to our health but also to our economic wellbeing is now highly recognized in the public and policy-makers’ minds.

- Engage in a public dialogue on how regulation can become more agile with adequate support to regulators

- Promote the use of master protocols and adaptive design, with platform trials becoming the norm rather than the exception

- Advance novel approaches to allow use of remote tools and decentralized approaches, to promote equity and access to research at the community level

WHO/Blink Media - Hannah Reyes Morales

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

Summary

The COVID-19 pandemic has exerted a heavy burden on countries with poorly developed health systems without the capacity to rapidly scale up hospital care delivery to meet the demands created by the massive number of people seriously ill with SARS-CoV-2.

In these settings, the availability of effective outpatient treatments will be economical and life-saving as it could relieve strain on the health system. As with vaccines, equitable distribution and availability of effective treatment is crucial.

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Several knowledge gaps remain

- Research to determine the efficacy of therapeutic agents should be prioritized. As the pandemic evolves, the characteristics of the population and the virus change due to mutations and improved vaccine coverage. This, as well as geography, can affect outcome measures. The focus of outpatient treatment should be on symptoms and recovery, not hospitalization and death. However, the dynamism of the disease makes such clear-cut differentiation cumbersome.

- Large simple trials offer unique advantages but have received little attention. So far, there are very few publicly funded pragmatic trials. Some drugs that have shown promise in outpatient trials were evaluated in unvaccinated populations; hence their efficacy in vaccinated patients remains unknown.

- The efficacy of post-exposure prophylaxis therapies is unknown. Patient-reported outcomes (PROs) are yet to be accorded the same attention as outcome measures in efficacy trials.

- Moreover, preparedness requires significant investment in infrastructure and manufacturing capabilities and the sustainability of research requires the transfer of knowledge and patents.

Critical research priorities

- Pragmatic adaptive trial designs should be prioritized and smaller, underpowered clinical discouraged. The methodological and statistical considerations that currently limit the understanding and acceptance of platform trials should be subject to scientifically rigorous discourse and resolved.

- An urgent resolution of the ethics and regulatory authorities' reservations about virtual clinical trials would go a long way in encouraging the conduct of these trials in future pandemics.

- Because the dynamism of an evolving pandemic makes it challenging to determine in advance which outcomes would be most important at the end of the trial, scientists should consider delaying the primary endpoints' decision until just before the analysis.

- Also, in a global trial, with different geographical needs, it should be possible to report different outcomes for different regions of the world. A composite endpoint that allows study participants to be graded along the full spectrum of possible outcomes could be ideal for this scenario.

Regulatory science and convergence between national regulatory authorities

Summary

Regulatory authorities play a critical role in facilitating access to safe, effective and quality-assured urgently needed vaccines and therapeutics during a pandemic. Interministerial coordination and collaboration with experts established at the early stage of the COVID-19 pandemic played a key role in providing prioritized R&D responses, rapidly identifying products that were needed and mobilizing the required resources. This well-coordinated governance has led to successful in-country development of PCR-test kits, biological antibody products and vaccines.

The International Coalition of Medicines Regulatory Authorities (ICMRA) is a strategic level coalition represented by heads of agencies from 37 members across the globe, with WHO an active observer. During the COVID-19 pandemic, regulators demonstrated unprecedented regulatory flexibilities, agilities and responsiveness.

In 2020, through the ICMRA's agile platform for rapid sharing and discussions, an accelerated parallel development process was accepted over a traditional sequential process; regulatory convergence on pre-clinical and clinical data requirements was proactively reached (early 2020), and a broad agreement on vaccine trial designs, population, endpoints, and statistical considerations facilitated the emergency or conditional authorization of investigational COVID-19 vaccines.

In May 2021, WHO and ICMRA urged the publication of clinical trial results for new medicines and vaccines to ensure greater transparency and data integrity to facilitate public health decision-making. In January 2022, ICMRA exchanged the regulatory requirements for changes in vaccine compositions when needed.

Several knowledge gaps remain

- All national regulatory authorities, including but not limited to those associated under the ICMRA, need to continue to work in collaboration to share information, further explore regulatory agility and flexibilities, and leverage lessons learned so far to rollout new vaccines, therapeutics and diagnostic tests.

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Critical research priorities

- Moving forward, establishment of an efficient global regulatory science governance and infrastructure with smarter regulatory pathway is absolutely critical.

- Deliverables in the regulatory science area include developing a reflection paper with considerations on clinical trials designs. This will contribute to ongoing efforts by clinical trials experts already working on platform approaches for large simple trials. The aim will be to facilitate understanding of obstacles, and explore ways to enable implementation of platform trials.

