



OPEN LETTER

Enabling evidence to tackle everyday diseases to mitigate another pandemic [version 1; peer review: 2 approved]

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Abstract

The next emergent novel pathogen is likely to occur where the ability to undertake health research and collect life-saving data is lacking. Without embedded and ongoing research activities in place spotting and stopping a new threat is not possible, thereby enabling undetected infection and unchecked transmission within a community. Without local existing capabilities to collect such data delay is catastrophic. Fundamental goals in pandemic preparedness should be to stop an outbreak before it becomes a pandemic. This requires immediate action from teams already in place with the right skills, this could be readily achieved if we shift our thinking and enable research capabilities to be present in every healthcare setting. Addressing fundamental gaps in health research capacity and equity could tackle this and then we would be better prepared, globally.

Keywords

pandemic preparedness; health research; outbreaks; global research equity; health research capacity; capacity strengthening

Open Peer Review

Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

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We need a whole ecosystem of health research studies

The need for the whole ecosystem of health research studies is true for any disease, and in an outbreak, we need these data all at once. During the coronavirus disease 2019 (COVID-19) pandemic there was fast and strong investment in hospital based clinical trials that evaluated therapies. These were highly successful for improving outcomes in severe disease^{1,2} but failed to generate effective, accessible and affordable anti-viral therapies that could be given before the disease progressed^{1,2}. Anti-viral therapies typically work by stopping replication and therefore are ideally given very early in the infection. It is important to collect all types of health research data, yet funding was highly siloed geographically and in the questions being addressed^{3,4}. The most important element in preventing a pandemic is to first be able to identify a new threat and then as quickly as possible characterise how the disease presents and how transmission can be blocked. These steps need surveillance in place and the capability to undertake observational studies. Addressing gaps in ability and ensuring funding is directed to the full range of health research are essential to mitigate another pandemic.

The skills, protocols, methods and resources for all health research studies are readily adaptable between diseases as has been reported and put into practice⁵. The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) developed a disease characterisation protocol for use firstly

in severe acute respiratory syndrome (SARS)⁶. This was then adapted for the Ebola outbreak, this was then again pivoted for Zika and taken up successfully across the globe for COVID-19⁷⁻⁹. The Zika outbreak highlights the importance of all forms of health research data. In this situation there were in fact no clinical trials as there were no drugs or vaccines to evaluate. Here at the outset, we initially faced an unknown pathogen causing devastating microcephaly in babies, the cause needed to be determined and then the nature of transmission and the harm that was being caused needed to be fully understood. The studies undertaken through the Zika outbreak that answered these questions included public health and social science studies, vector biology, genomics and disease characterisation. This shows us how all types of health-related research data should be valued equally and that clinical trials are just one element of the health research ecosystem, that needs to be considered as a whole, comprised of these critical elements. Figure 1 is an infographic used on the COVID Research Implementation Hub to direct research teams to protocols, tools, training and guidance during the COVID-19 across all the different types of studies that were needed.

We can consider this connected ecosystem further because once we have interventions, such as drug and vaccines we need to rapidly undertake well designed clinical trials that will tell us if these new interventions work and are safe. For a successful trial that produces strong evidence on the safety and efficacy of an intervention in any given community, then we need data on the nature of the disease and the epidemiology in different specific settings to guide the design of good protocols. Alongside these it is essential to firstly and then in parallel run social science-based studies to understand community perceptions,

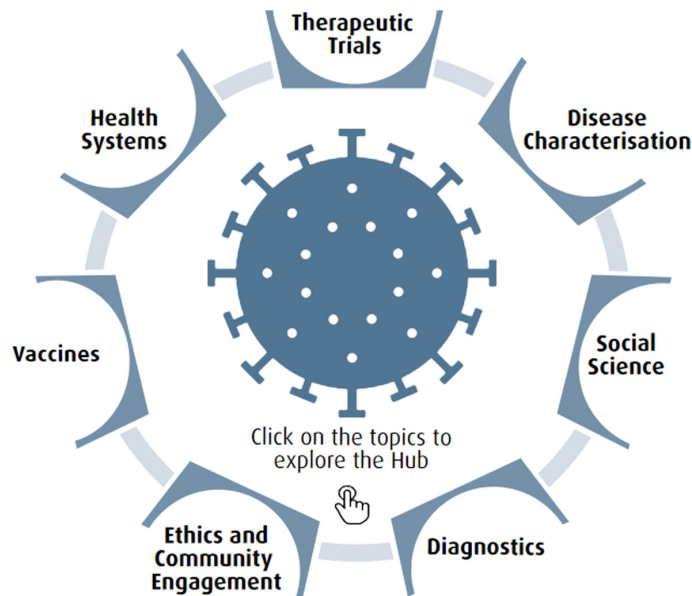


Figure 1. The COVID Research Implementation Hub: Infographic used to direct research team to protocols, tools, training and guidance during the coronavirus disease 2019 (COVID-19) pandemic across all the different types of studies that were needed.

