The R&D Preparedness Ecosystem: Preparedness for Health Emergencies

Report to the Global Preparedness Monitoring Board

9 August 2020

Gerald T. Keusch, Boston University National Emerging Infectious Diseases Laboratory

Nicole Lurie, Harvard Medical School

Commissioned by the US National Academy of Medicine.

Introduction

This paper responds to the request of the Global Preparedness Monitoring Board (GPMB) to examine the current R&D architecture and ecosystem, and to identify progress and remaining governance challenges and gaps that are likely to impact R&D in a pandemic. It focuses on issues that influence research, development, manufacturing, deployment and access to medical countermeasures (vaccines, therapeutics) and necessary tools and commodities (diagnostics, PPE, ventilators etc), and it proposes actions and recommendations for GPMB to consider.[1]

It builds specifically on the R&D focused chapter as well as the chapter on overall governance challenges prepared for the 2019 GPMB report, as these are so intertwined with R&D preparedness. It also takes the perspective that strong preparedness activities enable a strong R&D response when an outbreak with pandemic potential occurs. Further, elements of that R&D response are in themselves preparedness for the development of diagnostics, therapeutics and vaccines. The 2019 report highlighted the need to: sustain the commitment to R&D beyond immediate emergencies; strengthen in-country R&D capacity to become more epidemic sensitive than epidemic specific; and to align international and national research funders with regard to spending on R&D for epidemics. It also highlighted a number of other persistent challenges and introduced the need for systematic integration of social science into response program activities.

In preparing this report, we interviewed 54 individuals (see the appendix for name and affiliation), conducted desk research, and drew on our own experiences. Shortly after the request to prepare this report was made, the COVID-19[2] pandemic began, resulting in both unexpected challenges and opportunities. Without a doubt, the pandemic has made it extremely difficult to speak with key respondents. It has also enabled us to view progress and identify remaining gaps and shortcomings as they have presented themselves in 'real time'. It should be self-evident that we are at a unique moment, when the entire world is anxious and fearful of the prospect that a bit of RNA will upend life as we know it, a moment when the world's leaders share the anxiety and fear, and when the GPMB can respond to that fear by putting forth a vision for a post-COVID global system for health and public health. It is a moment when we must ask "If not now, then when"?

The report itself will discuss 9 R&D preparedness issues across the R&D ecosystem and make 1 recommendation for each of them.

We recognized that the evolution of the COVID-19 pandemic is a dynamic situation, and that much will have changed between the time this report was submitted (on April 24, 2020) and its release. We have noted a few areas of progress (as of August 9, 2020) but have not attempted to be exhaustive.

---

[1] Neither author has a financial interest in any company working to develop and market products for COVID-19 related purposes. Dr. Lurie serves as a consultant to CEPI and throughout much of the period this report was being prepared led its COVID Incident Management Team.

[2] COVID-19: The disease caused by the SARS-CoV-2 virus, first reported in December 2019.

1. The global R&D ecosystem

We attempted to anchor our report in a definition of the R&D ecosystem, and key informant interviews began by eliciting their perspectives. Two prevalent views emerged. Most interviewees saw the ecosystem as a loosely defined system comprised of actors and institutions working in a more-or-less linear progression, starting at some upstream research level and extending across product development, pre-clinical and clinical research at least through Phase 2 or 3 trials. The second view either extended the concept upstream to fundamental discovery research in microbiology and immune system mechanisms, or expanded the downstream end through regulatory approval to manufacturing. For a few it extended all the way to global access for all populations, enabled by global financing mechanisms for those unable to pay the real costs. A more nuanced view also emerged during these discussions, specifically that the ecosystem is actually not linear and progressive, but more accurately a series of non-linear mini-ecosystems, each with particular characteristics, business needs and incentives, pathways, problems, barriers, and proponents, each influencing one another. This suggests that it may be very productive to take a system dynamics approach to understanding the R&D ecosystem and the nonlinear behavior of complex systems over time. These different perspectives help explain why every individual we interviewed viewed the major ecosystem challenges as organizational and related to coordination, rather than scientific. We have not had the opportunity to delve more deeply into this challenge and determine how it might improve how we approach enhancement of R&D preparedness, but we believe taking up this challenge will reward the effort.

