World Health Organization

A COORDINATED GLOBAL RESEARCH ROADMAP: 2019 NOVEL CORONAVIRUS

MARCH 2020

There is broad consensus on the need for research to: focus on actions that can save lives now; facilitate actions so that those affected are promptly diagnosed and receive optimal care; and catalyse the full integration of all innovations within each research area.

Moreover, there is an imperative to support research priorities in a way that leads to the development of sustainable global research platforms pre-prepared for the next disease X epidemic. This will allow for accelerated research, innovative solutions and R&D of diagnostics, therapeutics and vaccines, as well as the timely and equitable access to these life-saving tools for those at highest risk.

R&DBlueprint

Powering research to prevent epidemics

Contents

About this document

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

The two-day meeting was convened by WHO, using the R&D Blueprint strategy as a framework. This is a strategy which aims to coordinate and accelerate global research work to target diseases that threaten humanity, develop diagnostics, medicines and vaccines fast, and promptly respond to outbreaks thereby preventing epidemics.

The goals of the meeting were two-fold:

Goal 1 (immediate priorities): To accelerate research that can contribute to containing the spread of this epidemic and facilitate that those affected receive optimal care; while integrating innovation fully within each thematic research area.

Goal 2 (mid-long term): To support research priorities in a way that leads to the development of global research platforms, aiding preparedness for the next unforeseen epidemic and encouraging accelerated research, development and equitable access, based on public health needs, to diagnostics, therapeutics and vaccines.

Over 400 participants from across the world came together at the Global Research and Innovation Forum, including scientists, Member States' representatives, public health professionals, funders and private sector representatives, to accelerate the development of innovations to control the epidemic.

The current epidemic of COVID-19 is unprecedented. Although some good progress has been made in epidemic preparedness since previous outbreaks over the last decade, there are still clear and significant challenges. Some of the biggest challenges are that there are currently no proven therapeutics or vaccines or rapid point of care diagnostic tests for COVID-19 and there are major research gaps in many other key research and innovation areas.

Since the West Africa Ebola outbreak, WHO has – at the request of the Member States – established the R&D Blueprint strategy. In this most recent outbreak this has allowed WHO to work closely with global experts, governments and partners to rapidly expand scientific knowledge on the virus, to track its spread and virulence, and to provide advice to countries and individuals on control measures.

Research topics discussed included: 1) virus: natural history, transmission and diagnostics; 2) animal and environmental research on the virus origin, and management measures at the human-animal interface; 3) epidemiological studies; 4) clinical characterization and management; 5) infection prevention and control, including health care workers' protection; 6) candidate therapeutics R&D; 7) candidate vaccines R&D; 8) ethical considerations for research and; 9) integrating social sciences in the outbreak response. These topics were addressed in thematic work groups and then brought back to the plenary for discussion and agreement. Experts identified key knowledge gaps and research priorities and shared scientific data on ongoing research, thereby accelerating the generation of critical scientific information to contribute to the control of the COVID-19 emergency.

Although experts recognized that an important amount of information is available just two months into the outbreak, there are still concerns about knowledge gaps and lack of clear evidence to support some interventions.

The importance of strengthening capacity was highlighted. Integration of research activities in the response to outbreaks and the lessons learnt on SARS, Ebola, Lassa fever, and Nipah have led to a prompt research response now. Participants emphasized that as we mobilize the research community for COVID-19, concerted efforts should be made to facilitate the sustainment of this capacity to support other ongoing or future outbreaks across the world.

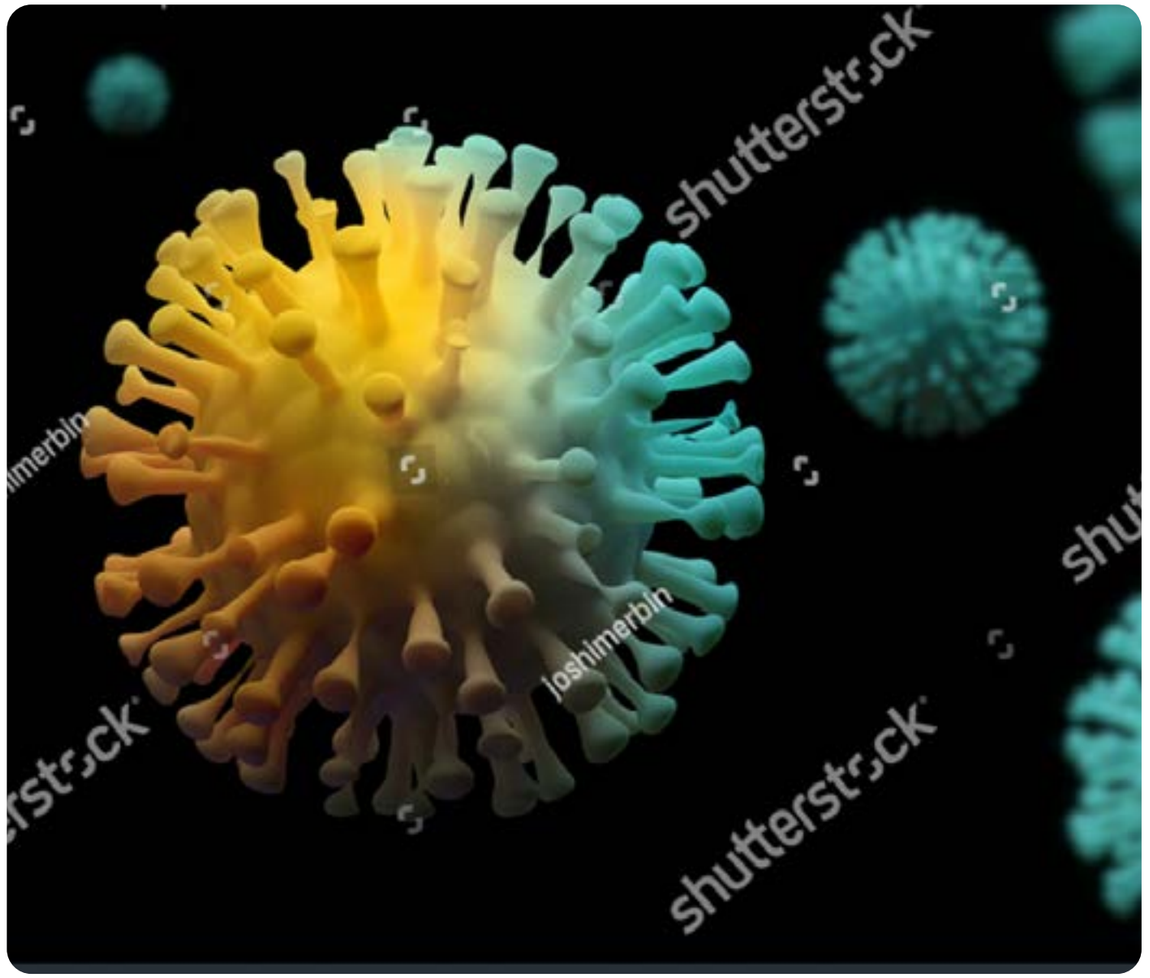
2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

The Scientific Advisory Group of the WHO R&D Blueprint met on 2 March 2020 to review the progress made since the Global Research Forum and to provide advice to WHO on additional prioritization of research actions for this outbreak.

This document presents a Global Research Roadmap with immediate, mid-term and longer-term priorities to build a robust global research response on the basis of the deliberations during the Global Research Forum.

"This outbreak is a test of political, financial and scientific solidarity for the world to fight a common enemy that does not respect borders... what matters now is stopping the outbreak and saving lives."

Dr Tedros,
Director General, WHO



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Goals of the Global Research Roadmap

Research and innovation play increasingly important roles during, after, and in anticipation of public health emergencies. Conducting research is linked to "a moral obligation to learn as much as possible, as quickly as possible".

It is important to underline that research - implemented as policy and practice - can save lives and needs to be integrated into the response from the start.

The global imperative for the research community is to maintain a high-level discussion platform which enables consensus on strategic directions, nurtures scientific collaborations, and supports optimal and rapid research to address crucial gaps, without duplication of efforts. Importantly there is a decisive pledge to collaboration, solidarity and to equitable access to all innovations developed.

The WHO R&D Blueprint is facilitating such platforms. In addition to the research actions ongoing, a comprehensive collaborative research agenda has been drawn up. The implementation of this collaborative research agenda has started.

Goals of the Global Research Roadmap

Goal A

To facilitate that those affected are promptly diagnosed and receive optimal care; while integrating innovation fully within each research area.

Goal B

To support research priorities that will lead to the development of sustainable global research platforms that are prepared for the next disease X epidemic.

The intense communications and information sharing among researchers is unprecedented and has resulted in a level of collaboration among scientists that, together with innovation advances, has led to research actions being implemented faster than ever before during an outbreak.

[1] WHO (2016) Guidance for managing ethical issues in infectious disease outbreaks, available at: apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1, at page 30.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Figure 1. Principles to guide the implementation of the Global Research Roadmap

Powering research

An understanding that science and research stays at the heart of the response

A global research and innovation roadmap, facilitated by WHO, to enable the implementation of priority research

Coordinating research

A series of critical research efforts so that those affected are promptly diagnosed and receive optimal care

A commitment to develop frameworks that would accelerate development, production and access to medical countermeasures

Committing to fair and equitable access

An unambiguous commitment to global solidarity and equitable access to advances made

A global effort to enable the scaling-up of any successful intervention

A coordinated effort to facilitate effective, fair and equitable access based on public health needs

Facilitating future research actions

A coordinated effort to maintain repositories of products pipelines, protocols, procedures, and tools.

A series of efforts enabling critical support for regulatory and ethics, and, use of platforms for developing vaccines and therapeutics that can be useful beyond COVID-19.

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Proposed strategic approaches and critical actions

There is an imperative for a coordinated and multi-disciplinary approach. The Global Research Roadmap is a critical tool but will only enable robust research and fast answers to critical knowledge gaps if indeed transparency and collaboration are maintained throughout.

Figure 2. Key components for successful implementation of the Global Research Roadmap

One challenge is how to handle the greater uncertainties associated with research during this outbreak. The potential acceptability of different risks will vary, depending on numerous factors including the type of research and the context in which it takes place.

It must be recognized that a 'one size fits all' approach towards the implementation of research may not be appropriate and therefore it is important that global priorities are contextualized, and protocols and interventions assessments are adjusted to local needs and realities as well as the translation of any results.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

A number of lessons learnt from previous and current outbreaks are essential in designing the strategy so that critical research is successfully implemented. These include:

1. Engagement with all communities including marginalized ones, those in resource constrained environments and those not engaged via Member States' representation. The research community needs to promote that research is prioritized aiming at protecting health care workers in the broadest sense.

2. Critical importance of the development, dissemination and use of high-quality generic/ core protocols , whether or not it is in the clinical management context, as part of social science research or as part of trials to evaluate experimental therapeutics and vaccines. The more the research community is encouraged to use such protocols, the better. They can be adaptable and will contribute to obtain robust answers, faster.

3. The facilitating role of governments is critical. This includes the development of national research plans and supporting their implementation, facilitating research oversight processes, streamlining importation of critical goods and experimental products, and advising health care workers and institutions to engage in priority research.

4. Availability of standardized serological assays, serum banks and population level seroepidemiological studies is critical to inform population levels of infection and immunity and inform containment measures, as well as to enable the prompt identification of cases and facilitate the evaluation of experimental therapeutics and vaccines.

5. Access to the benefits of research is critical. This involves equity and transparent allocation processes for diagnostics, therapeutics and vaccines.

6. While the research community focuses on human related research, it is important to continue conducting research to understand the origin of the virus, the animal host and the factors leading to the spill over events.

Immediate next steps to contribute to control the outbreak

The global community has a responsibility to provide the best evidence to inform public health interventions to curtail the current epidemic.

It is important to strike the right balance between stopping transmission now and preparing for the future. There is an imperative for research to focus on actions that can save lives now.

Eight immediate research actions were agreed as part of the Global Research Forum

1. **Mobilize research on rapid point of care diagnostics for use at the community level -** this is critical to be able to quickly identify sick people, treat them and better estimate how widely the virus has spread.
2. **Immediately assess available data to learn what standard of care approaches from China and elsewhere are the most effective** – there is an imperative to optimize standard of care given to patients at different stages of the disease and take advantage of all available technological innovations to improve survival and recovery.
3. **Evaluate as fast as possible the effect of adjunctive and supportive therapies.** The global research community needs to understand what other adjunctive treatments being used we have at our disposal that may help with the standard of care provided to patients, including the quick evaluation of interventions such as steroids and high flow oxygen.
4. **Optimize use of personal protective equipment and other infection prevention and control measures in health care and community settings** – It is critical to protect health care workers and the community from transmission and create a safe working environment.
5. **Review all evidence available to identify animal host(s), to prevent continued spill over and** to better understand the virus transmissibility in different contexts over time, the severity of disease and who is more susceptible to infection- Understanding transmission dynamics would help us appreciate the full spectrum of the disease, in terms of at risk groups, and conditions that make the disease more severe as well as the effectiveness of certain public health interventions.
6. **Accelerate the evaluation of investigational therapeutics and vaccines by using "Master Protocols".** Rapidly developing master protocols for clinical trials will accelerate the potential to assess what works and what does not, improve collaboration and comparison across different studies, streamline ethics review and optimize the evaluation of new investigational drugs, vaccines and diagnostics.
7. **Maintain a high degree of communication and interaction among funders so that critical research is implemented.** Funders reiterated their current financial commitments to tackling this outbreak and agreed that the priorities agreed at the Forum would help to coordinate existing investments and inform mobilization of additional resources in the coming days, weeks and months.
8. **Broadly and rapidly share virus materials, clinical samples and data for immediate public health purposes** – It was agreed that virus materials, clinical samples and associated data should be rapidly shared for immediate public health purposes and that fair and equitable access to any medical products or innovations that are developed using the materials must be part of such sharing.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Selected knowledge gaps

Some knowledge gaps merit being highlighted given their relevance to the goals that have been set forth.

Human-animal interface
1. Animal species of origin of the virus
2. Animal species involved in spill over to humans: reservoir/ intermediate host
3. Modalities of transmission between animals and humans
4. Risk factors due to animal trade and consumption

Clinical considerations
1. Spectrum of clinical disease
2. Groups at high risk of severe disease
3. Pathophysiology of severe disease
4. Clinical prognosis associated with viral loads and immunomarkers
5. Potential for antibody dependent enhancements to disease/infection
6. Adequate animal models that can mimic human disease characteristics

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

Behaviors and educations
1. How to address drivers of fear, anxieties, rumours, stigma
2. How to promote acceptance, uptake, adherence to public health measures and implement ethics, R&D innovations into education

Transmission
1. Modes/duration of person-to-person transmission, role of different age groups
2. Importance of pre-/asymptomatic transmission
3. Surrogate markers for infectivity
4. Environmental stability of the virus and conditions associated with increased transmission
5. Virus compartments of replication, duration shedding
6. Risk factors due to animals

Therapeutics
1. Optimal strategies for supportive care interventions
2. Role of host-targeted therapies
3. Safety and efficacy of candidate therapeutics and their combinations
4. Context for post-exposure prophylaxis trials conduct

Healthcare workers
1. Risks factors for healthcare workers' exposure
2. Approaches to support healthcare workers' health/ psychosocial needs
3. Perception/compliance to infection prevention and control measures
4. Isolation, quarantine, optimal pathways to deliver care safely

Ethical considerations
1. Ethics questions around the inclusion of vulnerable populations in research
2. Best methods to involve and sensitize communities regarding their participation in research

Cross-cutting research priorities

At the Global Research Forum, topics were addressed in thematic work groups and then brought back to the plenary for discussion and agreement. While several of the research priorities relate to more than one of these thematic areas, the following cross-cutting research priorities were highlighted by reviewing the deliberations of all thematic areas:

- Research that will enable better understanding of the nature of transmission of, and exposure to, the virus, including at the animal-human-environment interface, from human to human, compartments within humans, duration and sites of shedding and infection and infectiousness of different population subgroups. This affects diagnostics, therapeutics and vaccine development as well as choice of containment measures, clinical management and IPC.

- Research to understand immunity to, and pathophysiology of, the virus including development of, reliable serological testing as well as assays that monitor response to treatment and prognostic markers. These are needed for development of therapeutics and vaccines as well as to guide IPC and clinical management.

- Social sciences research to better understand how to enhance acceptability of, and adherence to, management, IPC and public health measures, and simultaneously how to minimize stigma and prejudice. This is essential to put evidence-based measures into practice for successful disease prevention and control.

- Development of assays and animal models required to develop therapeutics and vaccines. This critical cross-cutting area is dependent on access to reagents such as virus isolates, panels of clinical samples, research reagents and quality control reagents.

- Research to provide consensus best practice methodology for clinical trials established to answer priority questions. Without the highest quality trial design, the global community cannot have confidence that priority questions will be answered accurately and in time. This includes harmonization around core elements of Master Protocols.