- A new ICMRA Initiative — a Public Health Emergency Clinical Trials Working Group — has been created to facilitate the international acceptability of the use of a core protocol for multinational/multiregional platform trials of vaccines and therapeutics in a cross-border public health emergency.

- Deliverables of this working group include developing a reflection paper with considerations focused on protocol design for platform trials; facilitating understanding of obstacles, and exploring ways to enable implementation of platform trials.

- Finally, considering the importance of openness and transparency in increasing trust in regulatory decision-making, ICMRA is committed to explore new ways to enhance transparency and data integrity.

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

Summary

It is important to standardize assays in disease detection, surveillance, viral evolution and immune evasion, vaccine immunity and efficacy. This also applies to post-COVID-19 condition (long COVID) or post-COVID period.

The first WHO International Standard (IS) for anti-SARS-CoV-2 immunoglobulin played a critical role in facilitating vaccine development and evaluation, and a second IS is being prepared.

Several knowledge gaps remain

- Additional guidance may be needed for clinical evaluation of COVID-19 vaccines. In particular alternative clinical trial designs are required, especially in the context of a global public health emergency, and evolving or novel trial designs should be considered by regulators.
- For second-generation COVID-19 vaccines, efficacy evaluation in Phase 3 clinical trials would be difficult to do and alternative approaches would require standardized assays among other issues and conditions.
- Improved and standardized assays to evaluate non-neutralizing protective responses will facilitate interpretation, appraisal and synthesis of results.
- Availability of standards to harmonize assays would facilitate interpretation of the results from clinical trials.
- A better understanding of the intended use of WHO ISs is needed. Efforts made to educate users on the calibration of secondary/in-house standards and provision of tools (e.g. webinars, WHO manual) should also continue.
- There is a need for longer term investments to prepare for future pandemics and for other public health emergencies, as well as sustained efforts, and resources for work in all areas.
- Furthermore, methods for sourcing materials for development of standards need to be improved.

Critical research priorities

- Standards for other assays for Fc-mediated functions and cell-mediated responses also need to be developed and provided.
- While the WHO BioHub is recognized as a key facilitator in streamlining the preparation of candidate materials for WHO International Standards (ISs), a framework for source bulk materials collection is very much needed.
- The work with funding organizations to provide a preparedness framework for known priority pathogens and for Disease X should be a priority at the global level.

Access and intellectual property

Summary

While the COVID-19 pandemic response has undoubtedly demonstrated what many call a miracle of science, it has failed to ensure equitable access to the benefits of that science. Equitable access and the distribution of life-saving products to the world's highest risk populations thus remains a major challenge in the next research phase.

Many argue that a key barrier to access is intellectual property (IP). Supporters of this argument say that only with shared knowledge, IP and data will the world leverage the collective efforts necessary to advance scientific discovery, technology development and the broad sharing of the benefits of scientific advancement and its applications based on the right to health.

A global campaign has sought to remove COVID-19 vaccines from IP protection. A proposal to the World Trade Organization (WTO) requests that it waives certain provisions of the TRIPS agreement for COVID-19 health products and technologies.

An IP waiver would help stop companies that hold the IP for COVID-19 vaccines blocking vaccine production elsewhere and allow countries to produce COVID-19 vaccines locally and rapidly, and import or export them.

Opponents of the waiver say that the bigger barrier to global production is limited capacity especially in LMICs to safely produce and manufacture a complex vaccine such as COVID-19, suggesting a waiver would in fact suppress innovation and reduce future investments in R&D.

To address these concerns, in May 2020, WHO and partners launched the COVID-19 Technology Access Pool (C-TAP) to facilitate timely, equitable and affordable access of COVID-19 health products by boosting their supply. The WHO Technical Advisory Group (TAG) advises on scientific, technical and strategic matters related to C-TAP.

C-TAP provides a global one-stop shop for developers of COVID-19 therapeutics, diagnostics, vaccines and other health products to share their IP, knowledge and data, with quality-assured manufacturers through public health-driven voluntary, non-exclusive and transparent licences.

By sharing IP and know-how through pooling and these voluntary agreements, developers of COVID-19 health products can facilitate scale-up production through multiple manufacturers that currently have capacity that is not being used.