Most interviewees noted areas of progress, for example, the development of 'communities of research' around different virus families, leading to better collaboration and inclusion of researchers when an outbreak with a pathogen in that family occurred, or to work together to develop a vaccine against a specific disease, e.g. Lassa, or Nipah. The R&D Roadmap development process has helped to bring together researchers around various pathogens. However, many with whom we spoke were frustrated by the reality that many of these had not been finalized and released, that there was no overall 'coordinator' or 'conductor' who could lead, drive, and report on which issues were being funded or addressed, and by whom, and where remaining gaps were. Six weeks after the COVID-19 outbreak was reported to WHO, and 4 weeks following the first release of the viral genome sequence, WHO and GloPID-R[3] convened a meeting to develop a prioritized research agenda related to the pandemic. This was converted into a Global Research Roadmap with immediate, mid-term and longer-term priorities, released within 3 weeks by the Scientific Advisory Group of the WHO R&D Blueprint, intended "to build a robust global research response on the basis of the deliberations during the Global Research Forum."[4] However, it has taken most GloPID-R members considerable time to make funds available to support this agenda, given that each funder needed to prepare and issue its own calls for proposals, review them, and make awards. It has also been a challenge to ensure that work is not unnecessarily duplicated. Since mid-April, 2020 when the report was submitted to GPMB,

[3] GloPID-R: Global Research Collaboration for Infectious Disease Preparedness

[4] https://www.who.int/blueprint/priority-diseases/key-action/Coronavirus_Roadmap_V9.pdf?ua=1

the GloPID-R secretariat and the UK Collaborative on Development Research[5] [6] have convened working groups on priority research and have created an online database of funded research proposals mapped to the WHO Coordinated Global SARS-CoV-2 Research Roadmap. It is unclear to us how effectively coordination among the multiple funders has been, however this will be instrumental to insure maximum scientific output results.

Finally, as we discuss in the next section, because so much research is 'bottom-up' and funding requires a degree of entrepreneurism, it is often not clear who has the 'responsibility' to coordinate or even to monitor the conduct of certain types of R&D preparedness work, let alone in the stress of an outbreak. In other words, many funders and research groups are playing in what is essentially a 'conductorless orchestra', with strong strings, woodwinds, brass and percussion, but never quite in tune or in synch. Going forward, preparedness R&D could be organized better and more efficiently if it is understood and treated as a complex dynamic system. This would require each part of the ecosystem to identify its strengths, weaknesses, conceptual gaps, and its human capital and the financial resources needed to act, with the equivalent of a concertmaster for each section. In this way the interdependencies in the system can be better appreciated, and roles and responsibilities for different research funders and actors can be more clearly understood—and counted on to move more quickly—in the event of an outbreak. The choice of a trusted fully competent R&D 'conductor', however, remains unsettled.

Recommendation 1. GPMB should encourage a comprehensive effort to describe the pandemic preparedness R&D ecosystem, including opportunities, deficiencies, and gaps, as well as its interdependencies. In particular, it should identify where there are funding agencies or research groups who are or can be responsible for galvanizing necessary action. The GPMB should also consider what entity or entities should be vested with the responsibility to address and implement the R&D Roadmaps, identify persistent gaps, and encourage researchers and their funders to close those gaps. A coalition of funders, such as GloPID-R, seems necessary but not sufficient to accomplish this goal. GPMB should also examine public-private partnership models that include traditional research and government funders as well as private-sector research collaboration and funding. If such a system is developed, it could serve as a model for monitoring and facilitating better R&D coordination in an outbreak.

2. Enabling science networks to support product-specific and non-product specific R&D

The R&D ecosystem for pandemic preparedness depends on fundamental biological knowledge which leads to insights, platforms and prototypes prepositioned to rapidly develop, test and produce needed drugs, vaccines, diagnostics and other materials when a new pathogen emerges or a new outbreak occurs. It builds on research to understand the ecology, biology, molecular pathogenesis and host response to microbial threats which can be generated by creative scientists anywhere in the world if they have access to essential funding and open routes of communication. The R&D preparedness ecosystem itself requires predictable research

[5] https://www.glopid-r.org/wp-content/uploads/2020/08/covid-19-research-synergies-meetings-2020-summaries.pdf
[6] https://www.ukcdr.org.uk/funding-landscape/covid-19-research-project-tracker/

infrastructure and funding mechanisms for rapid and effective translational research to support product development in a new outbreak. This is why the basic research infrastructure and funding mechanisms must be in place prior to an outbreak, including those elements that explicitly support product development translational research. Then, at the earliest sign of an outbreak, it needs to be to be activated, ramped up, funded, and shared in the 'precompetitive space'. Because many of the core activities are predictable, the potential implementers of this research can and should be identified in advance through an inclusive global consensus process. As an example of progress, pathogen genome sequencing has advanced and been innovatively applied, as evidenced by rapid sequence sharing in the 2014 Nigeria Lassa outbreak, the 2015 Ebola outbreak in DRC, and for COVID-19 as well. Other areas, however, are lagging. For example, China did not share coronavirus samples outside of China, and researchers needed to wait until the disease appeared in other countries that were able to grow the virus and establish sharing mechanisms. In addition, the PIP framework, which was in the process of being updated when the COVID-19 pandemic began, does not apply to non-influenza pathogens other than as a model.