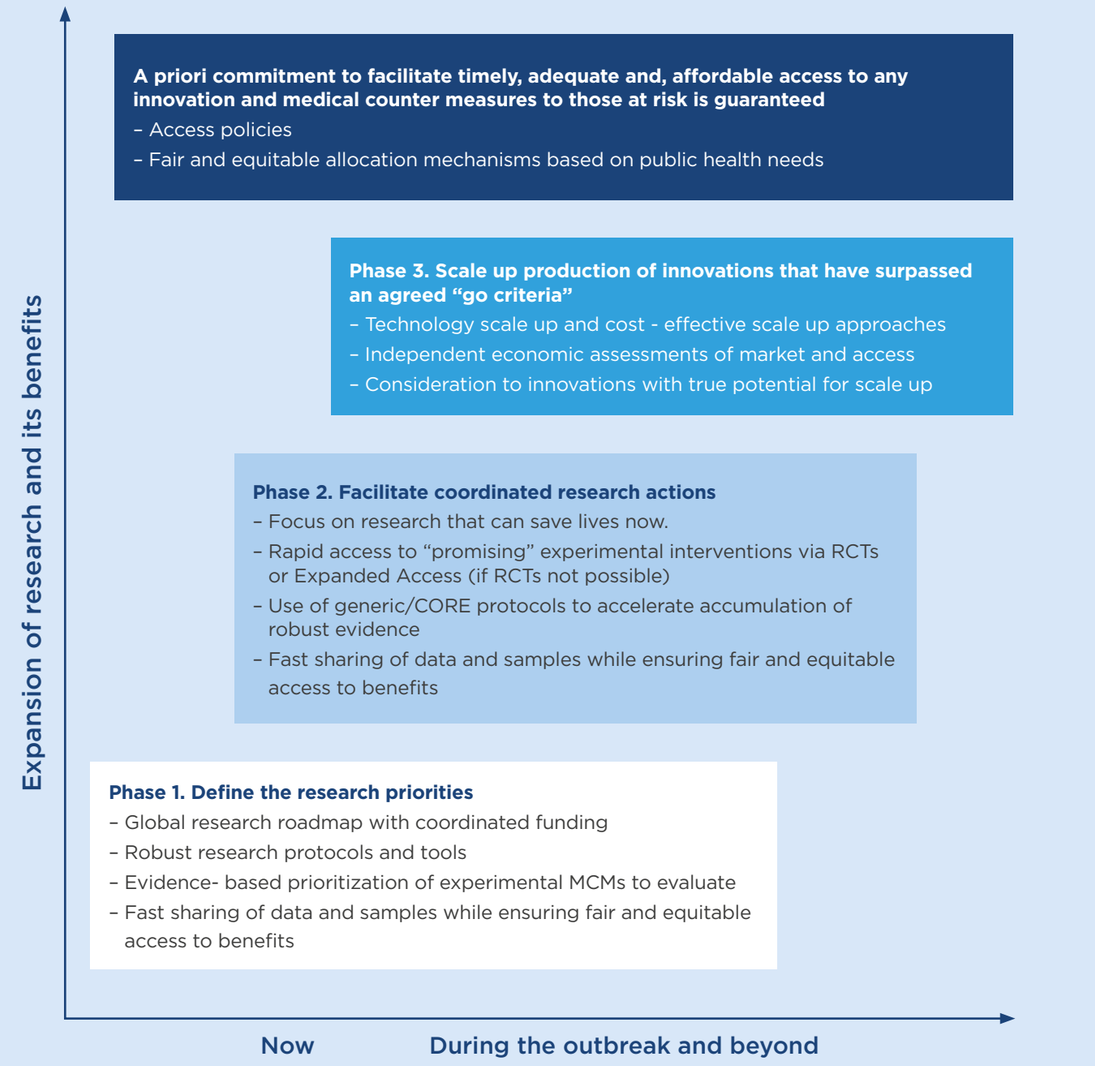
- An enabling priority on access to information, reagents, tools, protocols and standards without which none of the above can proceed efficiently.

- Throughout the thematic areas a recurring theme was the need to prioritize vulnerable population subgroups. The highest priority subgroup was considered to be health care workers without whom essential care cannot be provided. The global research community must at all times prioritize research that will protect and care for the staff who themselves are caring for populations suffering from COVID-19 disease. Other subgroups include those suffering from stigmatization, the elderly, those with co-morbidities and the immunocompromised. While research into children is also a priority, at the time of writing they have not been identified as a high-risk group, so the priority question for children may be whether they form an important link in transmission chains.

Scaling up research and innovation actions

Beyond the identification of critical research actions presented in this Roadmap, a coordinated end-to-end phased approach is needed to promote that any effective innovation can be scaled-up and be available as soon as possible

Figure 3. Implementation of critical research and key implementation phases



Timeline for implementation of selected research actions

Thematic area of research	Expected month for completion	Activity description
Candidate therapeutics	February-20	Master Protocol for evaluation of candidate therapeutics is available.
Candidate therapeutics		Data on Safety and efficacy of candidates (RCTs) are produced and analysed.
Data sharing		Monitor compliance with research data sharing norms.
Ethics considerations for research		Expedited evaluation of protocols.
Candidate therapeutics		Promote adequate supply of therapeutics showing efficacy with overview of available supply and production capacity. Negotiate agreements with manufacturers to facilitate access and long-term availability on reasonable/ equitable terms.
Candidate vaccines		Global TPP building on experience from MERS and Disease X.
Ethics considerations for research		4-pager on WHO ethics guidance for COVID-19.
Social sciences in the outbreak response		Establish mechanisms for dialogue and input into all relevant thematic areas (key focus areas: public health, clinical care and health systems, media and communications, engagement, sexual and reproductive health, international coordination)
Data sharing		Develop repository list of entities holding isolated novel corona viruses and other relevant materials, and related data and information.
Clinical management	March-20	Agree core clinical outcomes to be reported to WHO from all clinical datasets.
Ethics considerations for research		Four brief papers on key explanations of ethical values for COVID-19 (equity, solidarity, trust, vulnerability).
Virus natural history, transmission and diagnostics		Virus natural history, transmission and diagnostics
Virus natural history, transmission and diagnostics		Establish appropriate controls and EQA systems.
Candidate therapeutics		Candidate therapeutics identified for clinical studies.
Candidate therapeutics		Master Protocol for prophylaxis is available.
Candidate vaccines		Prioritization criteria for vaccine evaluation.
Candidate vaccines		Trial design synopsis for vaccine evaluation.
Ethics considerations for research		Trial design synopsis for vaccine evaluation.
Candidate therapeutics		Repository of data from in vitro/in vivo testing available to refine work of global community assumes continuous updates.

Thematic area of research	Expected month for completion	Activity description
Epidemiological studies	March-20	Modeling studies to consider measures to protect HCWs and other critical societal functions.
Clinical management		Preliminary data collection on aerosolization with high flow O2.
Clinical management		RCTs for steroids and high flow O2 – initiation.
Epidemiological studies		Cohort studies to clarify pre-symptomatic/ asymptomatic transmission.
Epidemiological studies		Retrospective review of hospital admissions to identify risk factors for severe disease.
Candidate vaccines		Animal models for both efficacy and disease enhancement-landscape and way forward.
Clinical management	April-20	Observational cohorts with viral sampling to better understand pathophysiology, risk factors for severe disease, shedding, explore best options for triage processes, and optimal specimen sampling strategies.
Virus natural history, transmission and diagnostics		Development and validation of kits meeting TPPs.
Candidate therapeutics		Prioritized potential combinations identified.
Candidate therapeutics		In vitro and In vivo combination testing data are available.
Candidate vaccines		Assay development and validation required for vaccine R&D.
Candidate vaccines		Vaccine Phase 2b/3 Master Protocol.
Ethics considerations for research		Vaccine Phase 2b/3 Master Protocol.
Candidate therapeutics	June-20	Adequate animal models available (mapping first then models testing).
Virus natural history, transmission and diagnostics		Distribution of kits meeting TPPs.
Virus natural history, transmission and diagnostics		Point of care testing available.
Virus natural history, transmission and diagnostics		Multiplex detection assays available.
Virus natural history, transmission and diagnostics		Shedding and replication compartment studies – results.
Virus natural history, transmission and diagnostics		Support to sequence sharing platforms including GISAID.
Virus natural history, transmission and diagnostics		Harmonization/standardization or EQA system for ELISA.
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Animal serological screening
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Inventory of banked animal samples for coronaviruses in bats and other wildlife in southern Asia.
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Data on diversity, number and origin of animals sold in live markets in China and South-East Asia.
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Animal-human-environment related risk awareness and information campaigns.
Epidemiological studies		Household transmission studies to determine role of different age groups in transmission.
Epidemiological studies		Prospective studies in different settings to estimate effects of alternate social distancing measures, and comparative analysis of impact of interventions.

Thematic area of research	Expected month for completion	Activity description
Candidate therapeutics	July-20	Standard protocols for in vitro testing/in vivo testing
Candidate therapeutics		Data on safety and efficacy of prophylaxis are available.
Data sharing		Promote sustainable sequence sharing platforms including public domain and public access models (such as GISAID).
Clinical management		Agree core clinical outcomes to be reported to WHO from all clinical datasets.
Ethics considerations for research		Four brief papers on key explanations of ethical values for COVID-19 (equity, solidarity, trust, vulnerability).
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Options for improved biosafety in live animal markets identified.
Virus natural history, transmission and diagnostics		High throughput and automation.
Infection prevention and control, including health care workers' protection		Effectiveness of movement restrictions determined through systematic reviews, surveys, ecological studies.
Candidate therapeutics		Data on safety and efficacy of combination therapies (RCTs).
Data sharing		Establish an evaluation of new model of information sharing including use of preprints to determine if new norms require modification case studies.
Animal and environmental research on the virus origin, and management measures at the human-animal interface	August-20	Options for improved biosafety in live animal markets piloted.
Virus natural history, transmission and diagnostics		Devices available to measure prognostic markers.
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Description of wildlife trade and its drivers in China and SE Asia.
Animal and environmental research on the virus origin, and management measures at the human-animal interface.		Risk factors for animal-human infection identified.
Infection prevention and control, including health care workers' protection		Effectiveness of specific PPE determined through systematic reviews, observational studies, case-control studies.
Infection prevention and control, including health care workers' protection		Effectiveness of activities to minimize the role of the environment.
Infection prevention and control, including health care workers' protection		Collaboration with social science groups on increasing compliance with evidence-based IPC measures through qualitative approaches to determine possible interventions.
Ethics considerations for research		Activate PHE Ethics network for COVID-19 - case studies.
Animal and environmental research on the virus origin, and management measures at the human-animal interface	November-20 February-21	Animal model studies on origin/routes of transmission.
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Additional sampling to identify animal reservoir.
Animal and environmental research on the virus origin, and management measures at the human-animal interface		Options for improved biosafety in live animal markets implemented with trainings.

Midterm and longterm priorities to contribute to control the outbreak

1. Virus natural history, transmission and diagnostics

a. Support development of diagnostic products to improve clinical processes.

b. Understand virus compartments, shedding and natural history of disease.

c. Develop tools and conduct studies to monitor phenotypic change and potential adaptation.

d. Characterize immunity (naturally acquired, population and vaccine-induced, including mucosal immunity).

e. Develop disease models (animal models and 3Rs approaches).

f. Virus stability in the environment.

2. Animal and environmental research on the virus origin, and management measures at the human-animal interface

a. Identify animal source and route of transmission (hosts, any evidence of continued spill over to humans and transmission between animals and humans).

b. Improve understanding of socioeconomic and behavioural risk factors for spill over and transmission between animals and humans (identify the risks linked to trade and consumption of potentially infected animal species and the communities or occupational groups more at risk across different interfaces).

c. Design and test suitable risk reduction strategies at the human-animal-environment interface, accordingly (limit infection in high risk areas and for at risk populations and the public).

3. Epidemiological studies

a. Describe transmission dynamics of COVID-19 and understand spread of disease nationally, regionally and globally (relative importance of pre-symptomatic/asymptomatic transmission, identify suitable cohorts and prospectively collect laboratory and outcome data).

b. Describe disease severity and susceptibility to facilitate effective clinical and public health response to COVID-19 (groups at high risk of severe infection, role of different age groups in transmission, household and serologic studies, retrospective review of hospital admissions and patient recovery data).

c. Evaluate impact of control and mitigation measures (predict the most effective measures to reduce the peak burden on healthcare providers and other societal functions, estimate the effects of social distancing measures and other non-pharmaceutical interventions on transmissibility, modelling research, prospective study in school/work and other closed settings, comparative analysis/impact assessment for intervention measures).

4. Clinical Management

a. Define the natural history of COVID-19 infection (Prognostic factors for severe disease, special populations, triage and clinical processes, sampling strategy).

b. Determine interventions that improve the clinical outcome of COVID-19 infected patients (viral load, disease and transmissibility, markers of protection).

c. Determine optimal clinical practice strategies to improve the processes of care (Improve processes of care, including early diagnosis, discharge criteria, optimal adjuvant therapies for patients and contacts).

d. Determine how best to link key research questions with researchers in affected regions who are able to recruit patients

e. Develop platform(s) to maximize commonality of data collection across trials, and collaborations between trials.

5. Infection prevention and control, including health care workers' protection

a. Understand the effectiveness of movement control strategies to prevent secondary transmission in health care and community settings (Effectiveness of restriction of movement of healthy exposed and infected persons to prevent secondary transmission - home, congregate setting, geographical restriction vs nothing).

b. Optimize the effectiveness of PPE and its use in reducing the risk of transmission in health care and community settings.

c. Minimize the role of the environment in transmission of the COVID-19 virus.

d. Understand behavioural and cultural factors influencing compliance with evidence-based IPC measures.

6. Candidate therapeutics R&D

a. Identification of candidates for clinical evaluation in addition to the ones already prioritized.

b. Multicentre Master Protocol to evaluate efficacy and safety.

c. Coordinated collaboration to implement clinical trials, for evaluation of safety/efficacy of therapeutics.

7. Candidate vaccines R&D

a. Identification of candidates for clinical evaluation in addition to the ones already prioritized.

b. To develop a multi-country Master Protocol for Phase 2b/Phase 3 vaccine evaluation to determine whether candidate vaccines are safe and effective before widespread distribution, using methodologically sound and ethically acceptable vaccine trial design. Vaccine efficacy trials should be done if such are feasible to implement.

To develop and standardize animal models to evaluate the potential for vaccine and therapeutics effectiveness and to understand the potential for enhanced disease after vaccination.

Results from animal models are expected to be important prior to large-scale efficacy studies and prior to studies in which enhanced disease is considered a significant possibility.

To develop and standardize assays to support vaccine development, particularly to support the evaluation of immune responses and to support clinical case definition. Basic reagents should be shared to accelerate the development of international standards and reference panels that will help support the development of ELISAs, pseudovirion neutralization and PCR assays.

To develop potency assays and manufacturing processes to rapidly enable the production of high-quality large quantities of clinical grade and GMP materials.

8. Ethics Considerations for Research

a. To enable the identification of key knowledge gaps and research priorities. (Articulate and translate existing ethical standards to salient issues in COVID-19, The impact of restrictive public health measures (e.g., quarantine, isolation, cordon sanitaire).

b. To formulate a clearly defined research governance framework which enables effective and ethical collaboration between multiple stakeholders, including WHO, the global research community, subject matter experts, public health officials, funders, and ethicists.

c. Sustained education, access, and capacity building to facilitate effective cross-working and collaboration across the research thematic areas.

9. Social Sciences in the Outbreak Response

a. Generate high-quality evidence to achieving the goals of the strategic public health response plan.

b. Promote the prioritization of knowledge needs according to epidemic dynamics.

c. Promote that knowledge is produced according to local, national and regional needs.

d. Promote that knowledge outputs and methodological limitations are easily understood by non-social scientists.

e. To develop and employ strong methodologies and theoretical frameworks to tackle current epidemic challenges.

f. Develop innovative interdisciplinary science.

g. Develop guidelines and Standard Operating Procedures (SOPs) to operationalized epidemic mitigation mechanisms.

h. Develop and connect global research networks with response partners.

i. Engage with communities to bring their voices to decision-making processes.

j. To understand non-intended consequences of epidemic-control decisions.

k. Understand contextual vulnerability.

l. Understand how decisions in the field may inadvertently undermine response goals.

m. Understand how social and economic impacts can be mitigated.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Optimizing funding efforts

The focus is on how the efforts of a large number of the world's funders of global health R&D could be coordinated and optimized.

Considering the geographic extension of this outbreak, coordination is even more paramount as well as leveraging each other's strengths.

It is critical that funders have a heightened sense of urgency and support research actions that have an impact on the epidemic and promote access to life saving innovations.

> "This Global Research Forum allowed us to identify the main urgent priorities for research. As a group of funders, we will continue to mobilize and coordinate to ensure support is in place for all critical research needed to tackle this crisis and stop the outbreak in partnership with WHO."
>
> **Yazdan Yazdanpanah**
> **Chair GLOPID-R**

The following actions are needed:

- **A coordinated funding system to prepare and respond to epidemics more effectively.**
- **Funding that focuses primarily on identified research priorities, avoids silos and unhealthy competition, and encourages multidisciplinary collaboration.**
- **Improved coordination for the launching of emergency funding calls.**
- **Considering simplification and use of generic application forms.**
- **Issuing of grants which includes clauses that promote timely sharing of research data relevant to the outbreak response.**
- **Regularly convening funders to facilitate coordination of efforts and transparent information exchanges via the Global Coordination Mechanism (GCM) of the WHO R&D Blueprint.**

GLOPID-R is coordinating funders to optimize resources, avoid duplication, cover priorities listed in the R&D Blueprint research roadmap and, contribute to the Global Coordination Mechanism (GCM).

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Table 2. Emergency calls launched by GloPID-R Members as of 4 March 2020

Organization	Amount of the call (in Millions)	Main priorities identified/Scope
BMGF	60 USD	Accelerate development of diagnostics, therapeutics and vaccines. R&D funding to help global partners.
DFID / Wellcome Trust	15 GBP	Clinical research (optimising clinical mgmt, population cohort studies)/development of treatments (understanding impact in moderate severe cases)/pathogenesis/ epidemiology/social sciences and ethics (impact, RCCE, response implementation)
European Commission	10 EUR	Development of therapeutics/point of care diagnostics/clinical and epidemiological studies/social sciences
European Commission (through IMI)	90 EUR	therapeutics, diagnostics
CIHR	6.8 USD	Medical countermeasures Social and policy countermeasures
UK-MRC Funded by DHSC through NIHR and UKRI	20 GBP	2 calls: 1. Active intervention development 2. Diagnosing and understanding COVID-19
AMED Japan	5 USD	Rapid diagnosis kit antiviral treatment Vx Dx Tx
France - Ministry of R&I and MoH	0.5 EUR	seed funding
CEPI	Unknown	Vaccine development
NIH	N/A (no set ceiling)	• Broad - basic pathogenesis, surveillance & ecological studies (including animal:human interface) animal model development, assay development, therapeutics and vaccine development. • Diagnostic, therapeutic and vaccine development for SARS-CoV-2
Germany	10 EUR	• Therapeutics, diagnostic, infection and transmission control measure, Epidemiological approaches • Research on ethical, legal and socio-economic

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Governance

A myriad of stakeholders play important roles in research and innovation during outbreaks. Those include but are not limited to: communities affected by the outbreak; national and international researchers and research institutions; Member State governments; multilateral agencies including WHO, humanitarian organizations; charitable foundations; developers and manufacturers from public and private sectors; multilateral organizations; and numerous collaborative research networks. Each stakeholder brings with it different and, at times, conflicting values, perspectives and priorities, adding yet a further layer of complexity. Tensions can arise out of the need to balance high costs associated with research and innovation, the need for resources to respond to the outbreak, and the concern that these innovations are affordable and accessible to those at highest risk. It is both a crucial and a rather complex task to differentiate between those interventions that are purely research and those that are response.

