The remaining unknowns: A determination of the current research priorities for COVID-19 by the global health research community

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Contributions

KM, CA, WM, JM and MA developed the original survey with input from MT, all the authors then contributed to further developing and delivering this global version with oversight from TL. AN and TL guided this analysis along with AD, NC, EA with support from ZA and JP. The workshops were delivered by TL and NF, with support from ZA and JP. TL led the drafting with AN and MT, PP and KM were closely involved throughout and contributed to the draft and review. The other authors contributed significantly and equally in conducting the study and analysing the data.

Abstract

Background

In March 2020 the World Health Organisation (WHO) released a Global Research Roadmap in an effort to coordinate and accelerate the global research response to combat COVID-19 based on deliberations of 400 experts across the world. Three months on, the disease and our understanding have both evolved significantly. As we now tackle a pandemic in very different contexts and with increased knowledge, we sought to build on the work of the WHO to gain a more current and global perspective on these initial priorities.

Methods and findings

We undertook a mixed methods study seeking the views of the global research community to i) assess which of the early WHO roadmap priorities are still most pressing; ii) understand whether they are still valid in different settings, regions or countries; and iii) identify any new emerging priorities.

Thematic analysis of the significant body of combined data shows the WHO roadmap is globally relevant, however, new important priorities have emerged, in particular, pertinent to low and lower-middle income countries (less resourced countries), where health systems are under significant competing pressures. We also found a shift from prioritising vaccine and therapeutic development towards a focus on assessing the effectiveness, risks, benefits and trust in the variety of public health interventions and measures. Our findings also provide insight into temporal nature of these research priorities, highlighting the urgency of research that can only be undertaken within the period of virus transmission, as well as other important research questions but which can be answered outside the transmission period. Both types of studies are key to help combat this pandemic but also importantly to ensure we are better prepared for the future.

Conclusions

We hope these findings will help guide decision making across the broad research system including the multi-lateral partners, research funders, public health practitioners, clinicians and civil society.

Introduction

COVID-19 was declared a public health emergency of international concern on 30th January 2020 (1) and then a global pandemic on 11th March 2020 (2). The World Health organisation (WHO) published their Global Research Roadmap (3) on 12th March 2020, within the context of the situation and the epicentre of infection at that time. The Roadmap was built on deliberations of the Global Research Forum, whereby 400 participants from different sectors across the world, identified 3-4 immediate research priorities for the following three months across each of 9 themes.

Now, in June 2020 we see the evolution of this pandemic at different points across the globe. We know from our previous experience with Ebola and other outbreaks (4, 5) that it is essential to embed research into the response to an outbreak, and that there is a finite and unknown window where these questions can be answered. COVID-19 is an unprecedented situation and therefore we must take every opportunity to undertake all the possible research that funding and capabilities allow; and high-quality studies should happen everywhere there are cases in order to maximise the evidence generated and ensure that the resultant data and findings are globally applicable. Therefore, it is important to assess now, what are the most key remaining questions that need to be addressed, both to ensure this pandemic can be halted and to learn for future outbreaks of this pathogen or another.

This research achieved its aim to determine the current global research priorities at this point in time to tackle the COVID-19 pandemic and to help learn for any future outbreaks.

Methods

An online multi-language survey was developed where ranking questions were coupled with open-ended questions. This was based on a previous survey led by the African Academy of Science (AAS) that was undertaken in March 2020 to assess how well the WHO priorities where applicable to Africa (6). Here we worked from the AAS survey so we could now assess whether the findings remained relevant across the globe, and if they had changed over time. Seventy-three potential priorities (41 from the original WHO document and 32 generated as part the AAS survey and consultations) were arranged under the nine topic headings used in the WHO Research Roadmap. Participants ranked their top three options for both short- and long-term priorities (18 total ranking questions). Free text boxes were provided under each of the broad topics, where participants were asked to list any research priority they felt was not included in the options provided.