and to develop and test diagnostics, understand the pathogen and prevent transmission, etc. Therefore, a connected ecosystem of studies are required to generate the full range of data that we need. Clinical trials are key at the end of the process but they do not occur in isolation and other data sets are just as important. This point is especially relevant to consider in low-resource settings where the ability to run trials must be considered alongside the ability to collect all the other types of data needed to design the right trials in the right place if we are to develop drugs and vaccines that will make a difference in varied patient populations.

The skills and systems needed are the same for any disease and so wider benefit and impact would be achieved

We know from our research and long-standing experience in addressing these gaps that the barriers to undertaking health research are the same irrespective of disease, region, organisation or type of study^{3,4}. This is good news because if we put in place highly practical solutions to tackle everyday disease priorities and burdens, then they are active and will spot a new threat. These teams can then pivot from their current research to focus on the new pathogen and stop it in its tracks before it escapes.

Many organisations, including the World Health Organisation, research consortia and funders, such as the [European and Developing Countries Clinical Trial Platform \(EDCTP\)](#) and the [Bill & Melinda Gates Foundation \(BMGF\)](#), are working with frontline health workers to deliver the ability to undertake research within their care delivery practices¹⁰⁻¹². Pragmatic research studies can be undertaken in any setting by all roles and levels of staff to measure the scale and burden of diseases that impact their communities, or identify and test practical and locally appropriate new treatments, care plans, or prevention approaches to address them. This approach is being delivered across Africa, Latin America and Asia and has resulted in new evidence for diseases such as tuberculosis (TB), malaria and dengue fever. These accessible and highly applicable initiatives drive changes such as better community-based practices to reduce maternal and new-born fatalities. With practical research skills and awareness in place, teams, such as the [REDE: The Latin America and Caribbean Network for Research Capacity Strengthening](#), have already pivoted their skills in-situ to work on Ebola, Zika and more recently COVID-19 showing that this approach works. Having research capabilities actively working within healthcare system is the most effective mechanism for a new outbreak to be spotted and the data captured immediately to determine how to stop further spread and manage the resultant cases. These same teams will also be ready with the skills and systems in place to run trial when products come through, which can be designed appropriately as there is local epidemiology and social science data.

Conversely, if these easily taught skills are absent the delay in detection and response could be the difference between an outbreak and a pandemic.

Thinking wider than pandemics will prevent a pandemic

Teaching skills to community health workers to survey, detect and assess an emergent new threat and putting response systems and protocols in place that sit in wait for a new event will not work. These skills need to be in practice, be present and embedded into healthcare delivery, rather than considered different and distinct from daily work and put away for the moment a response is needed.

Thankfully, these skills are no different than are needed for tackling ongoing, daily diseases that impact communities. Also, teaching and implementing these is neither difficult or expensive and can be undertaken at scale if we connect and build on the success of existing research networks and knowledge mobilising initiatives. We can develop this further by extending, connecting or setting up, new networks where there are gaps, which are then able to use and adapt infrastructure, expertise and extensive reach and reputation in low- and middle-income countries (LMICs) bringing a ready-made and proven cross-function resource for knowledge sharing, training and building communities of practice across and between partners, topic areas and research methods. This can bring immediate impact through tackling ongoing disease burdens, and then ready to immediately act in the event of a new threat.

Achieving global research equity

Lastly, COVID-19 at least highlighted to everyone the importance of health research. Whilst there has been incredible mobilisation to understand and mitigate COVID-19, this has also highlighted the ongoing stark and profound gaps. It remains true that 90% of all health research benefits only 10% of the world's population, primarily those in the wealthy north¹³. Diseases of poverty lack crucial evidence to change the appalling outcomes these illnesses bring to the poorest communities across the globe. It is readily achievable to work within healthcare teams in these settings to implement locally-led research in order to understand and develop interventions to tackle the diseases that devastate families and economies in these woefully underserved regions of the world. There is much that can be readily done to enable research teams in the global south to not get left behind and for research to happen at the same time everywhere. We can change how research is funded and rewarded to recognise team science and foster truly federated global partnerships. We can also work to ensure that funding flows across a required matrix to tackle every unanswered question and is not siloed geographically or in funding similar trials in the same settings. Low-income countries should have equitable access to the benefits of research and in taking part. Furthermore, unless research capacity is in place then the global risk is greater and we are not globally prepared.