> The global scale of the epidemic and the unprecedented level of global collaborative commitment to research and innovation calls for a reset of the functional model for global coordination. It should clarify roles and responsibilities, enhance inclusiveness and openness, while retaining the ability for rapid decision making to drive action at the appropriate level.

Research will be an integral part of the outbreak response structure and system, although it requires a different expertise than would be needed to govern emergency response alone. Such governance structure is needed to complement specialization and encourage collaboration between outbreak response and research, with existing policy making forums at WHO.

Improving coordination and fostering an enabling environment

The R&D Blueprint established a Global Coordination Mechanism (GCM) to facilitate a regular dialogue among main stakeholders for both R&D preparedness and response to emerging diseases. During this outbreak, the GCM will continue to facilitate the information sharing. Within the GCM, GLOPID-R will coordinate the contributions by various funders – including those who are not members - and monitor financial support for critical research.

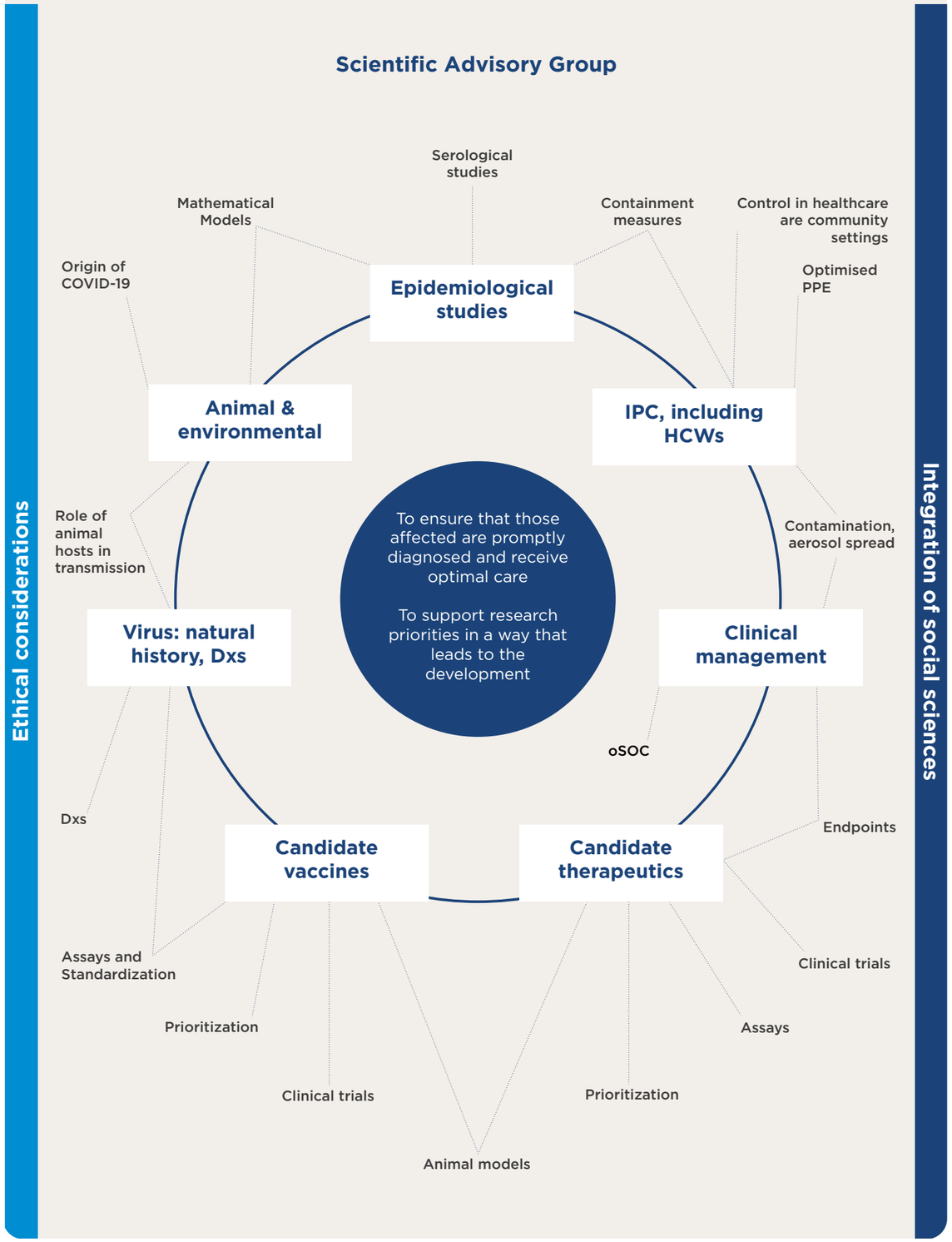
Scientific Advisory Group (SAG) of the WHO R&D Blueprint

WHO has convened a broad global coalition of experts to develop and implement the R&D Blueprint and a platform for accelerated research and development. The SAG provides strategic and scientific advice on research priorities and strategies. During this outbreak, the SAG will review the progress made towards the priority research and provide advice to WHO on additional prioritization of research actions for this outbreak.

The SAG recommendations inform the wider outbreak response efforts through its contributions to the Strategic and Technical Advisory Group for Infectious Hazards (STAG-IH). The STAG IH was created following the recommendation of the Review Committee on the Role of the International Health Regulations (2005) in the Ebola Outbreak and Response (WHA69/21). The STAG-IH provides independent advice and analysis to WHO Health Emergencies Programme on the infectious hazards that may pose a potential threat to global health security.

For the COVID-19 outbreak, the multidisciplinary contributions of hundreds of scientists and institutions worldwide have been structured in Working Parties called “Thematic Areas”. Within each Thematic Area, specialized ad-hoc independent expert groups are created to address each research priority. Given the interdependence of the various research areas and the need for a multi-disciplinary approach there is ongoing collaboration between experts in the various Thematic Areas. Each Thematic Area has two Chairs and report regularly to the SAG on progress and challenges. The establishment of a common database or web-based platform highlighting all ongoing research activities from the different research groups and thematic areas would facilitate effective collaboration and communication with the different groups being informed on parallel research efforts and enabled to unify efforts.

Figure 4. Schematic depiction of Thematic Areas and selected ad hoc independent expert groups under the leadership of the SAG



Virus natural history, transmission and diagnostics

State of the art

Several in-house RT-PCR assays were developed and in use within days of the publication of the whole genome sequence. Commercial lyophilized formulations are available on a research use only basis. In vitro diagnostic-qualified products are in the pipeline. WHO is distributing such assays to make them available in underserved areas. Point of care solutions could take the form of automated PCR instrument solutions or enhanced immunoassay for the detection of viral antigens. Virus isolation capacity is available in reference centres; COVID-19 virus is easy to isolate early in disease progression. Generic sequencing capacities are widely available and would be easy to scale up. In all these provisions there are severe bottlenecks in logistics e.g. a commitment to share the virus may take 2-3 weeks to fulfil due to limitations in personnel.

Knowledge gaps

Clinical virus detection

- Compartments of replication: Throat and sputum are known compartments of replication, but it needs to be known where else the virus replicates. Virus is not readily present in blood or urine but may be present in stool.
- Prognostic information from viral load or viral load trajectories: this is needed to create profiles of disease severity.
- Prognostic information from immuno-markers.
- Infectivity surrogates, discharge criteria: The degree to which viral load in the upper vs. lower respiratory tract can be relied upon as a surrogate marker for infectivity.
- Treatment-related monitoring: detecting escape mutants (in-vitro, empirical) and genotypic-to-phenotypic approaches.
- Phenotypic change: Link genetic markers to phenotypic reduced sensitivity to certain antivirals. More information is also needed on virus and host characteristics predicting virulence traits or severity of disease.
- Diagnostic drift: PCR assay compatibility could change over time due to mutations in probe or primer binding sites.
- There is a need to avoid that assays lose performance due to mutations. This remains true for commercially manufactured kits, which may not be as rapidly adaptable as in-house PCR and may be less likely to have published primer/probe sequences. This threat is minimized by creating PCR assays targeting conserved regions which are relatively stable.

Immunity and immune diagnostics

- Strength and duration of immunity is not clearly understood.
- Cross-reactivity gives importance to pre-existing immunity against heterologous human coronaviruses.
- Work is needed to create reliable antibody assays.
- The relevance of cellular immunity can be measured by cell-level surrogates (ELISpot etc.)
- The role of innate immunity to this class of virus needs testing.
- There may be added value in advanced immunity assays (e.g., whole proteome arrays).
- Sero-specificity and costimulation or crossreactivity in serological diagnostics.
- Technical gaps: simple IFA, differential IFA, ELISA, Neutralization assays, Neutralization assay surrogates including pseudotypes and competitive ELISA.

Tools for infection control

- Virus stability is incompletely studied (physical, chemical inactivation) but is likely to be comparable to SARS.
- Surrogate viruses (animal coronaviruses) may be useful for stability studies (BCoV, MHV, etc.)
- The infectivity of RNA needs study.
- Technical gaps: Infectivity assays (cell culture models, animal models).

Engineered solutions to clinical diagnostics

- High throughput and automated PCR analysis in hospitals.
- Point of care testing.
- Respiratory pathogens multiplex detection.
- Devices related to prognostic markers.
- Digital solutions for field lab assistance.
- Bedside and lab-based sequencing approaches.

Ongoing research efforts

The following studies are ongoing.

- Descriptive patient-centred studies based on individual cases or opportunity-driven cohorts
- Implementation-related work including validation of in-house protocols, validation of kits, logistics, reference laboratory services and, provision of virus and reference material through European Virus Archive.

Research priorities

Research priority	Why?	What type of studies/research are needed?
1. Support development of products to improve clinical processes	Supports containment measures, improving clinical management and development of interventions.	Impactful diagnostic countermeasures (e.g. POC tests, multiplex assays, effective serologics). R&D for development, partnering with industry. Sequencing to monitor genotypic change.
2. Shedding, natural history of disease	Supports clinical management and development of interventions. Knowledge about how the virus spreads and when patients cease to be infectious is a high priority need for clinical management of cases and for epidemiologists.	Observational trials. Correlation against detection, viral load and infectivity.
3. Tools and studies to monitor phenotypic change and potential adaptation	Supports clinical management and development of interventions. Newly emerged virus may change as it circulates. Important to track changes in virulence and possible drug resistance, implications for vaccines.	Treatment related monitoring. Reverse genetics (challenging).
4. Immunity	Supports public health measures, clinical management and development of interventions. Vital for tracing spread of the virus and informs vaccine development.	Strength and length of immune reaction, serospecificity.
5. Disease models	Supports clinical management and development of interventions. Support a range of studies in transmission and diagnostics, as well as the development of vaccines and therapeutics.	Small mammals, primate, respiratory tract models.

Other research priorities

- Virus stability (physical, chemical inactivation)
  - Surrogate virus studies were discussed, but the priority is studies that don't need validation i.e. those of Covid-19 itself
  - Monoclonal antibodies for mapping of virus antigenic characteristics

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

What are the key milestones per research priority

Research priority	Immediate steps	Mid- to long-term steps
Support development and implementation of products to improve clinical processes	• Determine profile of diagnostic products needed in the short and long term (TPP). • Development and validation of diagnostic kits meeting those needs (RUO and IVD-grade). • Distribution of reagents and test systems through mechanism that values quality and performance (against TPP). • Establish test stable, quantifiable, universal controls for assay qualification, proficiency testing and external quality assurance.	• Adapt TPP for epidemiologic situation as it evolves for this virus (endemicity, mortality). • High throughput and automation of virus detection. • Point of care testing for virus. • Respiratory pathogens multiplex detection. • Devices related to prognostic markers. • Development of assays to support vaccine trials.
Shedding, natural history of disease	• Establish compartments of replication, timing and quantification of viral shedding, receptor and coreceptor usage. • Specific assays for infectivity to define discharge criteria. • Observational trials to describe shedding patterns based on different patient groups and conditions (including performance of diagnostic tools).	• Biomarkers for clinical outcome and clinical trials stratification.
Tools and studies to monitor phenotypic change and potential adaptation	• Surveillance studies to characterize virus sequence evolution, including maintenance of existing platforms (i.e. GISAID) and support to information and materials sharing mechanisms.	• Harmonization of metadata related to virus sequence and disease phenotype. • Functional assays for essential virus features related to human adaptation (receptor affinity, cell tropism, immune interaction, virus isolation and replication studies including reverse genetics).
1. Immunity	• Characterization of naturally acquired immunity (humoral and cell-mediated; duration and kinetics of immune response).	• Characterization of population immunity and vaccine-induced immunity (humoral and cell-mediated). • Characterization of mucosal immunity.
2. Disease models	• Animal models for infection, disease, and transmission, and generation of biological materials. • 3R approaches including organoids, ex-vivo explant models, etc.	

Animal and environmental research

On the virus origin, and management measures at the human-animal interface

State of the art

COVID-19 (SARS-CoV-2) is likely to be a coronavirus of bat origin, exhibiting 96.2% full genome identity with a clade 2b β-CoV from Rhinolophus affinis bats in Yunnan, China. Table 1 provides a more comprehensive overview of genomic homology with other viruses.

% homology with				Source
SARS	MERS	Bat SARS-like CoV*	BatCoV RaTG13	
N.R.	N.R.	89.1%	N.R.	(Wu, et al. 2020)
79.0%	51.8%	87.6-87.7%		(Ren, et al. 2020)
82%	N.R.	89%	N.R.	(Jiang, Du and Shi 2020)
82%	N.R.	89%	N.R.	(Chan, et al. 2020)
79%	50%	88%	N.R.	(Lu, et al. 2020)
N.R.	N.R.	N.R.	96.3%	(Paraskevis, et al. 2020)
<80%	N.R.	N.R.	96.2%	(Zhou, et al. 2020)
79.7%	N.R.	87.9%	N.R.	(Chen, et al. 2020)

All clade 2b CoVs have been found in bats, with the exception of SARS-CoV. More than 500 CoVs have been identified in bats in China, with estimates of unknown bat CoV diversity reaching >5,000. Furthermore, Rhinolophus species are abundant and diverse in South China and across Asia, the Middle East, Africa and Europe, with Southwest China and neighbouring countries likely the centre of evolutionary diversification of clade 2b CoVs.

Wang et al. (2018) report a 2.9% bat-CoV seroprevalence in a small sample of rural Yunnan people. Extrapolating human seroprevalence across Rhinolophus spp. hotspots in Southeast Asia suggests there is large scale exposure to bat-CoVs in the community, with potentially several million people in the exposure group.

In the current outbreak, a high proportion of 1st and 2nd generation human cases were linked to the Huanan Seafood Wholesale Market in Wuhan, including 27 out of the 41 initially identified cases (66%). While bats are rare in markets in South China, they are being hunted and sold directly to restaurants for food (Li, et al. 2019), including reportedly in the Huanan Market.

However, while bats may be ancestral hosts of COVID-19, the route of spill-over from animals to humans remains unclear; it may involve other/ intermediate hosts such as domesticated mammals, farmed or hunted wildlife, as seen with civets as an intermediate host for SARS-CoV or camels acting as reservoirs for MERS CoV. Potential candidates have been proposed for COVID-19, based on genomic similarities with related coronaviruses they host (e.g. pangolins), at least for part of their genome. Finally, the original spill over event to humans may not have happened at the market itself but elsewhere, with the market serving as a location for viral contamination and further exposure of humans.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Research priorities

Global objective: Prevent transmission between animals and humans including future spill over and develop a One Health approach for risk reduction strategies at the human-animal-environment interface (virus, epi, ethics, social - e.g. a working group on socioeconomic and behavioural risk factors for spill over and transmission) to help promote multidisciplinary, multisectoral, and 'horizontal' working)

Knowledge gaps

Current unknowns are:

- The animal species of origin of the virus, although Rhinolophus bats appear likely to be at least hosting the ancestor of COVID-19
- The animal species involved in COVID-19 spill over to humans (reservoir host or intermediate host)
- Occurrence of spill-over (one occasion vs. risk of continued spill-over), and current risk associated with animals
- Geographic origin – endemic vs. imported via trade, wider distribution in neighbouring areas, etc.
- Virus maintenance and prevalence in various species of animals (reservoirs(s) and possible intermediate host(s))
- Modalities of transmission between animals and humans
- Risk factors due to animal trade and consumption, especially wildlife/farmed wildlife
- Risk reduction strategies for transmission between animals and humans as well as among different animal species

Ongoing research efforts

Ongoing studies currently are:

- Investigations into genetic relatedness to other animal CoVs (metagenomic, phylogeny, species signatures on samples (barcoding))
- Investigations into host susceptibility (in-vitro, receptor binding studies, cleavage site of the spike (S) protein etc.) and animal infection studies
- Development of serological tests for animal population screening

Research priority	Why?	What type of studies/research are needed?
1. Investigation of animal source and route of transmission	• To identify the animal species involved in the emergence of COVID-19 and clarify transmission pathways from animal reservoirs to potential intermediate hosts to humans.	A – Investigation of possible animal host ranges through 1) viral phylogeny (metagenomic, barcoding) of CoV sampled from a wide variety of animal species (including wildlife, farmed wildlife, livestock, companion animals, stray animals, pests/vermin); 2) virus-cells, receptor bindings (ACE2) in animals; 3) serological screening on multiple species (generic beta CoV + more specific COVID-19-like CoV) plus RT-PCR (CoV family testing followed by specific COVID-19 PCR); B – Confirmation of the role of candidate species through receptor binding affinity, virus persistence, amplification and excretion studies.
	• To increase knowledge about transmission pathways for COVID-19.	Performing additional studies on candidate animal-human interactions, including the persistence of the virus in the environment of this interface.
	• To increase knowledge of the role of bats and other animals as reservoir of CoVs to inform risk reduction strategies.	Identify diversity of COVID-19-like and other CoV's in bats and other animals.
2. Socioeconomic and behavioural risk factors for spill-over	• To identify the risks linked to trade and consumption of potentially infected animal species and the communities or occupational groups more at risk across different interfaces.	A – Analysis of the diversity, number and origin (including countries other than China) of animal species sold in live markets (farmed and wild caught wildlife, livestock) and the various involved actors along the value chain; B – Drivers of wildlife trade (farmed or wild caught) along the supply chain and socioeconomics to inform sustainable interventions to reduce risks associated with this trade and consumption (behaviour change); C – Identification of risk factors for infection, including specific animal exposures (e.g. species contacted, occupational exposures like handling, cleaning cages, butchering, trapping, purchasing at market; other market visits outside of Wuhan Seafood market).
3. Risk reduction strategies at the human-animal-environment interface	• To limit infection in high risk areas and for at risk populations and the public.	A – Develop options for improved biosafety in farms and live animal markets and explore their feasibility (e.g. all-in, all-out strategies, species segregations, clean out/ no overnight rule, partial to full ban of live trade in high-risk species), alternatives to live animal markets, and regulation, monitoring and surveillance of wildlife farming; B – Explore possible community and other occupational interventions; C – Explore feasibility of public communication strategies to reduce wildlife trade.