After the survey closed a virtual workshop was held to seek wider global comment and discussion on the survey findings and to discuss current priorities and unmet research areas. We conducted ten further open access workshops with research teams and health workers across the globe, led by the TGHN COVID-19 Research Implementation and Knowledge Hub between 14th April and 12th June 2020. These workshops meetings were recorded with permission of participants, and comments and questions captured. A thematic content analysis methodology was developed to report the findings of each (7). Here we applied this to the cumulative data of all 11 workshops to add to the survey data and better address the question*: what are the current global research priorities during the COVID19 pandemic?*

Quantitative Data Analysis Methods

Responses from the survey were download in excel format, all data was fully anonymised, password protected and access restricted to the study team. Descriptive analyses were undertaken within excel to provide a ranking score for each research priority for immediate and longer term, as per the survey. Priorities ranked as first were given a score of 3, those ranked second were given a score of 2 and those ranked third were given a score of 1. This analysis was conducted within the category headings from the WHO roadmap and included both the original WHO priorities and new priorities suggested in the AAS report. Therefore, these data show

us how responders currently rank the priorities set within the WHO roadmap and the AAS report. The data were split for comparison between the global researcher responses and those originating from less-resourced settings. Within the less-resourced setting category, we include low and lower-middle countries as defined by the World Bank.

Qualitative Data Analysis Method

The aim of the open-ended survey was to determine whether there are new priorities that were not included in the original WHO roadmap or the AAS survey findings. These written comments were imported into NVivo qualitative data analysis package and we undertook a pragmatic thematic content analysis. Analysing the data from the workshops allowed a further open consideration of current research priorities as this step expanded beyond the limitation that the survey had of asking questions within the framework of the WHO roadmap. Following the methodology established after the first workshop (7) we compiled a dataset by transcribing the spoken and written comments from each workshop. A coding framework was generated through an inductive and then deductive approach, following the same categories used in the survey.

Results

In total, 1,528 individuals completed the online survey and 2,559 attended the workshops, from across 137 countries, ensuring representation from all of the WHO regions (African region = 612 (40%); Americas region = 279 (18%); Eastern Mediterranean region = 32 (2%); European region = 460 (30%); South East Asia region = 87 (6%); Western Pacific region = 58 (4%)). Participants were most commonly employed in academia (47%), hospitals (14%) research organisations (11%) and non-government organisations (10%).

Current Global Ranking of the WHO Roadmap Priorities

The survey results (Table 1) shows how priorities were ranked across the immediate and longer term within the WHO categories. We present these globally, along with a sub-group analysis of less resourced countries to understand whether there are differences in priorities for less resourced countries.

128

129 **Table 1: Survey Results: Top three research priorities from the WHO Roadmap categories showing less**

130 **resources countries as a sub-set of the global responses.**

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<table>
<tr><th></th><th>Priority</th><th colspan="2">Immediate</th><th colspan="2">Longer-term</th></tr>
<tr><th></th><th></th><th>Global (n=1528)</th><th>Less resourced countries (n=694)</th><th>Global (n=1528)</th><th>Less resourced countries (n=694)</th></tr>
<tr><td rowspan="3">Virus natural history, transmission and diagnostics</td><td>1</td><td>Support work to develop cheaper, faster easier to use in field antigen tests (for virus detection)</td><td colspan="3">Support development of diagnostics products to improve clinical processes.</td></tr>
<tr><td>2</td><td>Support development of diagnostics products to improve clinical processes.</td><td colspan="3">Development of cheaper, faster easier to use in field antigen tests (for virus detection)</td></tr>
<tr><td>3</td><td colspan="2">Support work to develop cheaper, faster easier to use in field antibody test tests (for determining exposure).</td><td>Characterize immunity (naturally acquired, population and vaccine-induced, including mucosal immunity).</td><td>Support work to develop cheaper, faster easier to use in field antibody test tests (for determining exposure).</td></tr>
<tr><td rowspan="2">Animal and environmental research on the virus origin, and management measures at the human-animal interface</td><td>1</td><td colspan="3">Improve understanding of socioeconomic and behavioural risk factors for spill-over and transmission between animals and humans</td><td>Identify animal source and route of transmission (hosts, any evidence of continued spill-over to humans and transmission between animals and humans).</td></tr>
<tr><td>2</td><td colspan="3">Identify animal source and route of transmission (hosts, any evidence of continued spill-over to humans and transmission between animals and humans).</td><td>Improve understanding of socioeconomic and behavioural risk factors for spill-over and transmission between animals and humans</td></tr>
</table>