Data availability

No data are associated with this article.

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Current Peer Review Status:  

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Reviewer Report 19 July 2022

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Reviewers' comments on the open letter:

1. Well written open letter overall, addressing current key issues of research participation and funding worldwide.
2. Some suggested key points to be addressed:

Under the subheading: "We need a whole ecosystem of health research studies ", in addition to addressing gaps in ability to tackle outbreak and funding, it is very important for the global research community to:

1. Consider allocating funding following geographical repartition of research gaps where there is an urgent need of data worldwide (mainly in the global south, as many programs do works on collecting any type of data which could be beneficial for preparedness of future pandemics: cholera, Marburg, Ebola...).
2. Allocate more research grants to citizens from the global south (institutions, ...), as nowadays still many research grants have restrictive selection criteria (be a citizen of the global north...).

Under the subheading: "Thinking wider than pandemics will prevent a pandemic", the author could emphasize more on the importance of having research capabilities actively working within healthcare systems in the global south (TB, Malaria...) by giving some examples: like making global south countries (communicable or non-communicable disease programs) accountable for their management budget through publications in peer-reviewed journals of implementation activities' results. This might greatly contribute to pandemic preparedness.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease, molecular diagnostics, public health, capacity building.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 21 April 2022

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Mahesh K. Maskey

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Prof. Lang's central argument in this article is that the generation of evidence is not the prerogative solely of clinical trial. Crucial though clinical trial is, the whole ecosystem of health research needs to be in action for the development our understanding of any disease, particularly if we aim to be prepared for the pandemics of the future. Prof. Lang points to the disproportionate investment of health-research funding in clinical trials during the Covid-19 pandemic, and argues that while the result of this misplaced focus was a success in treating severe cases of the disease, but it also led to less attention to develop anti-viral therapies essential for stopping replication and disease progression. She draws on experience of the responses to the SARS, Ebola, and Zika viruses to underline the importance of surveillance and observational studies in evidence-generation. "The most important element in preventing a pandemic is to first be able to identify a new threat and then as quickly as possible characterize how the disease presents and how transmission can be blocked," Prof. Lang writes. The data needed, therefore, includes not only the "nature of the disease and the epidemiology in different specific settings," but information from social-scientific studies of community understandings of disease and transmission as well. Many different types of studies are needed to generate the full range of data, with clinical trials being

the endpoint of this process.

The priorities of the world's health-research institutions are increasingly becoming reductionist. Coming from a globally acclaimed expert in clinical trial, this article's emphasis on a more holistic approach to the generation of evidence is refreshing, welcome, and important. The arguments here appear to be a further development of the ones in Prof. Lang's July 2020 article in *Nature*, which drew on a survey of approximately 4000 researchers from 130 countries. In that article, Prof. Lang emphasized the stark geographical inequity of health-research funding investment, with 90% of such research benefitting only 10% of the world's population. The remaining 90% of the world's population represent countries where appropriate health research is sorely needed to prevent and manage the devastating effects of pandemics. This is where research capacity needs to be strengthened, and in the article reviewed here Prof. Lang provides examples from different parts of the world to show how that strengthening is possible and within reach. Basic skills in survey, detection, and assessment are easily and inexpensively taught, and are also what is needed for the routine treatment of diseases that impact communities. If these skills are not developed, she warns, then in the years to come, "delay in detection and response could be the difference between an outbreak and a pandemic." Unless low-income countries have equitable access to research funding and thereby to the benefits of research, and unless research capacity is in place in these countries through a federated global partnership, Prof. Lang advises that the global risk is greater for both the occurrence and management of future pandemics.

This important article would be further strengthened by a brief exploration of differing points of view. What are the viewpoints that maintain the current inequity in research-fund allocation, in spite of the advocacy of powerful health institutions such as the World Health Organization? What arguments are made to limit funding allocation to low-income countries? Is one such argument the belief that good research cannot be done in the Global South? Such thinking surely perpetuates a vicious cycle of low research capacity and low research funding. Similarly, what are the viewpoints and mindsets that maintain clinical trial as a grossly over-prioritized arena of health research? Why is there a blind spot with regards to the importance of effective intervention strategies in prevention and in the very early stages of infection when the virus replicates? Why is there such under-prioritization of socio-ethnographic studies and community engagement, despite the evidence that data from these is of critical importance to our ability to serve our communities?

I believe attention to these queries would have made a more balanced presentation of arguments while strengthening the core message of the open letter by Prof. Lang.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: , Maternal and Child health, Health systems research, Implementation research and Public Health policy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