What are the key milestones per research priority

Research priority	Milestones
1. Investigation of animal source and routes of transmission	• Serological screening (generic beta CoV + more specific COVID-19-like CoV) on a large range of animals plus RT-PCR enable pre-identification of potential animal species candidate.
	• Virological studies (virus isolation, virus kinetic…) and experimental infection provide further indications of possible incriminated species and route of transmission.
	• Inventory of coronaviruses and associated species of bats and other wildlife in Asia and Southern Asia through 1) screening of historical samples and 2) additional sampling.
2. Socioeconomic and behavioural risk factors for spill-over	• Description on the diversity, number and origin of animal species sold in live markets in China and South-East Asia and the actors along the value chain.
	• Description of wildlife trade and its drivers in China and South-East Asia, including possible changes in practices in recent past. • Identification of possible point of intervention for improved biosafety.
	• Risk factors for infection at the human-animal-environment interface identified.
3. Risk reduction strategies at the human animal interface	• Options for improved biosafety in live animal markets i) identified, then 2) piloted and 3) implemented, with training as requested.
	• Animal-human-environment related risk awareness and information campaigns for the public, farmers, and other relevant stakeholders.

Further remarks:

- The experts acknowledged that Veterinary Services in China or other countries in the region currently have other priorities to handle, e.g. animal health emergencies like African swine fever or avian influenza. Research institutions may be involved in field research for COVID-19 in animals or the environment instead. Banked animal (or human) samples taken in China and the South-East Asian region, especially from priority species and taken during the second half of 2019, should be tested retrospectively.

- Some research activities can build on existing data and studies, e.g. work done by PREDICT and others to identify and characterize animal-human-environment interface. Farm and market biosecurity measures / restructuring recommended for avian influenza and other zoonotic diseases are applicable also for other zoonotic pathogens and should be promoted for COVID-19.

- Coordinated multi-centric surveys should be designed to explore changes which may have triggered the emergence of COVID 19.

Essential references

1. Anthony, SJ, CK Johnson, DJ Greig, S Kramer, X Che, H Wells, AL Hicks, et al. 2017. “Global patterns in coronavirus diversity.” Virus Evolution 3 (1): vex012.
2. Chan, JF, KH Kok, Z Zhu, H Chu, KK To, S Yuan, and KY Yuen. 2020. “Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan.” Emerging Microbes and Infections 9 (1): 221-236.
3. Chen, L, W Liu, Q Zhang, K Xu, G Ye, W Wu, Z Sun, et al. 2020. “RNA based mNGS approach identifies a novel coronavirus from two individual pneumonia cases in 2019 Wuhan outbreak.” Emerging Microbes and Infections 9 (1): 313-319.
4. Jiang, S, L Du, and Z Shi. 2020. “An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies.” Emerging Microbes and Infections 9 (1): 275-277.
5. Li, H., E. Mendelsohn, C. Zong, W. Zhang, E. Hagan, N. Wang, S. Li, et al. 2019. “Human-animal interactions and bat coronavirus spillover potential among rural residents in Southern China.” Biosafety and Health 1 (2): 84-90.
6. Li, W, Z Shi, M Yu, W Ren, C Smith, JH Epstein, H Wang, et al. 2005. “Bats are natural reservoirs of SARS-like coronaviruses.” Science 310 (5748): 676-9.
7. Lu, R, X Zhao, J Li, P Niu, B Yang, H Wu, W Wang, et al. 2020. “Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding.” The Lancet pii: S0140-6736(20)30251-8.
8. Paraskevis, D, EG Kostaki, G Magiorkinis, G Panayiotakopoulos, G Sourvinos, and S Tsiodras. 2020. “Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event.” Infection, Genetics and Evolution 79:104212.
9. Ren, LL, YM Wang, ZQ Wu, ZC Xiang, L Guo, T Xu, YZ Jiang, et al. 2020. “Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study.” Chinese Medical Journal.
10. Wang, N., S.Y. Li, X.L. Yang, H.M. Huang, Y.J. Zhang, H. Guo, C.M. Luo, et al. 2018. “Serological evidence of bat SARS-related coronavirus infection in humans, China.” Virologica Sinica 33 (1): 104-107.
11. Wu, F, S Zhao, B Yu, YM Chen, W Wang, ZG Song, Y Hu, et al. 2020. “A new coronavirus associated with human respiratory disease in china.” Nature.
12. Zhou, P, XL Yang, XG Wang, B Hu, L Zhang, W Zhang, HR Si, et al. 2020. “A pneumonia outbreak associated with a new coronavirus of probable bat origin.” Nature.

Epidemiological studies

State of the art

In early January 2020, a novel coronavirus (COVID-19) was identified as the infectious agent causing an outbreak of viral pneumonia in Wuhan, China, where the first cases had their symptom onset in December 2019. The first four cases reported were all linked to the Huanan Seafood Wholesale Market and were identified by local hospitals using a surveillance mechanism for “pneumonia of unknown etiology” established in the wake of the 2003 SARS outbreak (Li et al, 2020).

Whilst the majority of the earliest cases were linked to the seafood market, indicating potential zoonotic transmission, there is evidence that indicates that human-to-human transmission has been occurring, and the epidemic has been rapidly spreading in China and other countries.
On January 23rd, 2020, quarantine of Wuhan and neighbouring cities was introduced to reduce the exportation of cases and help contain the outbreak. To date, this is thought to be the largest quarantine restriction in human history to prevent infectious disease spread exportation of cases and help contain the outbreak.

Key epidemiological parameters

Whilst further research is required to determine the epidemiological parameters of COVID-19, research on early identified cases has led to estimates of key parameters. These are highlighted and grouped into four domains – 1) Transmission dynamics, 2) Severity, 3) Susceptibility and 4) Control measures.

Transmission dynamics

Research undertaken in the early stages of the outbreak, has been used to estimate the early epidemiological characteristics of COVID-19 (Li et al, 2020). Based on 425 cases identified in early January 2020 in Wuhan, the mean incubation period was estimated to be 5.2 days, and in the early stages, the epidemic doubled in size every 7.4 days, with an estimated mean serial interval of 7.5 days (Li et al, 2020). Travel history and case detection of COVID-19 outside in China outside of Wuhan, also estimated the incubation period to be 5.5 days, ranging from 2 – 11.1 days (Backer et al, 2020).

The basic reproduction number (R0) has been estimated to be 2.2 indicating that on average, each patient has been spreading infection to 2.2 other people (Li et al, 2020). Average delays between infection and illness onset have been estimated at around 5–6 days, with an upper limit of around 11-14 days, and delays from illness onset to laboratory confirmation adding a further 10 days on average (Cowling and Leung, 2020). Delays in case detection and hospitalization can increase the risk of disease spread and raise the doubling time of the epidemic. Therefore, there is a need for further research to more accurately characterize estimates for the epidemiological parameters underlying the transmission dynamics of COVID-19 and identify effective control and mitigation measures.

There were early reports of an asymptomatic patient in Germany (Rothe et al, 2020), but there has been limited further research to support this thus far. However, China’s health minister has warned that there may be pre-symptomatic transmission occurring, and it is an urgent priority (Cowling and Lueng, 2020). Therefore, it is a matter of public health importance to determine whether asymptomatic or pre-symptomatic transmission is potentially happening, and the impact it has on transmission dynamics.

Disease severity

In order to determine the public health impact and the response required, characterizing the spectrum of clinical manifestations and disease severity of COVID-19 infections, and the factors (demographic, location etc.) associated is crucial. At present, the case fatality ratio (CFR) estimates are uncertain, and there are varying estimates, and limited data. A recent study in Wuhan, China, indicated that CFR was 14% (95% credible interval: 3.9-32%) among hospitalized cases (Wu et al. 2020), compared to an approximate overall CFR of 2.8% in China (Wang et al. 2020), and 1.4 (95% credible interval: 0.6-3.2%) outside of mainland China (Wilson et al. 2020). Several factors could affect these estimates (for example the likely underestimation of the number of cases or the lack of standardised case definition) which should be considered with caution.

Infection Fatality Ration (IFR) estimated at 1% (Imperial group), given the R0 of 2-3, suggests an attack rate of 75-80%, in the absence of any interventions and assuming homogeneous mixing, which are both unlikely in reality.
Early studies have also found that patients with underlying conditions such as diabetes, hypertension and cardiovascular disease had more severe infections, and the disease was more common in men. Very few cases have been reported in children. There is currently limited understanding of severity between different demographics, and which groups may be high risk.

Susceptibility

At present, little is known about susceptibility to COVID-19. Early studies have found that very few cases have been reported in children (Cowling and Leung, 2020). This may indicate that they are potentially less susceptible to the disease, naturally immune, or that they are infected but asymptomatic. If they are less susceptible or immune, there is a need to understand this further, particularly following the school closures implemented as a social distancing measure to curb the spread of infection. However, if they are infected but asymptomatic, it would be pertinent to determine if they are infectious and participate in the disease transmission.

Control and mitigation measures

Since the outbreak in Wuhan, a wide variety of measures have been put in place to prevent and reduce transmission. This includes large scale quarantine, travel and mobility restrictions, airport entry screening and social distancing measures such as school closures and work from home arrangements. Travel restrictions have been found to moderately slow down the dispersal of COVID-19, and mobility restriction in China was found to have slowed the spread from Wuhan to other cities in China by 2.9 days (Tian et al, 2020).

Another study indicated that as of 23rd January 2020 most Chinese cities had already received a large number of infected cases, and that travel quarantine delayed overall epidemic progression by only 3-5 days. The travel restrictions have had a more marked effect on an international scale, with modelling indicating that the number of case importations would be reduced by 80% by the end of February 2020. However, these modelling results also indicate that sustained 90% travel restrictions to and from mainland China only modestly affect the epidemic trajectory unless combined with a 50% or higher reduction of transmission in the community (Vespignani et al, 2020).
Airport screening measures have also been implemented by several countries, and the most recent data indicates that 46% of infected travellers would not be detected by airport screening (Quilty et al, 2020). This suggests that unlike the 2009 H1N1 epidemic, which found that airport entry screening was associated with an average delay of 7-12 days in local transmission (Cowling et al, 2010), for COVID-19, airport screening is unlikely to detect a sufficient proportion of infected travellers and prevent entry of infected travellers. Some countries have decided to raise the threshold for airport screening, to capture those with potentially less severe symptoms. This may have greater impact on disease transmission through air travel, but this requires further investigation to determine whether this makes a difference.

Additionally, social distancing measures have been implemented across China, including school and workplace closures. However, impact of these measures, including which are most effective is yet to be determined.

Dealing with previous respiratory pandemics, WHO issued guidelines for considerations for mass gatherings in the context of pandemic (H1N1) 2009 influenza that provide some guidance for the current event. In addition, WHO developed a complementary document outlining key planning considerations for organizers of mass gatherings in the context of the COVID-19 outbreak (available here: https://www.who.int/publications-detail/key-planning-recommendations-for-mass-gatherings-in-the-context-of-the-current-covid-19-outbreak).

Knowledge gaps

Transmission dynamics

- What is the relative importance of pre-symptomatic and asymptomatic transmission – does this exist and what is the impact? Can asymptomatic carriers shed virus and infect?
- What is the role of different age groups in transmission of COVID-19?
- What are the different modes of transmission of COVID-19?
- What is the cause, or what are the conditions that lead to super spreading events? What is their contribution to disease spread?
- What are the most accurate estimates of R0?
- What are the epidemiological time delays (e.g. onset to illness or onset to case detection delay, onset to hospitalization), and what impact does this have on epidemic doubling time?
- What are the environmental conditions associated with increased transmission (e.g. temperature and humidity; seasonality)?

Severity

- What is the spectrum of the clinical manifestations of disease? What are the clinical manifestations of mild to severe disease? (severity profile)
- How is severity mediated by either demographic factors (age, sex, other groupings), or pre-existing conditions?
- Who are the groups at high risk of severe disease?

Susceptibility

- Are children less susceptible to COVID-19? If so, why? If they are susceptible but asymptomatic, are they infectious? Do they shed virus?
- Does infection confer neutralizing antibodies? Are there antibody dependent enhancements to disease and infection?

Control and mitigation measures

- What social distancing measures have been most effective at preventing or reducing spread of COVID-19? If children are less susceptible or not infectious, should schools remain closed?
- How effective are international travel related measures at slowing spread?
- What community mitigation measures can best reduce local spread of disease?
- What control and mitigation measures are associated with reduced the effective reproductive (Rt)?
- What is the effectiveness of personal measures such as social distancing and face masks/PPE?

Ongoing research efforts

Transmission dynamics

- Mathematical modelling to estimate transmission parameters from different locations (Li et al, 2020; Wu et al, 2020; Imai et al, 2020; Read et al, 2020)
- Family cluster studies to determine human to human transmission (Chan et al, 2020)
- Case studies (suspected asymptomatic patient) (Rothe et al, 2020)
- Viral shedding studies (planned)

Severity

- Retrospective single centre case series to determine clinical characteristics (Wang et al, 2020)
- Prospective case control study to determine clinical featured of COVID19 (Huang et al, 2020)
- Population wide surveillance to determine severity
- Reports from clinical cohorts (for example, WHO initiated a study looking at evacuated cohorts)

Susceptibility

- Household transmission studies to determine differences in susceptibility, including secondary attack rates and paediatric infections
- Convalescent and population-based serological studies

Control and mitigation measures

- Modelling analysis to determine impact of large-scale quarantine in China - comparisons of different locations and mitigation measures (Wu et al, 2020)
- Modelling to determine impact of Wuhan travel restrictions (Tian et al, 2020)

Research priorities

Six key research priorities were identified for epidemiological studies for the COVID-19 outbreak, and these were grouped according to the four key domains of transmission dynamics, severity, susceptibility and control and mitigation measures.

	Research priority	Why?	What type of studies/research are needed?
Transmission dynamics	**Clarify the relative importance of pre-symptomatic/ asymptomatic transmission (including distinction between virus shedding and infectious transmission)**	If asymptomatic/ pre-symptomatic transmission is possible, risk of epidemic spread is significantly higher, Important to understand this to accurately understand transmission dynamics for public health & hospital infection control.	Detailed reports of transmission events and symptomatic status of infectors; viral shedding data; special studies in households, Cruise and other closed settings; detailed analysis for clusters. Of note, WHO initiated a study looking at evacuated cohorts, and is undertaking intensive follow-up of individuals captured in the global surveillance system.
Severity	**Identify groups at high risk of severe infection**	Determining the spectrum of clinical manifestations of infections is perhaps the most urgent research priority, as it will determine the strength of public health response required.	Case control studies; cohort studies.
	Determine the role of different age groups in transmission	Important to understand whether there is a different attack rate/ susceptibility between different demographics? E.g. children/ elderly? And other risk factors.	Case control studies; cohort studies.
Susceptibility	**Determine if children are infected, and if so, are they infectious?**	Children currently do not seem to be implicated in transmission of COVID-19 - need to understand if they are potentially infected but asymptomatic and potentially infectious. There are social implications as if they are not, should schools remain closed? Do children shed? Are they infective?	Transmission studies in households and other closed settings; serologic studies.
Control and mitigation measures	**Predict the most effective measures to reduce the peak burden on healthcare providers and other societal functions**	Effective community mitigation measures can reduce transmission and reduce growth rate of epidemic and total no. of infected persons.	Comparative analyses of transmissibility in different locations.
	Estimate the effects of social distancing measures and other non-pharmaceutical interventions on transmissibility	To determine whether the measures are effective and whether they can actually reduce the effective reproductive number – if so, measures can be implemented in other settings/countries.	Comparative analyses of transmissibility in different locations – potentially study those returning to work in different cities at different times, or those schools which closed at different times.

What are the key milestones per research priority

Research priority	Milestones
Clarify the relative importance of pre-symptomatic/ asymptomatic transmission (including distinction between virus shedding and infectious transmission)	• Identify suitable cohorts. • Prospectively collect laboratory and outcome data.
Identify groups at high risk of severe infection	• Retrospective review of hospital admissions. • Review recovery data.
Determine the role of different age groups in transmission	• Establish household transmission studies.
Determine if children are infected, and if so, are they infectious?	• Set up household transmission studies with serial testing. • Retrospective review.
Predict the most effective measures to reduce the peak burden on healthcare providers and other societal functions	• Modelling.
Estimate the effects of social distancing measures and other non-pharmaceutical interventions on transmissibility	• Prospective study in school/work and other closed settings. • Comparative analysis (impact assessment) for intervention measures.