	3	**Design and test suitable risk reduction strategies at the human-animal-environment interface**			
Epidemiological studies	**1**	**Describe transmission dynamics of COVID-19 and understand spread of disease nationally, regionally and globally.**			
	2	**Describe disease severity and susceptibility to facilitate effective clinical and public health response to COVID-19 – identify groups at high risk of severe infection**		Establish suitable cohorts and prospectively collect longitudinal laboratory and outcome data.	
	3	Perform rapid population cross sectional surveys to establish extent of virus transmission using standardised sampling framework		**Describe disease severity and susceptibility to facilitate effective clinical and public health response to COVID-19 – identify groups at high risk of severe infection**	Perform rapid population cross sectional surveys to establish extent of virus transmission using standardised sampling framework
Clinical Management	**1**	**Determine interventions that improve the clinical outcome of COVID-19 infected patients**		**Define the natural history of COVID-19 infection** though careful standardised and comprehensive clinical and laboratory description of cases	
	2	**Determine optimal clinical practice strategies to improve the processes of care (e.g. develop criteria for early diagnosis, when to discharge, when to use adjuvant therapies for patients and contacts).**		**Determine interventions that improve the clinical outcome of COVID-19 infected patients**	
	3	Develop protocols for management of severe disease in the absence of intensive care facilities.	**Define the natural history of COVID-19 infection** though careful standardised and comprehensive clinical and laboratory description of cases	**Determine optimal clinical practice strategies to improve the processes of care (e.g. develop criteria for early diagnosis, when to discharge, when to use adjuvant therapies for patients and contacts).**	
Infection prevention and control, including health care workers' protection	**1**	**Understand the effectiveness of movement control strategies to prevent secondary transmission in health care and community settings**			
	2	**Optimize the effectiveness of PPE and its use in reducing the risk of transmission in health care and community settings.**		Research to support health systems strengthening and building of resilience post the outbreak	**Optimize the effectiveness of PPE and its use in reducing the risk of transmission in health care and community settings.**

	3	Develop new PPE approaches using local materials and manufacturing processes		**Optimize the effectiveness of PPE and its use in reducing the risk of transmission in health care and community settings.**	Develop new PPE approaches using local materials and manufacturing processes
Candidate therapeutics R&D	**1**	**Develop mechanisms to support coordinated collaboration to implement clinical trials for evaluation of safety/efficacy of therapeutics.**	**Identification of existing candidates for clinical evaluation in addition to the ones already prioritized.**	**Develop mechanisms to support coordinated collaboration to implement clinical trials for evaluation of safety/efficacy of therapeutics.**	Support basic science to identify new drug targets
	2	Support basic science to identify new drug targets		**Identification of existing candidates for clinical evaluation in addition to the ones already prioritized.**	
	3	**Identification of existing candidates for clinical evaluation in addition to the ones already prioritized.**	**Develop mechanisms to support coordinated collaboration to implement clinical trials for evaluation of safety/efficacy of therapeutics.**	Support basic science to identify new drug targets	**Develop mechanisms to support coordinated collaboration to implement clinical trials for evaluation of safety/efficacy of therapeutics.**
Candidate vaccines R&D	**1**	**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.**	Capacity development for basic science and pre-clinical development of new vaccines		
	2	Capacity development for basic science and pre-clinical development of new vaccines	**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.**		

	3	**Identification of candidates for clinical evaluation in addition to the ones already prioritized.**	
Ethics Considerations for Research	**1**	**Identify key knowledge gaps and research priorities in relation to ethical issues arising out of proposed restrictive public health measures (e.g., quarantine, isolation, cordon sanitaire).**	
	2	**Define a research governance framework that enables effective and ethical collaboration between multiple stakeholders, including WHO, the global research community, subject matter experts, public health officials, funders, and ethicists.**	
	3	Establish processes for speeding up ethical review of COVID-19 related research proposals	**Sustained education, access, and capacity building to facilitate effective cross-working and collaboration across the research thematic areas.**
Social Sciences in the Outbreak Response	**1**	Investigate ways of ensuring transparency of information flow and mitigating false information spread by various mechanisms	**Ensure that knowledge is produced according to local, national and regional needs.**
	2	**Ensure that knowledge is produced according to local, national and regional needs.**	**Promote the prioritization of knowledge needs according to epidemic dynamics.**
	3	Examine optimal ways of communicating about potential interventions in high density low socioeconomic status urban settings	

The ranking of these priorities broadly indicates what researchers feel to be the most important research areas from the WHO roadmap at this point within this pandemic. The qualitative data from the survey and the workshops then provides further insight to guide where emphasis should be placed, particularly in low-resourced nations.