However, other areas of enabling science have continued to show persistent gaps or deficits in the speed of activation and release of information. For these gaps to close, the global R&D ecosystem must: 1. Agree on the core set of enabling activities; 2. Agree on a potential, globally representative set of participants and an outbreak-ready selection mechanism for implementers; 3. Identify initial funding sources and triggers for rapid release of funds; 4. Agree on full, open and rapid sharing of products. These enabling activities include, but are not limited to: 1. A structure (currently GISAID[7]) with sufficient funding to support the handling, quality checking, and curation of multiple gene sequences and rapidly release information; 2. Pre-designated regional entities able to receive virus isolates, safely prepare virus stock and quickly share them with authorized research laboratories; 3. Pre-designated regional entities that can collect and curate biological reference material for studies of the immune response and ultimately define markers of protective immunity, and to develop derivative products such as assays and biological standards; 4. Pre-designated entities to collect and develop validation and evaluation panels for diagnostic tests; 5. Pre-designated entities to develop, validate and share animal models. Each will need the ability to manage Consent, Non-Disclosure Agreements (NDAs), and Material Transfer Agreements (MTAs) to develop derivative products such as assays and biological standards.

For this to be successful, there must be: 1. An established expert mechanism to equitably prioritize recipients for these regional/global resources, to maximize public health benefits, operating for the public good, serving regional and national needs, consistent with WHO principles of data sharing; 2. Established mechanisms for regional and/or global sample sharing and material transfer agreements; 3. A mechanism for rapid release of funds at the beginning of an outbreak; and 4. Agreed on mechanisms for information exchange and research with private sector entities. It should also be acknowledged that not all outbreaks will become pandemics, and for this system to be effective, there will of necessity be occasions when the global system and expenditure is activated, and then winds down if the outbreak can be well contained with minimal new

[7] GISAID Initiative: Originally known as the Global Initiative on Sharing All Influenza Data

countermeasure development. In this sense rapid activation should be viewed as a 'cost of preparedness.' CEPI[8] has taken this approach as part of its preparedness efforts, but this should be global and not limited to vaccine development. The GPMB needs to press the global funders to agree on a reasonable, 'no regret' annual budget for this element of preparedness, ensure those resources are always available, and can be rapidly released, ideally aiming for less than a week following a request. A trusted mechanism for coordinating this effort is essential. GloPID-R was created with funder and research coordination in mind, however, it has not been able to move as quickly as needed in the COVID-19 pandemic, in part because there was no ready pool of funding for it to draw on and because country limitations with regard to speed were not fully anticipated at the outset.

Recommendation 2. GPMB should examine whether treaty-like options can increase the pressure on countries to rapidly share relevant data and truly coordinate and together prioritize and assign research to the most appropriate partner. This would be carried out through the accelerated maturation of a global mechanism for science agencies in high and LMIC[9] countries, in collaboration with WHO, to develop and prioritize the preparedness R&D agenda, and be better primed and prepared to activate research at the time of an outbreak. It would require an effective governance structure, preposition of funds, and identified networks of investigators for this purpose. The World Bank could maintain a multi-donor trust fund for this effort, which would insure LMIC's that can contribute scientifically but lack the necessary national resources are included. WHO must be at this table to advocate for the global public health needs and the role and responsibility of LMICs to actively participate.

3. Epidemiological, clinical care, and clinical trials research

Identification of an outbreak at the earliest opportunity requires an effective routine surveillance system to quickly detect a cluster of unusual clinical cases, and ideally to identify its cause. While required under the IHR (2005), it is no secret that many countries still lack this capacity, although continued progress is evident, for example, through regional networks funded by the World Bank's REDISSE[10] project. Epidemiology and surveillance expertise are fundamental competencies for the R&D ecosystem. But even before formal surveillance mechanisms kick in astute clinicians recognizing unusual clusters of cases often provide an early warning of an outbreak in progress. This was true in the West Africa Ebola outbreak in the first two weeks of January 2014, and again in Wuhan in early December 2019. What was really unique in the latter setting was the initiative taken to send samples to two private laboratories for next generation sequencing, the basis to rapidly identify the cause as the novel SARS-CoV-2 virus.[11] This access to and early use of sequencing from clinical samples is an important harbinger of the way forward. What followed next was a crush of clinical research in China to try to understand the natural history of the disease, define context specific standards of care, and identify safe and effective therapy. However, the vast majority of studies were poorly designed, uncontrolled, with a small number of

[8] CEPI: Coalition for Epidemic Preparedness Innovations
[9] LMIC: Low and middle-income countries
[10] REDISSE: Regional Disease Surveillance Systems Enhancement
[11] SARS-CoV-2: The virus causing COVID-19, which we abbreviate as CoV-2

subjects, in effect creating anecdotal reports at best. They were then rapidly published on non-peer reviewed portals and have contributed virtually no evaluable information on efficacy or safety of products. In fact, many of these reports have served to set back attempts to generate reliable information. Similar concerns apply to many rapidly implemented studies around the world. Both pre-peer review portals and reputed journals have not served the need for *reliable information* rapidly released very well; a better balance between rapid information sharing and publication of vetted, peer-reviewed data is needed.