Essential references

1. Li et al, Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia,; NJEM 2020
2. Backer et al,; Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020, Euro Surveill 2020
3. Cowling and Leung,; Epidemiological research priorities for public health control of the ongoing global novel coronavirus (2019-nCoV) outbreak, Euro Surveil l2020
4. Rothe et al, 2020; Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany, NEJM
5. Dorigatti et al Report 4: Severity of 2019-novel coronavirus (nCoV); WHO Collaborating Centre for Infectious Disease Modelling; MRC Centre for Global Infectious Disease Analysis, J-IDEA, Imperial College London, UK 2020.
6. Tian et al. Early evaluation of Wuhan City travel restrictions in response to the 2019 novel coronavirus outbreak, 2020; Pre-print https://www.medrxiv.org/content/10.1101/2020.01.30.20019844v2
7. Vespignani et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (2019-nCoV) outbreak, , 2020; Pre-print https://www.medrxiv.org/content/10.1101/2020.02.09.20021261v1
8. Quilty et al. Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV) separator, 2020; Euro Surveill
9. Wu et al. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study, 2020; The Lancet
10. Imai et al. Report 2: Estimating the potential total number of novel Coronavirus cases in Wuhan City, China, , 2020; WHO Collaborating Centre for Infectious Disease Modelling; MRC Centre for Global Infectious Disease Analysis, J-IDEA, Imperial College London, UK
11. Read et al. Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions, , 2020; pre-print https://www.medrxiv.org/content/10.1101/2020.01.23.20018549v1.full.pdf
12. Chan et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, 2020; The Lancet
13. A novel coronavirus outbreak of global health concern, Wang et al, 2020; JAMA
14. Wu P et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020., 2020; Eurosurveillance. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.3.2000044#r11
15. Wang et al. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, , 2020. Journal of Medical Virology. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25689
16. Wilson et al. Estimating the Case Fatality Risk of COVID-19 using Cases from Outside China, , 2020; MedRixv. https://www.medrxiv.org/content/10.1101/2020.02.15.20023499v1

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Clinical characterization and management

State of the art

Early data on COVID-19 clinical disease is emerging from affected regions. What is becoming clear is that severe illness is not uncommon. Beyond that, reliable data on risk factors for severe illness, biology of clinical worsening, and peak periods of transmissibility remain unavailable.

Anecdotal feedback from clinicians on the ground in China, reported a spectrum of disease, with no gender predilection. Many patients were mild early – but can progress rapidly over a day. Also, evidence of prolonged prodrome, with interval of 7 to 10 days after hospitalization before acute deterioration and requirement for ICU admission. Many patients still hospitalized, so final outcome not known. Severity was reported to be related to the burden of co-morbidities, with progressive disease with increasing age. CT scan was being used as an early diagnostic, proving much more sensitive than chest x-rays. Co-infections were not systematically screened, although a majority of patients had received anti-influenza and anti-bacterial treatments. Processes of care varied, with discharge criteria being changed depending on a variety of factors. Most striking is the varying severity across regions, with non-Hubei cases being notably less sick.

Reference	N	Site/region	ICU	Fatality rate (censored at publication)
Chen et al., Lancet	99	Wuhan	23%	11%
Huan et al., Lancet	41	Wuhan	32%	15%
Wang et al., JAMA	138	Wuhan	26%	4.3%
Guan et al, MedRixv (pre-print)	1099	Wuhan	5%	1.36%
China CDC	72314	China	5%	2.3 % overall; 14.8% in. those 80 years of age; 50% critically ill

Knowledge gaps

Scientific gaps

- Natural history and clinical course particularly in special populations (severely ill, pregnant, children, elderly), (note that JAMA paper from Wuhan shows arrhythmias as complications in 44% - this is not typical for ARDS, viral pneumonia, and needs to be incorporated into treatment plans)
- Optimal selection of anti-viral agents and interventions targeting the virus – convalescent plasma, poly- and monoclonal antibodies, IV-Immunoglobulins. Currently a wide array of treatments being used via compassionate use in the absence of controlled trials
- Optimal selection of strategies for supportive care of seriously ill patients – immunomodulatory agents (IL-1ra, interferon), steroids, ACE inhibitors, vitamin C, statins, or anti-arrhythmics
- Optimal strategies for supportive care interventions such as oxygen therapy, fluid management, invasive vs non-invasive ventilation
- Reducing nosocomial spread
- Viral kinetics and pathophysiology of severe disease.

Operational gaps

- How best to engage existing international networks and research infrastructure in response
- How best to support ongoing trials in China – mentorship, scientific cafes
- How to develop common definitions and endpoints as core study metrics to facilitate rapid pooling and comparing of results
- How to best disseminate findings, including principles of data sharing and accessibility.
- Can we develop common communications hubs to facilitate data sharing and coordination, i.e. pre-clinical data, observational studies in progress, clinical trials in progress (ambulatory, hospital, ICU-based) and mechanism for regular communication amongst these.

As the natural history of illness is being clarified within China, key questions are emerging about COVID-19 infection outside China:

- Do the patchy outbreaks reported so far reflect incomplete case reporting – probability of community spread appears substantial given infectivity (as evidenced by progress of outbreak on Diamond Princess), non-specific early symptoms, lag time before serious illness, and extensive travel connections between China and geographic regions such as Africa.
- An outbreak in countries already facing health-system challenges maybe difficult to recognize.
- Is illness severity less outside of China, or does this simply reflect a prolonged prodrome between symptom onset and severity.

Ongoing research efforts

There are currently over 200 clinical trials registered on the Chinese clinical trials registry, testing a variety of interventions with a variety of endpoints. Outside of China, there is a global data platform facilitated by the World Health Organization with the goal of producing a global cohort of hospitalized patients. Clinical characterization protocols are available to inform sampling strategies and sharing. A number of large-scale randomized trials are being planned, both inside and outside China (see Chinese clinical trials registry for updated information). Epidemiologic studies as conducted by public health authorities have been conducted by the relevant groups in the United States, Europe, and other regions with exported cases.

Prioritization activities for which interventions to study, so as to optimize the outcome of individual patients, from antivirals to immunomodulators to supportive care interventions, are ongoing. In addition, work to coordinate research is ongoing, with the hoped-for standard data variable and outcome collection by a variety of international networks.

The most important issue is ensuring adequate coordination of these efforts to achieve useable results across regions.

Research priorities

Objective 1

Define the natural history of COVID-19 infection

- Clinical characterization of disease in different populations and risk groups, across the spectrum of severity through detailed observational studies.
  - Use standardized data collection tool, such as Case Record Form (CRF)
  - Contribute to the WHO Global COVID-19 Clinical Data Platform (using third -party host)
  - WHO assembled Clinical Advisory Group to guide analysis and reporting off the Global Clinical Data Platform
  - Importance of focusing on streamlining collection to avoid over-burdening clinicians, especially when resources are limited
- Clinical Characterization using biologic sampling protocols, including mapping antibody response, viral kinetics, and viral dissemination across fluids, in specific populations.
- Value of autopsies or post-mortem biopsies of lung if autopsy not possible.

Objective 2

Determine interventions that improve the clinical outcome of COVID-19 infected patients

- Anti-viral agents – defer to other groups
- Immunomodulatory agents, particularly steroids
- Supportive care
- Co-infections and their treatment

Of these, it is urgent to address the steroid point, ideally, informed by more granular data on viral kinetics and host response. There are a variety of possible ways that this study can be organized, from adaptive platform studies or multi-arm trial designs, in addition to the traditional frequentist studies which often have challenges in enrolling patients effectively for steroid studies in sick patients. Other adjunctive interventions with biologic plausibility include Vitamin C, ACE inhibitors, and other anti-infectives, depending upon the burden of co-infections in these patients. Further reviews of these interventions are necessary. For non-pharmacologic, supportive care interventions, use of oxygen delivery systems deemed to be highest priority, specifically the role of high-flow nasal cannulaes (HFNC) and their applicability across regions and resource availabilities. Knowledge on infection control and HFNC use unknown. Specific targeting of data collection in pregnancy to better define interventions in this population.

Objective 3

Determine optimal clinical practice strategies to improve the processes of care

- Prevention of nosocomial transmission and protection of healthcare workers, including post-exposure prophylaxis and type of ventilatory care provided (For IPC group)
- Determination of discharge criteria and home-based care
- Optimizing care of pregnant woman
- Integrating early testing and diagnosis into care pathways

Objective 4

Determine how best to link key research questions with researchers in affected regions who are able to recruit patients

- Engagement of existing networks currently conducting research and positioned to conduct research.
- Support and mentoring from existing networks for researchers in areas where outbreak is active
- Determine target regions where research preparedness activities should be a focus

Objective 5

Develop platform(s) to maximize commonality of data collection across trials, and collaborations between trials

- Common CRF
- Core outcome measure sets
- Standardized sampling protocols
- Platform for data sharing and communications

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What are the research priorities for clinical research for this outbreak and beyond?

Research priority	Why?	What type of studies/research are needed?
Prognostic factors for severe disease	• Early assessments of severity in specific populations, i.e. pregnancy, elderly. • Natural history of COVID infection. • Optimize triage and clinical processes. • Determine the optimal sampling strategy for clinical care (location, timing).	Observational cohort of all COVID-infected patients, with viral sampling (when possible).
Understand pathophysiology of COVID-19 infection, including understanding mild disease and the role of co-infections	• To better understand relationships between viral load, viral location, antibody responses, and clinical disease and transmissibility. • To possibly generate markers of protection and produce a supply of convalescent plasma.	• Standardized biological sampling of COVID-19 infected patients in a variety of body fluids (pregnancy-related fluids, blood, stool, etc.), including antibody responses and persistence studies. • Histopathologic studies.
Optimal endpoints for clinical trials	Determine how to structure and analyse diverse sets of clinical trials for greatest benefit.	Delphi process with trial-based modelling with currently available datasets with goal of developing core outcomes to be collected across all trials.
Improve processes of care, including early diagnosis, discharge criteria	Manage available resources, reduce transmissibility, and optimize care of infected patients.	Observational cohort of COVID-19 infected patients with viral sampling, with screening of asymptomatic contacts.
Optimal adjuvant therapies for patients (and contacts)	To best improve outcomes from individual infections and reduce transmissibility.	• Randomized clinical trials of affected patients with adjuvant therapies across spectrum of disease (defined as hospitalized or severely ill). • Pre-planned SR of currently conducted trials with subgroups of special populations (i.e. pregnancy, children). • Assessing transmissibility of use of HFNC. • Prioritization process for future trials.

What are the key milestones per research priority

Research priority	Milestones
Natural history of disease: **Prognostic factors for severe disease** **Different populations (pregnancy, young children)** **Different risk groups (immunosuppressed)**	• Contribution to WHO Global COVID-19 Clinical Data Platform. • Clinical advisory group assembled. • 1st Global Report published WHO website.
Natural history of disease: **Understand pathophysiology of COVID-19 infection, transmissibility, viral shedding**	• Biological sampling protocols and reference labs scaled up to collect specimens. • Prospective observational cohort studies approved by Ethics review boards.
Develop core clinical outcomes **to maximize usability of data across range of trials**	• Delphi process. • Articulation of core outcomes set.
Determine interventions that improve the clinical outcome of infected patients **Steroids** **High flow oxygen therapy**	• Protocol review for steroids. • Preliminary in vivo and patient-based data collection for aerosolization and transmissibility with HFNC use.

Other research priorities considered:

Objectives	Why	Research Priority	Fatality rate (censored at publication)
Improve processes of care, including discharge criteria	Optimize resource allocation and reduce community transmission	Medium	Epi, IPC, social sciences
Improve early diagnosis pathways	When labs are overwhelmed with testing, integrating alternate diagnostic pathways	Medium	Epi/lab, social sciences
Role of co-infections in mediating disease outcome	Impact of influenza or bacterial pathogens on COVID-19 outcomes	Medium	Lab/IPC
Clinically characterizing very mild disease	Better understanding risk prognostication amongst severely ill	Medium	EPI
Histologic studies	Better understanding on pathophysiology	Medium	Ethics, social science, lab

Essential references

1. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S., Lau, E.H., Wong, J.Y. and Xing, X., 2020. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine.
2. Paules, C.I., Marston, H.D. and Fauci, A.S., 2020. Coronavirus infections—more than just the common cold. JAMA.
3. Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., Zimmer, T., Thiel, V., Janke, C., Guggemos, W. and Seilmaier, M., 2020. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. New England Journal of Medicine.
4. Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y., Zhu, H., Zhao, W., Han, Y. and Qin, C., 2019. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses, 11(1), p.59.
5. Wang, C., Horby, P.W., Hayden, F.G. and Gao, G.F., 2020. A novel coronavirus outbreak of global health concern. The Lancet.
6. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L. and Chen, H.D., 2020. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv.
7. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R. and Niu, P., 2020. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine.

Infection prevention and control, including health care workers' protection

State of the art

As of the date of this report, no peer reviewed publication has provided data on infection prevention and control (IPC) measures to reduce transmission of COVID-19 during the current outbreak. However, modelling by Tang et al, suggests that enhancing quarantine/isolation (including travel restriction) following contact tracing and reducing contact rates may significantly lower the peak and reduce the cumulative predicted number of infected individuals (Tang, Clin Med 2020).

However, previous literature on other zoonotic coronaviruses and currently available evidence on modes of transmission and isolation of the COVID-19 virus from clinical samples is relevant for the identification of priority IPC measures to be implemented to prevent and contain transmission. So far, viral isolation has been possible from broncho-alveolar lavage (BAL) samples, nasopharyngeal and oropharyngeal swabs and blood from COVID-19 patients (Zhu et al, NEJM 2020; Chan et al, Lancet 2020); RT-PCR was positive also on stool samples (ProMed, Holshue, NEJM 2020). In addition, there is evidence to support person-to-person transmission of the COVID-19 virus among close contacts (Li et al, NEJM 2020).

Furthermore, RT-PCR was also positive from several environmental specimens taken at the Wuhan Seafood Market (ProMed) suggesting the presence of virus on either surfaces or food products.

In the absence of evidence on effectiveness of IPC measures during the current COVID-19 outbreak, it is critical to review the data from previous coronavirus outbreaks; such as the SARS and MERS outbreaks. Multiple studies demonstrated that compliance with hand hygiene, medical masks or N95 respirators, gloves, and gowns was effective to prevent transmission for SARS-CoV (Seto 2003; Teleman 2004; Nishiyama 2008; Nishiura 2005).

Conversely, inconsistent use of goggles, gowns, gloves, and caps was associated with a higher risk for SARS infection (Lau 2004). No association with contact with urine/stool of affected individuals was demonstrated to be responsible for any transmission events. Overcrowding in the emergency room and ward and sub-optimal control of visitors were identified as risk factors for nosocomial spread of MERS-CoV in two large outbreaks in Saudi Arabia and South Korea. Airflow and ventilation were identified as important factors influencing efficient spread in hospitals (Baharoon Trav Med Infec Dis 2019). The proportion of infections in health care workers (HCWs) was 22% and 25% for SARS and MERS, respectively. In a series of 425 Chinese COVID-19 patients from Wuhan (Li, NEJM), HCW infections were reported to be 0%, 3%, and 7% at three separate time intervals (before Jan 1, Jan 1-11, Jan 12-22), respectively. In a single-centre case series of 138 hospitalized COVID-19 confirmed cases in Wuhan, China, presumed hospital-related transmission was suspected in 41% of patients (Wang, JAMA).

Knowledge gaps

Significant knowledge gaps that limit the identification of the best IPC measures to be implemented to contain the current spread of COVID-19 have been identified and are outlined below:

Modes and duration of transmission
(these gaps influence the selection of the most appropriate IPC measures and their optimal duration)
Identification of all target tissues for virus entry, all body fluids that contain the virus and which can transmit the virus (detection of RNA vs live virus, and determining the viral load); relevance of airborne and "opportunistic airborne" spread, and of vertical transmission; duration of shedding and the possibility of asymptomatic shedding; ability of the virus to transmit to others via asymptomatic shedding and if demonstrated, relative frequency of such transmission events.

Environmental stability of the virus and effective methods to minimize the role of the environment in transmission
Viral survival on surfaces and other media, factors influencing stability (e.g., surface type, humidity, temperature, amount of proteinaceous material); efficacy of different disinfectants for cleaning surfaces of patient surroundings including a broad range to be used in different situations (cleaning body fluids splashes vs regular cleaning of surfaces) and in settings with different levels of resources.

Personal protective equipment (PPE) and IPC measures
Relative importance of specific PPE/IPC measures; type of mask and eye protection; need for airborne vs droplet precautions in specific settings (regular care vs. aerosol-generating procedures); PPEs for triage, optimal spatial separation distances, risks factors for HCW exposure.

Isolation, quarantine, and optimal healthcare pathways
Cohorting vs single rooms, costs and resource implications of cohorting; criteria for, principles and cost-effectiveness of quarantine; unintended consequences of quarantine and isolation; context appropriate and responsive health care pathways and access points to minimize exposure and deliver care safely; electronic monitoring of syndromic signatures of people under surveillance at home and of patients in isolation (e.g., use of point of care sensors and wearable monitoring, and artificial intelligence support).

Understanding IPC compliance and perception using behavioural change and social science
Best approaches to communicate IPC policy recommendations; role of media coverage, precautions for home care; most frequent IPC lapses; barriers and facilitators influencing HCWs compliance; human factors and ergonomics; isolation and PPE and isolation/PPE fatigue.

IPC in the community setting
Use of masks by healthy people; precautions for home care; community/family members; education; and management of dead bodies.

Ongoing research efforts

In the WHO-International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/AdvSearch.aspx?SearchTermStat=117&ReturnUrl=%7e%2fListBy.aspx%3fTypeListing%3d0), 84 ongoing research studies on COVID-19 were registered as of 10 February 2020, but none of them were related to IPC.

WHO has received information on the following ongoing studies that are relevant for IPC:
- Systematic review on effectiveness of use of masks in the community
- Feasibility of environmental sampling and the screening of people under quarantine
- Environmental sampling of surfaces surrounding the affected inpatients in Singapore
- PCR tests on respiratory secretions of affected inpatients in Singapore, by day of illness

Research priorities

Objective 1
Understand the effectiveness of movement control strategies to prevent secondary transmission in health care and community settings

Objective 2
Optimize the effectiveness of PPE and its use in reducing the risk of transmission in health care and community settings

Objective 3
Minimize the role of the environment in transmission of the COVID-19 virus

Objective 4
Understand behavioural and cultural factors influencing compliance with evidence-based IPC measures

What are the research priorities for clinical research for this outbreak and beyond?