The qualitative data analysis from the survey, workshops and working groups supported the existing WHO Roadmap and highlights where greater research emphasis is needed at this later point in the pandemic. However, most importantly new priorities have also come through from this study (Table 2).

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142 **Table 2: Existing priorities now requiring greater research emphasis and new priorities not in the WHO**

143 **Roadmap or AAS list**

Existing priorities now requiring greater research emphasis	
Infection recurrence	
Understanding infections and outcomes in vulnerable populations including children, persons living with disabilities, ethnic groups and refugees.	
Relationship between repeated viral exposure and disease severity (in frontline workers)	
The effects of the disease on pregnant women	
Effective use of PPE for frontline healthcare workers (emphasis on Nurses)	
Health Systems research & strengthening to mitigate impact of COVID-19 on capacity	
Understanding zoonotic leap between human and animals	
The impact of redirecting resources and public health interventions towards COVID-19 on other disease burdens	
Adherence to and trust in public health interventions such as quarantine and social distancing	
Evaluation of public health interventions in varied settings	
Public health messaging and addressing myths and mistrust	
Engaging relevant stakeholders (including religious leaders) in research to enhance community sensitization, adherence to public health measures, detection and surveillance	
Effective and feasible ways of community engagement during lockdowns and social distancing.	
New Priorities	
Virus natural history, transmission and diagnostics	Improved diagnostic tools for safer sample collection, faster and easier assays
Epidemiological studies	Examine relationships to other lung diseases The impact of improved WASH practices on WASH-related infections diseases. Long-term health impacts and complications of contracting COVID-19 – with emphasis on children/those with comorbidities
Clinical management	Clinical guidelines for post-hospitalisation home management and community rehabilitation. Palliative care for COVID-19 patients Vitamin D levels in COVID-19 severity
Candidate therapeutics R&D	Investigate the potential role of natural/traditional remedies What would the target therapeutic be with our new knowledge Evaluate therapeutics in the community in early infection
Candidate vaccines R&D	Innovative vaccine delivery modalities
Ethical considerations for research	Ethical considerations for resource allocation to LMICs Ethical considerations of recruiting final year medical/nursing students

Social sciences in the outbreak response	Understanding COVID-19 in the contexts of conflict, civil war, and refugee situations Examine the effects of the pandemic on the participation of the public in democratic processes
Infection prevention and control	How to ensure effective social distancing in public spaces and congregate settings post lockdown.
The environmental impact of the response to COVID-19.	Determine the impact of: PHIs on the environment (including air pollution and carbon dioxide emissions) • Disinfectants and hand sanitisers on the environment • Large-scale PPE production and disposal.
Preparing for the next pandemic.	Ensure effective measures including community surveillance and animal screening techniques are in place to rapidly identify emerging zoonotic diseases. Evaluation of governmental policies and lessons learnt in preparation for the next pandemic.
Cross-cutting	The use of technology in various aspects of pandemic response. Assess effective ways of conducting cross-disciplinary research

Discussion

These data suggest that that original WHO COVID-19 Research Roadmap remains broadly globally applicable. Here we also show which research questions require the most emphasis and also that potential new priorities have emerged that were not within the initial roadmap.

Some new suggested priorities reflect the progress of the pandemic and acquisition of knowledge as to where the gaps lie; notably research in children, pregnancy, long-term health impacts of the disease and that there is a strong call for research that assesses the effectiveness of public health measurers put into place across the globe to reduce transmission of this virus. These were alongside a demand for greater social science research to determine public perception, and better ways to change behaviours and build trust. We also identified a range of new priorities relating to addressing COVID-19 in lower resource settings, where multiple pressures including ongoing endemic infectious diseases and other co-morbidities are competing within the health and policy systems for limited resources.