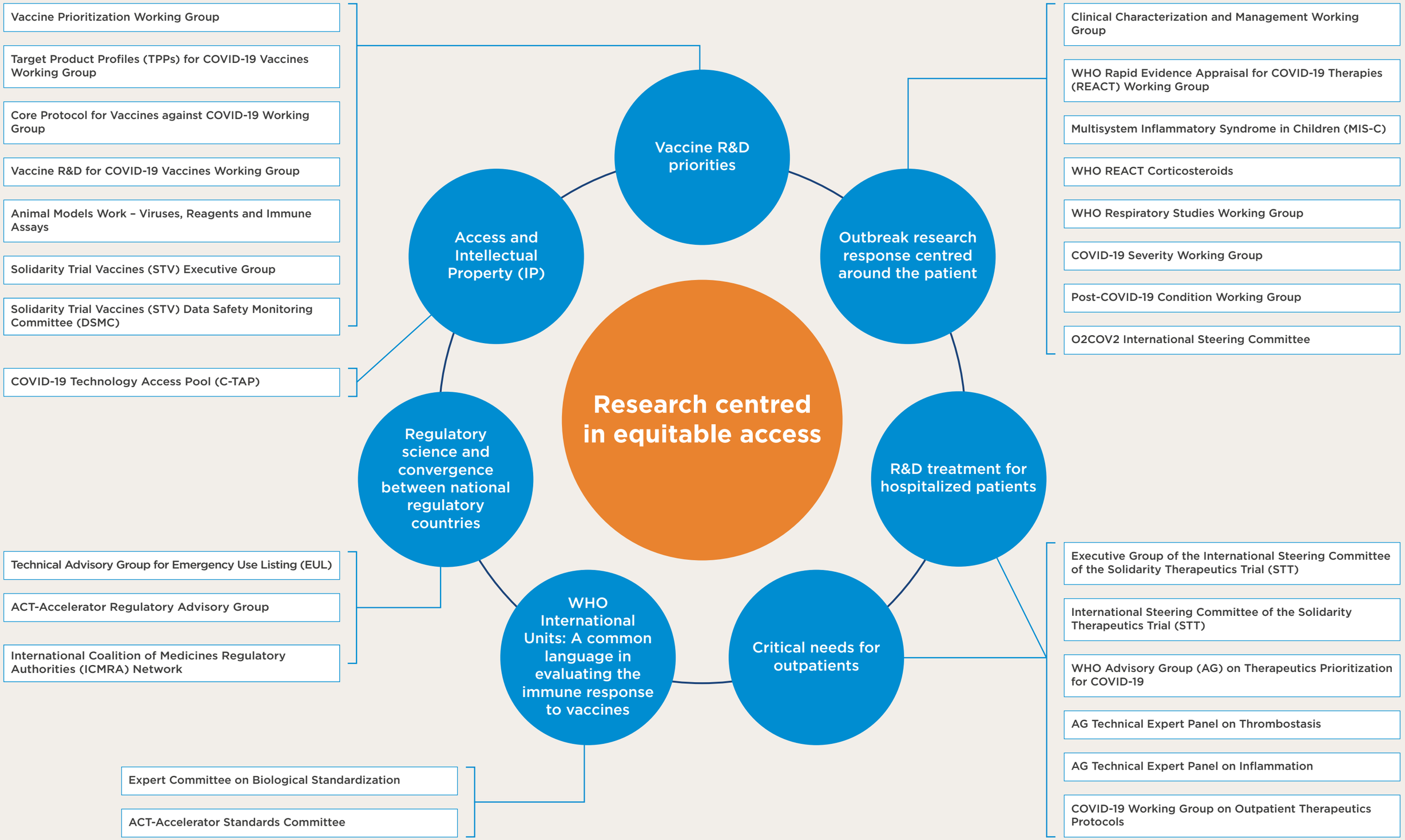
In addition, the World Intellectual Property Organization (WIPO), WHO and WTO joined forces to implement a tripartite technical assistance package to countries relating to their needs for COVID-19 medical technologies, and providing a one-stop shop that will make available the full range of expertise on access, IP and trade matters.

During the pandemic the Medicines Patent Pool (MPP) has been able to increase access worldwide to various treatments (molnupiravir and nirmatrelvi) and diagnostics especially in Africa. MPP is a UN-backed public health organization working to increase access to, and facilitate the development of life-saving medicines for LMICs.

It operates through voluntary licenses to facilitate early entry of generic manufacturers in LMICs. MPP identifies which patents to license and then sub-license these to manufacturers in LMICs who can produce cheaper generic versions of the medicine.

On vaccines, WHO together with MPP launched an mRNA technology transfer hub to provide the logistical training, and know-how support for manufacturers in LMICs to repurpose or expand existing manufacturing capacity to produce COVID-19 vaccines and to help them to access IP rights for this technology.