Research priority	Why?	What type of studies/research are needed?
Effectiveness of restriction of movement of healthy exposed and infected persons to prevent secondary transmission (home, congregate setting, geographical restriction vs nothing)	• Limited evidence • Patient and population safety • Ethics concerns • Risk of amplification and super-spreading events • Unintended consequences • Massive impact on resource and health system utilization	**Research needed on:** • Effectiveness • Cost-effectiveness and resource implications • Unintended consequences • Knowledge, attitudes and perception • Responsive patient pathways • Innovation and technology **Type(s) of studies:** • Systematic Review • Multi-country survey to understand methods applied for quarantine • Ecological study • Comparative prospective cohort study • Qualitative studies • Systems dynamic modelling • Technological innovation and adoption
Effectiveness of specific PPE to reduce the risk of COVID-19 transmission among HCWs, patients and individuals in the community	• Need for higher quality evidence • Patient, public and HCW safety • Widespread over/misuse based on fear and on misinterpretation of evidence • Potential direct role in transmission and acquisition	**Research needed on:** • PPE for – Screening/entry points – Triage – Aerosol-generating procedures/emergency situations – Home care for suspected/confirmed cases – Community settings • Comparison of different types of masks and eye protection, innovative PPE **Type(s) of studies:** • Systematic Review • Large population-based cohort study involving different income countries network surveillance of HCWs) • Cluster randomised trial (CRT) • Materials, design and engineering • Human factor studies
Effectiveness of activities to minimize the role of the environment in COVID-19 transmission	• Contact (direct & indirect) and droplet transmission • Patient, HCW & population safety • Over/misuse of agents • Environmental toxicity • Potential emergence of resistance • Impact on resource utilization	**Research needed on:** • Agents and methods for environmental disinfection (common disinfectants, H2O2, Ultraviolet germicidal irradiation [UVGI], treatment of sewage) • Design and innovation of self-cleaning surfaces • Design to minimize touchpoints **Type(s) of studies:** • In-vitro studies with clinical conditions • R&D with bioengineering, chemistry and industry • Design engineering, human factors & workflow studies
Factors and methods influencing compliance with evidence-based IPC interventions during outbreak response	• Widespread over/misuse based on fear and misinterpretation of evidence • Strong influence by media • Unintended consequences (shortage of supplies, false sense of security, misplaced activity)	**Research needed on:** • Barriers and cultural factors influencing HCWs compliance with IPC evidence-based guidelines • Perception and cultural factors in the community • Factors influencing policy makers • Creative work with the media and with communications experts **Type of studies:** • Observational studies • Perception survey • Qualitative studies • Communications analytics • Intervention studies

What are the key milestones per research priority

Research priority	Milestones
Effectiveness of restriction of movement of healthy exposed and infected persons to prevent secondary transmission (home, congregate setting, geographical restriction vs nothing)	• Rapid systematic review (SR) conducted and report published. • Scientific committee established. • Protocol for ecological study of the use of quarantine e.g. cruise ships finalized and approved by WHO ERC. • Protocol for multi-country survey on methods applied for quarantine finalized and approved by WHO ERC. • Technologies and innovations to support case identification, management and surveillance, and inform responsive health care pathways identified. • Results described in WHO reports and articles in peer reviewed journals.
Effectiveness of specific PPE to reduce the risk of COVID-19 transmission among HCWs, patients and individuals in the community	• Scientific committee established. • Settings for the research including within affected countries identified. • Research groups, innovative PPE producing companies and human factors expertise. • Protocols for SR, observational study on IPC practices, case-control study on risk factors of HWCs exposure, innovative PPEs finalised and approved by WHO ERC. • Results described in WHO reports and articles in peer reviewed journals.
Effectiveness of activities to minimize the role of the environment in COVID-19 transmission	• Scientific committee established. • List of ongoing studies. • Laboratories, research groups, and companies producing innovative. disinfection methods and self-cleaning surfaces conducting research on this priority identified.
Factors and methods influencing compliance with evidence-based IPC interventions during outbreak response	• Formal collaboration with social science group established. • Settings for the research including within affected countries. • Research groups engaged. • Questionnaires and protocols developed closely with social science colleagues and approved by WHO ERC. • Scenario testing and communications analytics performed. • Interventions to improve compliance with IPC, informed by the results, developed. • Results described in WHO reports and articles in peer reviewed journals.

Essential references

1. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY, 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet.
2. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK, 2020. Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. New England Journal of Medicine.
3. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S., Lau, E.H., Wong, J.Y. and Xing, X., 2020. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine.
4. Paules, C.I., Marston, H.D. and Fauci, A.S., 2020. Coronavirus infections—more than just the common cold. JAMA.
5. Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., Zimmer, T., Thiel, V., Janke, C., Guggemos, W. and Seilmaier, M., 2020. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. New England Journal of Medicine.
6. Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y., Zhu, H., Zhao, W., Han, Y. and Qin, C., 2019. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses, 11(1), p.59.
7. Tang B, Wang X, Li Q, Bragazzi NL, Tang S, Xiao Y, Wu J, 2020. Estimation of the Transmission Risk of the 2019-nCoV and Its Implication for Public Health Interventions. Journal of Clinical Medicine.
8. Wang, C., Horby, P.W., Hayden, F.G. and Gao, G.F., 2020. A novel coronavirus outbreak of global health concern. The Lancet.
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z, 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA.
10. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L. and Chen, H.D., 2020. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv.
11. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R. and Niu, P., 2020. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Candidate therapeutics R&D

State of the art

Currently there are no therapeutic agents licensed and available for COVID-19.

Although there is incomplete information about several aspects related to the clinical evolution and severity of the disease, and with respect to the safety and potential efficacy of available candidate therapeutics, there is an urgent need to progress with the prioritization of candidate therapeutics to be tested in clinical trials, with a view to identifying successful candidates that could reduce mortality and improve clinical disease outcome in regions affected by the disease.

A preliminary landscape analysis of the current pipeline of candidates for treatment of the COVID-19, at different stages of development, was conducted based on available information and notwithstanding the current knowledge gaps around the new virus.

The overview of candidate therapeutics includes monoclonal and polyclonal antibodies, as well as repurposed or in development antiviral drugs such as nucleoside analogues and protease inhibitors.

Two options emerged for immediate evaluation:

1. Among the different therapeutic options, Remdesivir was considered a first priority, based on the broad antiviral spectrum, the in vitro and in vivo data available including against coronaviruses and the extensive clinical safety database (used in the Ebola epidemic in DRC).

2. Among the repurposed drugs, the investigation of the antiretroviral medicine (HIV protease inhibitors), lopinavir/ritonavir (Kaletra®), either alone or in combination with Interferon β was considered a suitable second option for rapid implementation in clinical trials.

It was also agreed that other options, like immune-therapies, the use of convalescent sera or other agents (antiviral or non-antiviral products), remain important to consider.

A landscape of candidate therapeutics was drawn to summarize and map the existing evidence to support their use against COVID-19. As part of this ongoing activity, there will be continued efforts for the identification of additional candidate therapeutics as well as determining the impact of emerging and growing evidence on each of the candidates.

In parallel, WHO R&D Blueprint has been coordinating a clinical trials experts group aiming to develop a master protocol for a multi-center adaptive Randomized Control Trial to evaluate efficacy and safety of investigational and repurposed compounds.

Knowledge gaps

There are major knowledge gaps in knowledge around the new virus, in particular the extent of its susceptibility to the different therapeutic options considered, as none of these were developed specifically for COVID-19.

In addition to the current prioritized therapeutics (Remdesivir, Lopinavir/ Ritonavir), other candidates with potential for clinical evaluation should be identified (e.g. other repurposed drugs, mAbs, polyclonal Abs, convalescent plasma, new compounds), and a better understanding of the role of host-targeted therapies is also required.

Among others, data on in vitro/in vivo activity of the candidate therapeutics against COVID-19, PK/PD analysis, considerations regarding dosage, route of and time for administration, as well as safety and efficacy data in humans are crucially needed.

To promote informative in vivo preclinical testing, there is an urgent need to identify and/or develop adequate animal models that can mimic the human disease characteristics as closely as possible. Such studies would be of critical importance to define the therapeutic potential of investigational agents, particularly for those that don't have a direct antiviral activity and for immunotherapies to exclude potential occurrence of disease enhancement.

There is insufficient knowledge of the clinical evolution of COVID-19, and insufficient epidemiological information to precisely guide the definition of the target population and end-points

for efficacy trials. The optimized standard of care requires standardization of key components to the extent possible to facilitate the conducting of interpretable clinical trials. The clinical window for treatment with different agents, primarily for antivirals, needs to be defined. Definition of context for conduction of post-exposure prophylaxis and/or prophylaxis trials is also of importance. In light of the uncertainties around the efficacy in humans of each individual therapeutic agent, it would look appropriate to explore the role of combination therapies, for example combining antivirals with different mechanism of action. Nevertheless, it is important that a high-level prioritization is made based on the limited information available and updated as further pertinent data emerges.

Ongoing research efforts

What studies are ongoing or are planned?

There is currently on-going research aimed at identifying and testing candidate therapeutics. In particular, in vitro studies of antiviral agents against COVID-19 are being carried out, as well as cross-reactivity studies evaluating antibodies developed against SARS.

There are more than 200 clinical trials targeting COVID-19 recorded in China. These include 35 RCTs to evaluate antivirals and other agents, such as Remdesivir, Lopinavir+Ritonavir, Tenofovir, Oseltamivir, Baloxivir Marboxil, Umifenovir, Interferons, Chloroquine, or Traditional Chinese Medicines (e.g. Lianhua Qingwen).

Research priorities

Objective 1

Identification of candidates for clinical evaluation in addition to the ones already prioritized.

Objective 2

Multicentre Master Protocol to evaluate efficacy and safety.

Objective 3

Coordinated collaboration to implement clinical trials, for evaluation of safety/efficacy of therapeutics.

What are the research priorities for clinical research for this outbreak and beyond?

Research priority	Why?	What type of studies/research are needed?
Develop in vitro and in vivo testing	Identify candidate therapeutics to be tested in clinical trials.	• Make repository list of laboratories holding isolated COVID-19. • Standardizing virus propagation protocols. • Develop adequate animal models from mice to NHPs. • Foster standardization and harmonization of in vitro/in vivo testing (e.g. cell lines, positive / negative controls). • Perform screening of repurposed products and discovery libraries. • Select existing and/or develop new monoclonal and polyclonal antibodies. Carry out preclinical evaluation, including for immunopathology. • Put data collected into repository to inform and adjust methods for preclinical and clinical testing.
Evaluate efficacy and safety in prophylactic use	To protect those at risk (e.g. health care workers) with antiviral agents. Reduce nosocomial transmission and to promote their licensing to promote facilitate access.	• Prophylaxis clinical trials (e.g. health care workers) according to Master Protocol.
Promote adequate supply of therapeutics showing efficacy	To promote and facilitate fair, affordable and equitable access to treatment.	• Evaluate production capacity. • Foster technology transfer. • Confirm affordable and equitable access to all affected countries.
Evaluate safety and efficacy of candidate therapeutics through randomised clinical trials	To identify therapeutics that can reduce mortality and improve clinical disease outcome; and promote their licensing to facilitate access. Of note, it is important that research agendas also cover prophylaxis, as indicated above (Point 2).	• RCTs through Master protocols (according to the severity of the disease).
Investigate combination therapies	To maximize the efficacy of the treatment and reduce the risk of development of resistance.	• In vitro/in vivo studies for synergic effect of drugs combinations. • RCTs for combination therapies.

What are the key milestones per research priority

Research priority	Milestones
3. Develop in vitro and in vivo testing	1. A repository list of laboratories holding isolated COVID-19 is accessible. 2. Adequate animal models are available. 3. Standardized protocols are produced and shared for virus propagation and in vitro/in vivo testing. 4. A repository of data collated from in vitro/ in vivo testing is provided and updated to inform and adjust methods for preclinical and clinical testin.g
4. Evaluate efficacy and safety in prophylactic use	1. Agreements are negotiated with the manufacturers to facilitate access and long-term availability on reasonable/equitable terms without disrupting supply for other diseases.
5. Promote adequate supply of therapeutics showing efficacy	1. An overview of the availability and production capacity for candidate therapeutics is accessible. 2. Agreements are negotiated with the manufacturers to facilitate access and long-term availability on reasonable/equitable terms without disrupting supply for other diseases.
6. Evaluate safety and efficacy or candidate therapeutics through randomized clinical trials	1. Adequate candidate therapeutics for clinical evaluation are identified. 2. Master protocols for RCT are available (mild/severe disease). 3. Data on safety and efficacy of candidate therapeutics are produced (RCTs) and analysed.
7. Combination therapies	1. Potential therapeutics combination for clinical evaluation are identified. 2. Results from in vitro and in vivo testing of combination therapies are produced. 3. Data on safety and efficacy of combination therapies are produced (RCTs) and analysed.

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What are the most important actions to facilitate the successful evaluation and use of any of the investigational medical countermeasures?

Animal models: set up and standardize challenge studies in BSL3 labs with NHPs (or other suitable animal model) ensuring capacity and testing combination therapy;
Animal models currently available for other coronaviruses have to be adapted to COVID-19 and ensure robustness. An appropriate route of exposure with disease course mimicking the human disease as closely as possible is warranted.

If funding was made available, some labs should be approached for conducting this work, noting that the limitation in supply of NHPs and the timing for implementation and conduction of studies could be problematic in an emergency situation.

A key aspect to consider will be reproducibility across labs as well as prioritization of NHP assets when candidate drugs come forward for testing.

Prophylaxis clinical studies in Health Care Workers;
It can be argued that antivirals could exert a clinically meaningful benefit in preventing infection and disease. Recognizing that clinical trials in prophylaxis are going to be context specific and studies should be designed maximizing the chances of generating interpretable data, it is felt that prophylaxis in health care workers could be an adequate and relevant setting for such trials to be conducted.

Promote adequate supply of therapeutics showing efficacy (cost/affordable, equitable access, production capacity, technology transfer).
All decisions will need to be taken considering cost, availability and sustainability of products. A target product profile (TPP) is needed for treatment and on prophylaxis. However, a TPP is difficult to craft at this stage, given to the uncertainties on best use antivirals against COVID-19. Consideration should be given to draft TPPs as soon as enough evidence is available.

Effort should be made to facilitate the broadest access possible to therapeutics, particularly considering Low- and Middle-Income Countries (LMICs) and impact of ethnicity on therapeutics pharmacology.

If e.g. lopinavir+Ritonavir and/or remdesivir are proven to be efficacious against COVID-19, there may be a need to increase supply of these drugs.

Essential references

See Table, latest version available at:
https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1

Candidate vaccines R&D

State of the art

Several vaccine candidates are in preclinical development. The Expert Group for COVID-19 Vaccine Prioritization recommended that, given current knowledge and vaccine development status, vaccine approaches targeting the novel coronavirus should be prioritized for further development over vaccine approaches targeting other coronaviruses in the context of the COVID-19 global outbreak, noting that the development of vaccines for other coronaviruses remains a public health priority. However, there are many questions about how development should proceed and be fast-tracked, building on the lessons learned from vaccine development with other coronaviruses and from platform-based approached developed for disease X.

Some animal studies of several but not all coronavirus vaccine candidates have shown that enhanced disease can occur in immunized animals upon subsequent exposure to live virus. This has been studied for both SARS and MERS-CoV vaccine candidates with most descriptions of the pathology occurring in mice. Evaluating the potential for enhanced disease in humans is critical before the vaccine can be assessed through large-scale studies.

Viruses and reagents are being globally mapped out to facilitate the sharing of samples and sequences and to accelerate the development of international standards and reference panels that will help support the development of assays for vaccine development.

The development of a multi-country Master Protocol for Phase 2b/Phase 3 has been initiated and will provide a collaborative research framework under which key research questions will be collectively defined by key stakeholders to facilitate coordination and efficiency of vaccine evaluation.

Critical knowledge gaps

What is the critical evidence that needs to be generated?

1. Animal models relevant for prioritizing vaccines and for evaluating potential for vaccine-enhanced disease have not yet been developed.
2. More information is needed to determine whether the possibility of enhanced disease after vaccination may limit choices of vaccine types and increase the complexity of clinical trials.
3. Assays relevant for evaluating immune response to new vaccines have not yet been developed and standardized.
4. While there is good understanding of what will need to be done in early phase clinical trials, key decisions need to be made about design of later phase clinical trials.
5. Other gaps considered: evaluation and process development for individual vaccines, cell culture optimization, cross-reactivity with other coronaviruses, issues around vaccinating pregnant women.

Key research priorities

1. To develop and standardize animal models to evaluate the potential for vaccine effectiveness and to understand the potential for enhanced disease after vaccination. Results from animal models are expected to be important prior to large-scale efficacy studies and prior to studies in which enhanced disease is considered a significant possibility.
2. To develop and standardize assays to support vaccine development, particularly to support the evaluation of immune responses and to support clinical case definition. Basic reagents should be shared to accelerate the development of international standards and reference panels that will help support the development of ELISAs, pseudovirion neutralization and PCR assays.
3. To develop a multi-country Master Protocol for Phase 2b/Phase 3 vaccine evaluation to determine whether candidate vaccines are safe and effective before widespread distribution, using methodologically sound and ethically acceptable vaccine trial design. Vaccine efficacy trials should be done if such are feasible to implement.
4. To develop potency assays and manufacturing processes to rapidly enable the production of high-quality large quantities of clinical grade and GMP materials.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

In order to coordinate these research priorities, WHO shall establish new expert working groups for animal models and immune assays and continue to convene a current expert group on development of the Master Protocol for vaccines.

A Target Product Profile for COVID-19 vaccines will be immediately developed to provide aspirational guidance to vaccine developers and a web-based information sharing platform will be established to facilitate the sharing of key information.

Working Group	Key terms of reference
WG on Vaccine Target Product Profile	• To develop a global TPP (and the criteria) building on the experience with the development of the TPPs for MERS and Disease X.
WG on Animal Models	• To accelerate and standardize the development of animal models to evaluate disease enhancement. • To coordinate and standardize the development of animal models to evaluate effectiveness.
WG on Assay Development	• To accelerate the development and validation of assays required for vaccine development and to map out reagents globally.
WG on Master Protocol Writing	• To develop a Master Protocol for Phase 2b/Phase 3 vaccine evaluation based on the guidance provided by the WG on clinical trial design.
WG on Clinical Trial Design	• To provide a Trial Design Synopsis for Phase 2b/Phase 3 vaccine evaluation.
WG on Vaccine prioritization	• To develop prioritization criteria and to prioritize the most promising candidate vaccines for consideration under clinical trials.

Ethics considerations for research

State of the art

Authoritative and useful ethical guidance is already in place and is supported by a substantial, well-established background literature on ethical considerations for research in global health emergencies (See Table 1 and Core References). Lessons from previous outbreaks, including SARS, Ebola, and H1N1 Influenza, have informed this body of literature. Within this literature, ethical issues have been well-characterised and researched, particularly in the domain of research ethics. A January 2020 report on ethical issues related to research in global health emergencies, published by the Nuffield Council on Bioethics, represents the State of the art on this topic (Nuffield Council on Bioethics, 2020).