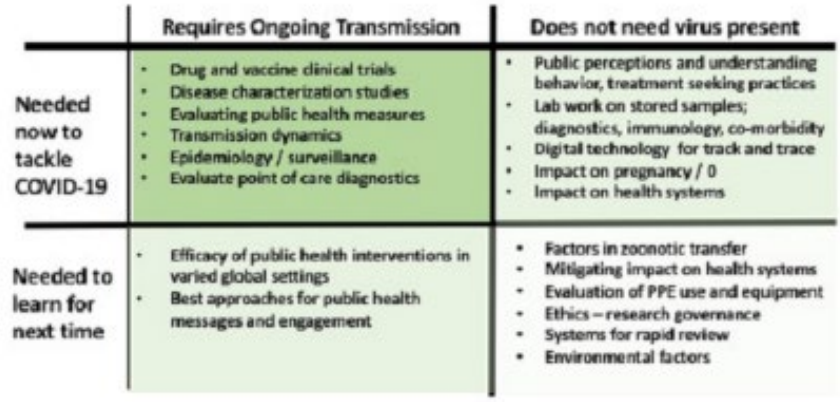
Limitations of our approach include the fact that we built the questions to align with the original WHO broad priority headings, and this meant that some headings (for example the animal human interface) had relatively few suggested priorities while others (for example social sciences in the outbreak response) had much larger numbers. We also retained the original order of priorities from the WHO Research Roadmap and the AAS survey and this may have influenced the ranking given by respondents. The workshops however were open and purposefully invited researchers to make whatever comments they wanted in regard to where current research priorities lie. Therefore, taken together we suggest that these data support the importance of the WHO research roadmap approach and highlights where funders and researcher should be placing emphasis as well as identifying potential new areas that should be tackled within this pandemic.

Given that no really effective anti-virals have yet been identified, and with the prospect of a globally accessible vaccine being still some way off, the only interventions that have been deployable by countries are public health measures to prevent transmission. It is therefore unsurprising then that the survey respondents and workshop participants ranked highly the need for further studies to evaluate the value of such measures as well as studies on other potential interventions as they arise.

These studies must be undertaken as quickly as possible if we are to gain evidence now on just how effective measures such as lockdown, handwashing and social distancing are on reducing transmission. These studies are needed in highly varied social contexts to understand the relative risks and benefits. The need for social science research and mixed methods came through very strongly, with an emphasis on determining how to gain the trust and successfully deliver public health messages. This needs evidence-based community engagement strategies; tested and evaluated everywhere.

Consideration of both immediate and long-term priorities is important to address this specific pandemic and to better prepare for the future. There are studies that need ongoing transmission, at a high enough rate to answer the question they set. These might be essential for this pandemic, for example clinical trials to

185 determine the efficacy of drugs or vaccines, or address questions to guide future outbreaks, such as evaluating
186 the effectiveness of public health interventions. Other studies do not need circulating virus, and could still
187 guide the effort to address COVID-19 or might help for future pandemics. Fig 1 shows these four situations
188 and gives examples.
189
190 **Fig 1. Priority assessment matrix for research within the COVID-19 pandemic**



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192 Consideration of these findings in the context of where we are now with the global shifting and evolution of
193 the pandemic requires both research teams and funders to ensure research across all these key areas within
194 this finite window. Here we have suggested a matrix that groups these priorities which might help guide
195 resource allocation and research planning (Fig 1). This complements ongoing work by the UK Collaborative
196 on Development Research and Global Research Collaboration for Infectious Disease Preparedness to map
197 research funding against the WHO roadmap priorities to enable funders and researchers identify gaps and
198 opportunities and inform future research investments or coordination needs (8).
199
200 Finally, we want to highlight both the importance of fully involving the global research community in priority
201 setting, as well as the ongoing need to review priorities where knowledge and practice is advancing rapidly.

Here we have shown that the global research community support the recommendations of the WHO research roadmap, but that important new priorities have emerged both due to the transition through the pandemic and consideration of differing global epidemiological, health system, policy and research contexts.

Acknowledgments

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