Figure 5. WHO R&D Blueprint for action to prevent epidemics: coordinated and flexible global architecture that underpins R&D delivery: Expert groups and committees guiding the policies



5. Pandemic preparedness and action is a long-term investment

> **“Without dedicated and accelerated investment to manage the current pandemic and prepare for the next one, we will continue to face more frequent and more complex epidemics in the years ahead.”**
>
> **Ngozi Okonjo-Iweala,**
> **Director-General, World Trade Organization (WTO)**

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5. Pandemic preparedness and action is a long-term investment

> **“Not only is our health at risk, our economy is at risk. The economic losses from the pandemic have been literally in the trillions of dollars, and the IMF [International Monetary Fund] estimates that if the pandemic continues we will lose more trillions of dollars. This is an example of what I could call a ‘no brainer’.”**

Professor Joseph E. Stiglitz, Nobel Laureate, Columbia University

Outbreaks of deadly new pathogens will happen in the future. This is fact not fiction.

In recent history there have more than six influenza pandemics and epidemics. And other diseases such as Ebola show that the transmission of viruses from animal to human have happened multiple times in the last few decades.

We cannot completely prevent epidemics or pandemics, but we can be much better prepared and coordinated in responding to future outbreaks ensuring they are detected and even prevented at an early stage.

There have been some interesting overall strategies discussed across the globe regarding R&D’s broad role in pandemic preparedness. One of these has emphasized a two-fold strategy — firstly prioritizing research work on existing pathogens that pose the greatest threat to the world. This can utilize the WHO R&D Blueprint’s annual list of priority diseases that have the greatest potential to cause a global public health emergency.

The second strand focuses on identifying ‘prototype pathogens’ — new viruses that could emerge within viral families with the potential to cause significant human disease.

At a wider level, there is a broad consensus internationally that a comprehensive research and innovation effort should continue to be at the core of pandemic response and preparations. By embedding research at the centre 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.

Within this global effort, there are certain specific elements of global R&D infrastructure we need to build on and strengthen. These include:

- **Greater global surveillance to detect pathogens quickly**

  Stronger global surveillance would include augmented international data output which monitors the spread of pathogens. Every day counts in the critical effort to contain new threats.
  At present there are parts of the world which are surveillance ‘black spots’. It is thus imperative we resource more locally-owned, surveillance centres that plug into an international system. This will help us to shine a light on potential dangers before they become a major problem.

- **Resourcing regional R&D infrastructure in LMICs**

  Possibly the greatest priority should be empowering existing research institutions and researchers in low- and middle-income countries (LMICs), and building research capacity where it is lower than in higher-income countries. There is a vital need for sustainable and well-distributed global research capacity to ensure that all Member States are endowed to contribute to the global research effort. This strategy should also include a focus on increasing regional manufacturing capacity in LMICs. This will ensure those at highest risk will have access to life-saving treatments and vaccines now and in the future.

- **Evidence-based public engagement and communications**

  Campaigns to inform and educate the public about actions they need to take in a pandemic are key to pandemic control. Moving forward they should be centred around a strong communications and behavioural science evidence base — which takes into account local cultural issues, context and audiences.

While the short-term research goal may be to help end this pandemic through strong surveillance, treatment and vaccines, our long-term goal must be investment towards universal health coverage (UHC) that includes primary health care (PHC) and pandemic preparedness as part of a sustainable long-term vision for any country.

The benefit-cost ratio of long-term investment is huge. The economic losses from this pandemic are already estimated to be in the trillions of dollars. Investing now and adopting a long-term approach to investment will bring a vast return. It will save the world vast sums of money in the future. It will also save millions of lives.

We cannot afford to turn research on and off like a switch. Investment needs to be constant, evidence-based and globally coordinated.

Research has saved the lives and livelihoods of people right across the world. It can, and will do so, again. But this requires constant and long-term investment, building on the existing global R&D infrastructure and research achievements so far, helping fight this pandemic and also preparing ourselves for the next one.

Macro and micro global research action needed

- → Secure funding to move the world to endemic status for COVID-19 whilst building the foundations to prepare for the next pandemic
- → Continue to strengthen existing mechanisms to fund global research priorities and sustain investments in existing research networks, platforms, and partnerships
- → Build research capacities, capabilities and infrastructure for research especially in LMICs
- → Continue and further promote large platform research trials
- → Support global monitoring efforts and strengthen national linkages to address the challenges of emerging variants
- → Build on identified research weaknesses
- → Further consolidate the Global COVID-19 R&D Roadmap into an end-to-end approach to ensure efficiency and global equity

> **By embedding research at the heart of the pandemic response we can achieve two goals: to help end the acute phase of the current pandemic and protect us from the epidemics and pandemics of the future.**
>
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R&DBlueprint
Powering research
to prevent epidemics