It is widely accepted that infectious disease emergencies do not overrule the need to uphold universal ethical standards. With that said, it is accepted that ethical standards can be adaptive and responsive to changing circumstances and to what is culturally appropriate. Universally accepted ethical standards that should guide research in this context include:

- Collaborative partnerships
- Social value
- Scientific validity
- Fair selection of study populations
- Favourable risk-benefit ratio
- Independent ethical review
- Informed consent
- Respect for recruited participants and study communities (Emanuel et al., 2004)

In general, key ethical issues can be anticipated during infectious disease outbreaks (Nuffield Council on Bioethics, 2020; Smith and Upshur, 2019). The recent Nuffield Council report, for example, sets out research guidance in relation to community engagement, data-sharing and data transparency, priority setting of scarce resources, and health care worker responsibilities and supports. Experience from the two most recent Ebola outbreaks have illustrated that ethics review and oversight generally do not restrict or delay progress in the development of clinical interventions. However, it is vital that learning from recent successes is continued and taken forward in shaping future response efforts.

Ethical issues and the need to uphold the highest ethical standards figured prominently in the February meeting. The Director General of the WHO emphasized the importance of solidarity on several occasions. Equity, fairness, trust, and benefit sharing were repeatedly mentioned as high-level ethical aspirations.

Key Ethical Guidance Documents

Nuffield Council on Bioethics - Research in Global Health Emergencies: Ethical Issues (2020)

Saxena et al - Ethics Preparedness: Facilitating Ethics Review during Outbreaks: Recommendations from an Expert Panel (2019)

The Ethics Working Group on ZIKV Research & Pregnancy - Pregnant Women & the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation (2017)

WHO - Guidance for Managing Ethical Issues in Infectious Disease Outbreaks (2016)

CIOMS - International Ethical Guidelines for Health-related Research Involving Humans (2016)

WHO - Ethics in Epidemics, Emergencies and Disasters: Research, Surveillance and Patient Care: Training Manual (2015)

WHO - Ethical Considerations for Use of Unregistered Interventions for Ebola Virus Disease: Report of an Advisory Panel to WHO (2014)

Médecins Sans Frontières Research Ethics Framework - Guidance Document (2013)

WHO - Meeting Report: Research Ethics in International Epidemic Response (2010)

WHO - Ethical Considerations in Developing a Public Health Response to Pandemic Influenza (2007)

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Knowledge gaps

Despite the plethora of authoritative, intentionally accepted ethics guidance, ethical insights routinely fail to be integrated into emergency research and response. The continued integration of ethics across the epidemic research response spectrum along with the development of a robust knowledge translation strategy therefore remain high priorities. To that end, early and sustained engagement will help to operationalize and integrate ethics knowledge into practice.

The capacity of local contexts or countries to provide independent ethics review may be diminished due to the outbreak or a lack of expertise and resources. Efforts should therefore be made to support and coordinate local capacities for independent ethics review. In an effort to minimize duplication of ethics review and oversight, in most cases independent ethics review should proceed collaboratively between one local and one international review body. Mechanisms such as the advance review of generic protocols are largely in place to facilitate accelerated ethics review in emergency situations without compromising human participants' protection.

Continued open and honest conversations around the sharing of biological samples are still needed particularly in navigating the sustainability and ownership of biobanks and the implications this has on matters of consent and engagement.

As with previous infectious disease outbreaks, the questions around the inclusion of pregnant women, children and other vulnerable populations in clinical trials must be explored in the context of COVID-19. Research participants should be selected in such a way that minimizes risk, protects vulnerable populations, maximizes social value and collaborative partnerships, and does not jeopardize the scientific validity of the research. Pregnant women and children should not be routinely excluded from research participation.

Implementation of ethics as well as R&D innovations into health systems education remains a critical research gap.

Research priorities

Objective 1

To enable the identification of key knowledge gaps and research priorities.

Objective 2

To formulate a clearly defined research governance framework which enables effective and ethical collaboration between multiple stakeholders, including WHO, the global research community, subject matter experts, public health officials, funders, and ethicists.

Objective 3

To facilitate effective cross-working and collaboration across the research thematic areas.

Research priority	Why?	What type of studies/research are needed?
Articulate and translate existing ethical standards to salient issues in COVID-19	Extensive robust ethical guidelines in the context of epidemic research and response are already in place but these need to be used effectively, particularly in 'on the ground scenarios'.	• Development of a brief, 4-page document distilling and translating universally accepted ethical standards for research in order to evaluate the usefulness of new materials/procedures put in place during the outbreak and after emergencies to support COVID-19 R&D. • Develop 1-page documents explaining meaning and nature of key ethical values invoked in R&D roadmap: equity, solidarity, trust, vulnerability. • Implementation research in order to evaluate the usefulness of new materials/procedures put in place during and following the outbreak.
Sustained education, access, and capacity building	Integration of ethics across thematic disciplines and on a global scale in local contexts requires reciprocal increased capacity building to facilitate this. Healthcare worker education has also been identified as a potential knowledge gap. This comes under the wider aim of achieving increased community engagement in the research ethics process.	• Rapid synthesis and scoping of research/surveys/qualitative ethics readiness for emergency research in order to evaluate capacity building processes. • Development and evaluation of educational tools. • Implementation research/surveys/qualitative research in order to evaluate capacity building processes.
The impact of restrictive public health measures (e.g., quarantine, isolation, cordon sanitaire)	Reference to contention around previous quarantine measures, particularly in relation to implementation of travel restrictions and balancing against efficacy in preventing further disease spread.	• Surveys and qualitative research. • Collaborate with social science thematic area to add questions focused on ethical dimensions of the response
Public health communications and the 'infodemic'; ensuring accurate and responsible communications	Clarity in communication between officials/professionals and the wider public is vital and cannot be compromised in epidemic research and response. However, concerns around miscommunication have already been reported in this outbreak.	• Surveys and qualitative research. • Critical analysis of the ethical issues found on social media platforms. • Interventions to enable promote accurate and responsible communications.
Ethical governance of global epidemic research	With numerous researchers, funders, regulators, and corporations involved in R&D during the outbreak, ethical governance will be critical.	• Produce descriptive and comparative analysis of ethical pathways and governance for research with respect to COVID-19 and 2013-2016 Ebola virus disease outbreaks. • Analyse distinct roles and responsibilities of main actors in global collaborative research endeavour. • Watching brief on how new technologies are introduced into epidemic response.

What are the key milestones per research priority

Research priority	Milestones
Articulate and translate existing ethical standards to salient issues in COVID-19	• Development of a 4-page document specifying ethical requirements for research. • Development of four 1-page explanations of key ethical values invoked in R&D roadmap: equity, solidarity, trust, and vulnerability.
Sustained education, access, and capacity building	Leverage newly created Public Health Emergency Ethics Preparedness and Response (PHEEPR) Network.
The impact of restrictive public health measures (e.g., quarantine, isolation, cordon sanitaire)	Research protocol outlined and developed.

What are the most important actions to enable the successful evaluation and use of any of the investigational medical countermeasures?

The R&D Blueprint and Research Roadmap enumerate a number of ethical values that are expected to be achieved through research activities, including solidarity, equity, and trust. The successful evaluation and use of investigational medical countermeasures will require a careful examination of the degree to which the research conducted in this context realizes these key ethical values.

Key processes for the activation and implementation of the R&D Blueprint and Research Roadmap, including the prioritization of vaccine and therapeutics candidates and deciding which populations to target in clinical trials, have critical ethical components. The successful evaluation and use of investigational medical countermeasures therefore requires ethical analysis at the outset and throughout these activities.

The newly established Public Health Emergency Ethics Preparedness and Response (PHEEPR) Network will be critical for the provision of well-integrated real-time ethics supports for researchers in epidemic contexts. As such, engagement with the Network, and evaluation of this Network and its role in this outbreak, will be important.

At all points, appropriate and ethical monitoring and governance structures must be put in place to guide global R&D in this epidemic context.

Essential references

1. World Health Organization. Guidance for Managing Ethical Issues in Infectious Disease Outbreaks. Available from: https://apps.who.int/iris/rest/bitstreams/1063213/retrieve.
2. Smith MJ, Upshur REG. (2019). Pandemic Disease, Public Health, and Ethics. In Oxford Handbook of Public Health Ethics, ed. Mastroianni AC, Kahn JP, Kass NE. New York, NY: Oxford University Press.
3. Eccleston-Turner, Mark, McArdle, Scarlett, Upshur, Ross. Inter-Institutional Relationships in Global Health: Regulating Coordination and Ensuring Accountability. Global Health Governance. 2018;12(2): p. 83-99.
4. Mezinska, Signe , Kakuk, Péter, Mijaljica, Goran, Waligóra, Marcin, O'Mathúna, Dónal P. Research in disaster settings: a systematic qualitative review of ethical guidelines. BMC Medical Ethics. 2016;17(62).
5. Alirol, Emilie, Kuesel, Annette C., Guraiib, Maria Magdalena, Fuente-Núñez, Vânia dela, Saxena, Abha, Gomes, Melba F. Ethics review of studies during public health emergencies - the experience of the WHO ethics review committee during the Ebola virus disease epidemic. BMC Medical Ethics. 2017;18: p. 43.
6. Smith, Maxwell J., Upshur, Ross E.G. Ebola and Learning Lessons from Moral Failures: Who Cares about Ethics? Public Health Ethics. 2015;8(3): p. 305–318.
7. London, Alex John, Omotade, Olayemi O., Mello, Michelle M., Keusch, Gerald T. Ethics of randomized trials in a public health emergency. PLoS Neglected Tropical Diseases. 2018;12(5): p. e0006313.
8. Hunt, Matthew, Tansey, Catherine M., Anderson, James, Boulanger, Renaud F., Eckenwiler, Lisa, Pringle, John, Schwartz, Lisa. The Challenge of Timely, Responsive and Rigorous Ethics Review of Disaster Research: Views of Research Ethics Committee Members. PLoS One. 2016;11(6): p. e0157142.
9. Tansey, Catherine M., Anderson, James, Boulanger, Renaud F., Eckenwiler, Lisa, Pringle, John, Schwartz, Lisa, Hunt, Matthew. Familiar ethical issues amplified: how members of research ethics committees describe ethical distinctions between disaster and non-disaster research. BMC Medical Ethics. 2017;18: p. 44.
10. Schopper, Doris, Research Ethics Governance in Disaster Situations, in Disaster Bioethics: Normative Issues When Nothing is Normal, D. O'Mathúna, B. Gordijn, and M. Clarke, Editors. 2014, Springer Science & Business Media. p. 175-190.
11. Sumathipala, Athula, Jafarey, Aamir, De Castro, Leonardo D., Ahmad, Aasim, Marcer, Darryl, Srinivasan, Sandya, et al.Siriwardhana, Chesmal. Ethical Issues in Post-Disaster Clinical Interventions and Research: A Developing World Perspective. Key Findings Global Public Health Emergency Ethics Preparedness and Response Network Pilot Discussion and Proposal from a Drafting and Consensus Generation Meeting of the Working Group on Disaster Research and Ethics (WGDRE) 2007. Asian Bioethics Review. 2010;2(2): p. 124-142.
12. Calain, Philippe. The Ebola clinical trials: a precedent for research ethics in disasters. Journal of Medical Ethics. 2018;33: p. 3-8.
13. Schopper, Doris, Ravinetto, Raffaella, Schwartz, Lisa, Kamaara, Eunice, Sheel, Sunita, Selgelid, Michael J., et al.Upshur, Ross. Research Ethics Governance in Times of Ebola. Public Health Ethics. 2017;10(1): p. 49-61.
14. Bain, Luchuo Engelbert, Ngwain, Chia Gerald, Nwobegahay, Julius, Sumboh, Jeffery Gabriel, Nditanchou, Rogers, Awah, Paschal Kum. Research Ethics Committees (RECs) and epidemic response in low and middle income countries. The Pan African Medical Journal. 2018;31(209).
15. Rid, Annette, Emanuel, Ezekiel J. Ethical considerations of experimental interventions in the Ebola outbreak. The Lancet. 2014;384: p. 1896–1899.
16. Richardson, Thomas, Johnston, Andrew McDonald, Draper, Heather. A Systematic Review of Ebola Treatment Trials to Assess the Extent to Which They Adhere to Ethical Guidelines. PLoS ONE 2017;12(1): p. e0168975.
17. Folayan, Morenike Oluwatoyin, Peterson, Kristin, Kombe, Frances. Ethics, emergencies and Ebola clinical trials: the role of governments and communities in offshored research. The Pan African Medical Journal. 2015;22(Suppl 1): p. 10.
18. Eckenwiler, Lisa, Pringle, John, Boulanger, Renaud, Hunt, Matthew. Real-time Responsiveness for Ethics Oversight During Disaster Research. Bioethics. 2015;29(9): p. 653-661.
19. Millum, Joseph, Beecroft, Blythe, Hardcastle, Timothy Craig, Hirshon, Jon Mark, Hyder, Adnan A., Newberry, Jennifer A., Saenz, Carla. Emergency care research ethics in low-income and middle-income countries. BMJ Global Health. 2019;4(Suppl 6).
20. Calain, Philippe, Fiore, Nathalie, Poncin, Marc, Hurst, Samia A. Research ethics and international epidemic response: the case of Ebola and Marburg hemorrhagic fevers. Public Health Ethics. 2009;2(1): p. 7–29.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

21. Adebamowo, Clement, Bah-Sow, Oumou, Binka, Fred, Bruzzone, Roberto, Caplan, Arthur, Delfraissy, Jean-François, et al.Whitehead, John. Randomised controlled trials for Ebola: practical and ethical issues. The Lancet. 2014;384(9952): p. 1423-1424.
22. Tansey, Catherine M., Herridge, Margaret S., Heslegrave, Ronald J., Lavery, James V. A framework for research ethics review during public emergencies. Canadian Medical Association Journal. 2010;182(14): p. 1533-1537.
23. Curry, David R., Waldman, Ronald J., Caplan, Arthur L. An Ethical Framework for the development and review of health research proposals involving humanitarian contexts: Project final report. Available from: http://www.elrha.org/wp-content/uploads/2015/01/FINAL-R2HC-Ethical-Framework_Final-Report_24-January-2014_0.pdf.
24. Council for International Organizations of Medical Science (CIOMS). International ethical guidelines for health- related research involving humans. Accessed December 15, 2019. Available from: https://cioms.ch/wp- content/uploads/2017/01/WEB- CIOMSEthicalGuidelines.pdf.
25. Médecins Sans Frontières. Research Ethics Framework Guidance Document. Accessed Available from: https://samumsf.org/sites/default/files/2019-04/9.%20MSF%20Research%20Ethics%20Framework_Guidance%20document%20%28Dec2013%29.pdf.
26. World Health Organization. Ethics in epidemics, emergencies and disasters: Research, surveillance and patient care. Training manual. Available from: https://www.who.int/ethics/publications/epidemics-emergencies-research/en/.
27. Sethi, Nayha. Research and Global Health Emergencies: On the Essential Role of Best Practice. Public Health Ethics. 2018;11(3): p. 237–250.
28. Schopper, Doris, Upshur, Ross, Matthys, Francine, Singh, Jerome Amir, Bandewar, Sunita Sheel, Ahmad, Aasim, van Dongen, Els. Research Ethics Review in Humanitarian Contexts: The Experience of the Independent Ethics Review Board of Medecins Sans Frontieres. PLoS Medicine. 2009;6(7): p. e1000115.
29. De Crop, Maaike, Dela Mou, Alexandre, Van Griensven, Johan, Ravinetto, Raffaella. Multiple ethical review in North-South collaborative research: the experience of the Ebola-Tx trial in Guinea. Indian Journal of Medical Ethics. 2016;1(2): p. 76-82.
30. Schopper, Doris, Dawson, Angus, Upshur, Ross, Ahmad, Aasim, Jesani, Amar, Ravinetto, Raffaella, et al.Singh, Jerome. Innovations in research ethics governance in humanitarian settings. BMC Medical Ethics. 2015;16: p. 10.
31. World Health Organization. Ethical considerations for use of unregistered interventions for Ebola viral disease. Report of an advisory panel to WHO. Available from: http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/.
32. Aung, Myo Nyein, Murray, Virginia, Kayano, Ryoma. Research Methods and Ethics in Health Emergency and Disaster Risk Management: The Result of the Kobe Expert Meeting. International Journal of Environmental Research and Public Health. 2019;16: p. 770.
33. Saxena, Abha, Horby, Peter, Amuasi, John, Aagaard, Nic, Köhler, Johannes, Gooshki, Ehsan Shamsi, et al.Ravinetto, Raffaella. Ethics preparedness: facilitating ethics review during outbreaks - recommendations from an expert panel. BMC Medical Ethics. 2019;20: p. 29.
34. World Health Organization. Research Ethics in International Epidemic Response: WHO Technical Consultation. Meeting Report. Available from: http://www.who.int/ethics/gip_research_ethics_.pdf.
35. Gailits, Nicola, Nouvet, Elysée, Pringle, John, Hunt, Matthew, Lu, Daniel, Bernard, Carrie, et al.Schwartz, Lisa. Blurring Lines: Complexities of Ethical Challenges in the Conduct of West African Ebola Research.
36. Aarons, Derrick. Research in epidemic and emergency situations: A model for collaboration and expediting ethics review in two Caribbean countries. Developing World Bioethics. 2018;18: p. 375–384.

Social sciences in the outbreak response

State of the art

Social science research brings rich and detailed insights regarding social, behavioural and contextual aspects of the communities, societies and populations affected by infectious disease epidemics. In developing our agenda for COVID-19, we drew on perspectives from multiple social science disciplines, including anthropology, psychology, social epidemiology and political science. The research community overarching aim is to bring social science technical expertise to integrate with biomedical understandings of the COVID-19 epidemic, to strengthen the response at international, regional, national and local levels in order to stop the spread of COVID-19 and mitigate its social and economic impacts. As such, there is a clear line of sight between the research priorities we propose here and the objectives of the strategic response plan.

Method for identifying research priorities

Researchers conducted a rapid review of published and pre-pre-published research relevant to social science considerations for COVID-19. We also drew on published social science research from previous respiratory epidemics, particularly Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Important thematic areas relevant to COVID-19 were identified at a round table event of social science experts (3 February 2020) [1] and through discussions with operational partners and technical experts from across the COVID-19 Incident Management System (IMS) to shape a working agenda framed around key areas of the response (6 February 2020). At the Global Research and Innovation forum (11 February 2020), discussions among invited social science academics led to further detailing of the agenda, relevant research questions, and prioritization.

Rapid evidence review for COVID-19

While much of published research regarding COVID-19 has focused on virology, epidemiology and clinical aspects of COVID-19, commentaries, editorials and letters from sociologists, economists and political scientists have highlighted the social impacts of COVID-19, particularly in China. Analysis and critique has drawn attention to China's economic expansion and global political influence [1], to political structures and their impacts on epidemic response domestically and internationally [2], on the geopolitical tensions that threaten international cooperation, [3], and one the limits of coordination mechanisms, for example, through violation of article 43 of the International Health Regulation when countries implement travel restrictions [4].

Authorities across the world have pressed ahead with measures to stop or contain the spread of COVID-19 infection: in China, these measures include quarantine, school closures, and business closures; globally, quarantine and isolation measures are also in effect and there has been mass purchase of surgical masks. These measures all have secondary impacts. Quarantine, for instance, has impacts on the mental [5-7] and physical health [8] of populations. Historical accounts of quarantine events highlight the challenges of practicing mass quarantine, and also raise questions regarding human rights, and public health effectiveness [1, 9]. A rapid systematic review of publications reporting previous events of quarantine for infectious disease outbreaks, identified how knowledge of the disease, clear information regarding quarantine procedures, social norms, perceived benefits of quarantine, perceived risk of disease, and ensuring sufficient supplies of food, medicines and other essentials were important factors to promote adherence to the uncomfortable realities of quarantine measures [10]. Others have highlighted the critical role of trust, interpersonal and international cooperation that emerge in response to a collective effort in tackling a major public health crisis [11].

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

These kinds of insights are important for national public health officials looking to implement control measures that may have clear biomedical rationale but require social and behavioural cooperation from citizens to be effective. Shortages in the global supply of surgical facemasks [12], and panic purchasing of surgical masks by citizens, particularly in countries where these practices are not culturally embedded, are further examples of secondary impacts. Rapid identification of these impacts, and research is necessary to generate evidence that can inform approaches to mitigate them. Public health authorities will not be operating in a vacuum, but in already functioning communities and societies with established socio-cultural systems that include different forms of authority, organization and coping and resilience mechanisms to face adversity. Local knowledge and perception of COVID-19 and biomedical interventions will drive local reactions and responses. In a crisis, it is often forgotten that communities have well recognized potential to self-organize and adapt and that these processes are influential to epidemic trajectories.

Disease transmission is driven by social as well as biological factors. In China, for example, the past decades have witnessed China's critical role in global commodity supply chains, infrastructure expansion and population mobility though domestic and international travel. These factors are all highly relevant to the spread of COVID-19 infection [13] and its impacts. Systematically identifying social drivers and accounting for them, for example, in epidemiological models, results in better data across sectors to inform response actions. New evidence regarding groups at risk of COVID-19 infection is also emerging. Older age groups and those with underlying co-morbidities, including (potentially) cancer [14], have thus far been identified. While there does not now appear to be evidence of intrauterine vertical transmission [15], uncertainties regarding potential transmission had raised concern among those providing care to these groups [16]. Beyond biomedical vulnerability, there is also a need to identify which groups are vulnerable from social and economic perspectives. These assessments are dynamic and contextual [17]. Understanding which groups are most at risk of harm is key to shaping effective approaches to public engagement and tailoring public health responses that account for social inequalities, rather than perpetuate them [18].

The impact of COVID-19 infection on front line workers, particularly in China, but also in other global regions, has raised concern regarding the best way to protect their physical and mental health. Countries preparing to manage potential COVID-19 spread need to ready their workforce to deliver effective prevention and control procedures and organizations need to build resilience among staff, anticipate psychosocial needs and plan to enable clinical continuity. A substantive body of evidence from SARS, highlights institutional, social and psychological factors that affect the wellbeing of health care workers, as well as the factors that were associated with post event burnout and also resilience [19-22]. These insights can help organizations develop evidence-based strategies for health care worker protection.

Communication, and the spread of misinformation and dis-information, has been of central concern for this epidemic, particularly in terms of generating panic and fear. Panic shapes societies during epidemics in multiple ways [23]. Social media platforms enable rapid spread of information across networks, and these networks can be instrumental in driving particular behaviours offline [24]. While these processes can result in influencing important pro-social, health prevention and health-seeking behaviours [25], they can equally exacerbate scapegoating, discrimination and stigma of particular groups [1]. Identifying effective strategies to disrupt these flows are important to mitigate harmful effects and may require engaging new actors and technologies.

Knowledge gaps

Priority thematic areas for social science research contribution at this stage in COVID-19 epidemic are (1) public health, (2) Clinical care and health systems, (3) Engagement in public health response and clinical research, (4) Media and communication, (5) Sexual and reproductive health, (6) International cooperation. We identified priority research questions in each of these thematic areas.

Critical evidence needs that can have maximal immediate impact for COVID-19 response are:

- **Public health:** what are relevant, feasible, effective approaches to promote acceptance, uptake, and adherence to public health measures for COVID-19 prevention and control, and how can secondary impacts be rapidly identified and mitigated?

- **Care, access and health systems:** What are the relevant, acceptable and feasible approaches for supporting the physical health and psychosocial needs of those providing care for COVID-19 patients?
- **Media and communication:** What are the most effective ways to address the underlying drivers of fear, anxieties, rumours, stigma regarding COVID-19, and how to improve public knowledge, awareness, and trust during the response?

Additionally, critical cross cutting research area, particularly in the context of research for development of new medical countermeasures for COVID-19, involves identifying the best methods to rapidly and systematically involve and sensitize communities regarding their participation in clinical research. We stress that the thematic areas we have identified here do not delineate the full scope of social science research contribution.

Agendas and research questions will also need to be closely specified and contextualized at regional, national and local level. New evidence emerging in other technical areas of the response will shape the social science research agenda too.

Ongoing research efforts

Universities and research groups in China are actively involved in social science research activities aimed at understanding the specific impact of public health measures, on psychological and behavioural responses of communities and also on other aspects such as the economic impact of extended business closures. We are aware of groups that are active in Africa, Australia, Europe and North America focusing on various aspects including media surveillance, healthcare workers protection, and public trust in national response. See appendix for an overview of research planned or in process, and research related activities for COVID-19.

Research priorities

Objective 1

Generate high-quality evidence to achieving the goals of the strategic public health response plan.

- Promote the prioritization of knowledge needs according to epidemic dynamics
- Promote the production of knowledge according to local, national and regional needs
- Promote that knowledge outputs and methodological limitations are easily understood by non-social scientists

Objective 2

To develop and employ strong methodologies and theoretical frameworks to tackle current epidemic challenges

- Develop innovative interdisciplinary science
- Develop guidelines and Standard Operating Procedures (SOPs) to operationalized epidemic mitigation mechanisms
- Develop and connect global research networks with response partners
- Engage with communities to bring their voices to decision-making processes

Objective 3

To understand non-intended consequences of epidemic-control decisions

- Understand contextual vulnerability
- Understand how decisions in the field may inadvertently undermine response goals
- Understand how social and economic impacts need to be mitigated

What are the research priorities for – each individual thematic area -for this outbreak and beyond?

Research priority	Why?	What type of studies/research are needed?
Public Health What are relevant, feasible, effective approaches to promote acceptance, uptake, and adherence to public health measures for COVID-19 prevention and control; and how can secondary impacts be rapidly identified and mitigated?	Public health interventions to infectious disease epidemics are the backbone of any response. Many of these interventions have a clear biomedical or scientific logic but require social or behavioural cooperation from citizens to be effective. When public health interventions are designed in a way that accounts for social, behavioural and contextual realities, and builds on existing systems and structures, they are more likely to be accepted and thus acted upon by affected communities. Public health interventions also have secondary social, economic impacts and these need to be anticipated and mitigated.	• Consultation with citizens and communities via online surveys, qualitative methods (focus group discussions, interviews) (online and face to face). • Citizen science. • Participatory practice and intervention co-design. • Systematic evidence reviews. • Media and social media surveillance and analysis. • Global, international, national, and regional governance studies.
(Clinical) care and health Systems What are the relevant, acceptable and feasible approaches for supporting the physical health and psychosocial needs of those providing care for COVID-19 patients?	The rapid increase in demand on health systems places severe strain on clinical services and health care staff. This includes reducing provision for more specialist services such as chronic care, sexual and reproductive health. In countries preparing to support COVID-19 patients, there is an urgent need to develop system resilience and to enable clinical continuity plans. This may involve understanding informal structures of care, how best to leverage and strengthen these, how best to support those caring for patients with COVID-19, best approaches for managing patient flows and impacts on the health needs of vulnerable groups. We also expect traditional care-seeking and delivery practices to shift at household level.	• Longitudinal investigations of how care-seeking practices shift during the outbreak • Rapid approaches to capture healthcare worker views (surveys, interviews). • Rapid ethnographies in healthcare settings. • Heath service mapping; mapping of informal care structures.
Media and communication How are individuals and communities communicating and making sense of COVID-19? What are the most effective ways to address the underlying drivers of fear, anxieties, rumours, stigma regarding COVID-19, and improve public knowledge, awareness, and trust during the response?	Understanding representations and practices associated to the outbreak allows building a dynamic picture of fears, panic, and practices. There is an urgent need to disrupt the flow of misinformation, xenophobia and stigma-inducing discourses to stop rising anxiety, and to promote that evidence-based biomedical information is communicated effectively, responding to the questions of the public.	• Media and social media surveillance. • Review of effective technological methods to disrupt flows of misinformation. • Consultation with citizens and communities via (online) surveys, qualitative methods focus group discussions. • Outcome evaluation and related models to assess effectiveness of social media campaigns.

Research priority	Why?	What type of studies/research are needed?
Engagement What are the relevant, acceptable and feasible approaches for rapid engagement and good participatory practice that includes communities in the public health response.?	There is a need in this context to understand the best methods and approaches to engage with large, urbanised populations, more isolated rural populations and mobile populations. This priority is also key to systematically addressing stigma and xenophobia related to novel COVID19. Optimal design, delivery and dissemination of medical research and clinical trials require successful, ethical engagement of participant groups.	• Power mapping. • Consultation with citizens and communities via (online) surveys, qualitative methods focus group discussions. • Participatory practice and intervention co-design. • Outcome evaluation regarding impact of good participatory practice on participant experience and on trial indicators.
Sexual and reproductive health What are the relevant, acceptable and feasible approaches to communicating uncertainty regarding mother to child transmission of COVID-19, and possible sexual transmission?	Given the current uncertainties regarding potential mother to child transmission, there is a need for social science support in understanding the best way of communicating the knowledge gaps in sexual and reproductive health. Early observational studies published in China have also revealed that knock-on impacts of the high clinical demand in Chinese cities and quarantine measures are impacting other services, including sexual health clinics etc.	• Consultation with citizens and communities via (online) surveys, qualitative methods focus group discussions. • Participatory practice and intervention co-design.
International cooperation What international coordination mechanisms can optimize the international response to COVID-19?	There is a need to identify and remove any barriers that would otherwise prevent a rapid, coordinated, international response to this outbreak. There is also a need to consider the global economic and trade implications that may be the result of international actions that significantly interfere with international traffic	• Identifying practical steps to improve fairness, efficiency and transparency of governance processes and/or new mechanisms of cooperation.

What are the key milestones per research priority?

The social science research community can accelerate critical research in affected countries and globally in the following way. First, wider inclusion of multiple social science disciplines and global representation is needed to deliver this broad and cross-cutting research agenda. Second, mechanisms to dialogue with disciplines beyond social science are needed to better articulate and address cross cutting research areas.

Third, the social science research community can accelerate research for COVID-19 by ensuring transparent and methodological rigour, clarifying how methodological limitations might impact interpretation of research findings, sharing research protocols and data collection tools, and sharing results at the earliest point possible. Fourth, mechanisms for engaging with policy makers and publics, building trust, also in research and scientific evidence, are further important steps.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

Research priority	Milestones
Public health	1. Establish mechanisms for dialogue with relevant stakeholders. 2. Establish mechanisms to identify and track relevant research activity including via publication regarding public health responses. 3. Establish a mechanism for sharing of research protocols and associated tools. 4. Establish and test pathways for dynamic knowledge flow to enable rapid sharing of evidence.
(Clinical) care and health Systems	1. Establish mechanisms for dialogue with relevant stakeholders. 2. Establish a mechanism to identify and track relevant research activity including via publication regarding to (clinical) care and health systems. 3. Establish a mechanism for sharing of research protocols and associated tools. 4. Establish and test pathways for dynamic knowledge flow to enable rapid sharing of evidence.
Media and communications	1. Establish mechanisms for dialogue with relevant stakeholders. 2. Establish a mechanism to identify and track relevant research activity including via publication regarding media and communications. 3. Establish a mechanism for sharing of research protocols, associated tools and research findings. 4. Build framework to understand changing practices.
Engagement	1. Establish mechanisms for dialogue with relevant stakeholders 2. Establish and test pathways for dynamic knowledge flow to enable rapid sharing of evidence
Sexual and Reproductive health	1. Establish mechanisms for dialogue with relevant stakeholders. 2. Establish a mechanism to identify and track relevant research activity including via publication regarding sexual and reproductive health. 3. Establish and test pathways for dynamic knowledge flow to enable rapid sharing of evidence.
International coordination	1. Establish mechanisms for dialogue with relevant stakeholders. 2. Establish a mechanism to identify and track relevant research activity including via publication regarding international coordinatio. 3. Establish and test pathways for dynamic knowledge flow to enable rapid sharing of evidence.

Essential references

1. Social Science in Humanitarian Action Platform, Social dimensions of the novel coronavirus (nCoV) outbreak and response: meeting report. 2020.
2. Kavanagh, M.M., Authoritarianism, outbreaks, and information politics. The Lancet Public Health, 2020.
3. Kickbusch, I. and G. Leung, Response to the emerging novel coronavirus outbreak. Bmj, 2020. 368: p. m406.
4. Habibi, R., et al., Do not violate the International Health Regulations during the COVID-19 outbreak. The Lancet, 2020.
5. Brooks SK, W.R., Smith LE, Woodland L, Wessely S, Greenberg N, Rubin GJ. , The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. (under review). The Lancet 2020.
6. Rubin, G.J. and S. Wessley, Coronavirus: the psychological effects of quarantining a city. BMJ OPinion, 2020.
7. Xiang, Y.-T., et al., Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. The Lancet Psychiatry, 2020.
8. Chen, P., et al., Wuhan coronavirus (2019-nCoV): The need to maintain regular physical activity while taking precautions. Journal of Sport and Health Science, 2020.
9. Baldwin, P., Contagion and the State in Europe, 1830-1930. 2015, Cambridge: Cambridge University Press.
10. Webster, R.K., et al., How to improve adherence with quarantine: rapid review of the evidence. in preparation, 2020.
11. Vargha, D., Polio across the Iron Curtain : Hungary's Cold War with an Epidemic. Cambridge 2018, New York, Ny, : Cambridge University Press.
12. Mahase, E., Novel coronavirus: Australian GPs raise concerns about shortage of face masks. Bmj, 2020. 368: p. m477.
13. Zhao, S., et al., The association between domestic train transportation and novel coronavirus (2019-nCoV) outbreak in China from 2019 to 2020: A data-driven correlational report. Travel Med Infect Dis, 2020: p. 101568.
14. Liang, W., et al., Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. The Lancet Oncology, 2020.
15. Chen, H., et al., Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet, 2020.
16. Favre, G., et al., 2019-nCoV epidemic: what about pregnancies? The Lancet, 2020.
17. Birkman, J., et al., Framig vulnerability, risk and societal responses: the MOVE framework. Natural Hazards, 2013. 67(2): p. 193-211.
18. Chan, E.Y.Y., et al., Weather Information Acquisition and Health Significance during extreme cold weather in a subtropical city: a cross-sectional survey in Hong Kong. International Journal of Disaster Risk Science, 2017. 8(2): p. 134-144.
19. Imai, T., et al., Perception in relation to a potential influenza pandemic among healthcare workers in Japan: Implications for preparedness. Journal of Occupational Health, 2008. 50(1): p. 13-23.
20. Brooks, S.K., et al., A Systematic, Thematic Review of Social and Occupational Factors Associated With Psychological Outcomes in Healthcare Employees During an Infectious Disease Outbreak. Journal of Occupational and Environmental Medicine, 2017. 60(3): p. 248-257.
21. Yassi, A., et al., Research gaps in protecting healthcare workers from SARS and other respiratory pathogens: An interdisciplinary, multi-stakeholder, evidence-based approach. Journal of Occupational and Environmental Medicine, 2005. 47(1): p. 41-50.
22. Wu, P., et al., The Psychological Impact of the SARS Epidemic on Hospital Employees in China: Exposure, Risk Perception, and Altruistic Acceptance of Risk. The Canadian Journal of Psychiatry, 20019. 54(5): p. 302-311.
23. Peckham, R.S., Empires of Panic : Epidemics and Colonial Anxieties. . 2015, Hong Kong: Hong Kong University Press.
24. Jones, J.J., et al., Social influence and political mobilization: Further evidence from a randomized experiment in the 2012 U.S. presidential election. PLOS ONE, 2017. 12(4): p. e0173851.
25. Freeman, B., et al., Social media campaigns that make a difference: what can public health learn from the corporate sector and other social change marketers? Public Health Research & Practice, 2015.
26. Hankins, C., Good participatory practice guidelines for trials of emerging (and re-emerging) pathogens that are likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist (GPP-EP). 2016, WHO: WHO.
27. Council for International Organisations of Medical Sciences, International Ethical Guidelines for Health-related Research Involving Humans. 2016, CIOMS publications: Geneva.
28. World Health Organisation, Guidance for Managing Ethical Issues in Infectious Disease Outbreaks. 2016, WHO: Geneva, Switzerland.
29. Greenhalgh, T., et al., Frameworks for supporting patient and public involvement in research: Systematic review and co-design pilot. Health Expectations, 2019. 22(4): p. 785-801.
30. WHO, Health Emergency and Disaster Risk Management Framework. 2019, WHO: Geneva.

2019 NOVEL CORONAVIRUS GLOBAL RESEARCH AND INNOVATION FORUM: TOWARDS A RESEARCH ROADMAP

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