That said, there has also been progress as well as missed opportunities in preparing for and implementing therapeutics trials in outbreaks. The PREPARE[12] network, funded by the European Commission, had put in place a research network for therapeutics trials in the event of an influenza pandemic, over time tackling challenges in ethics, informed consent, and innovative study design. This network has now rapidly pivoted to COVID-19. WHO has made substantial progress in highlighting the essential elements of such trials. Similarly, although the protocol was not in place when the Ebola outbreak in North Kivu, DRC, began the PALM[13] therapeutics trial, designed to test four different therapies (one serving as the control for the other three), launched just three months later. The trial was stopped early by the DSMB because the results clearly identified two treatment arms to be superior to the other two. Most early therapeutics trials for COVID-19 in the U.S., at least at the time of this writing, have been opportunistic, small in size, and do not include appropriate control groups. An important exception is the Adaptive COVID-19 Treatment Trial (ACTT) [14] mechanism for randomized controlled trials to study potential therapeutics and vaccines initiated by NIAID that can be adapted to accommodate additional arms. Given the large number of infected patients in the U.S., it has been possible to reach study endpoints and evaluate and release the results. The UK RECOVERY trial is another example that has generated important findings with respect to hydroxychloroquine, antiretrovirals, and the use of dexamethasone, especially the ability to rapidly mobilize this prestanding trials network to pivot to COVID-19 research. These experiences highlight the need to rapidly act and the value of pre-established protocols with country and investigator buy-in prior to an outbreak. Compassionate use must be organized so that well designed trials can move forward without delaying or slowing subject accrual into proper controlled trials, as these are the fastest way to identify effective and safe treatment options. WHO also launched a multi-country, multi-armed therapeutics trial (SOLIDARITY)[15] engaging investigators from multiple LMICs as well. It enrolled 1000 patients from 5 countries in the first month and has since generated relevant information on the lack of efficacy of hydroxychloroquine and lopinavir/ritonavir. A number of the sites need technical support to participate, and WHO has to generate the resources required to provide systematic assistance. None the less this represents a novel, potential capacity-building effort in real-time. Mechanisms to provide advanced funding to sustain and build upon this initiative, once this pandemic ends, remains a challenge.

---

[12] PREPARE: Platform foR European Preparedness Against (Re-) emerging Epidemics (https://www.prepare-europe.eu/)

[13] PALM: Pamoja Tulinde Maisha, which means"Together Save Lives" in Kiswahili

[14] https://www.niaid.nih.gov/diseases-conditions/covid-19-clinical-research

[15] SOLIDARITY Trial: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

Unfortunately, the predominant perspective of the interviewees is that the governance structure for this essential research effort was chaotic before COVID-19 and remains so, with multiple players, partnerships, and alliances competing, collaborating, and overlapping at the same time. The consensus is that WHO has important convening and norm-setting roles to play, laying out principles and practices for clinical research and clinical trials that should be adhered to, and advocating for LMICs to be engaged in the planning, decision-making and execution. However, nearly all of our interviewees agreed that WHO should not sponsor or conduct trials in pandemic settings, for reasons that include the need to focus on WHO's core mission to represent the public health needs of all countries, its human resources capacity limits, and because of significant concerns about potential conflict of interest with its normative and policy responsibilities. Going forward, it will be critical to asses this while identifying the characteristics required of potential sponsors, and the types of trial support that will be needed. For example, CEPI recently released an Expression of Interest call for such services for vaccine trials; the response confirms a significant pool of talent exists around the world to do such work.

Recommendation 3. Research funders, acting in a concerted and coordinated way, must insure there are strong and growing networks of clinical trial sites and investigators in place, so that clinical trials for therapeutics and vaccines can proceed quickly when the need and opportunity arise. They should have close links to country's epidemiologic and clinical care infrastructures. Core protocols should be in place and be socialized broadly in countries around the world. Such a consortium of research funders should identify essential criteria for, and maintain a network of potential sponsors, acting in coordination with WHO, that can be rapidly activated for multi-country, multi-product trials before and/or during outbreaks. GPMB will play an important role by monitoring progress, identifying gaps, and promoting solutions.

4. Diagnostics

Diagnostics are essential at the front end of R&D to determine the cause of an outbreak, identify who is infected, enable focused efforts to control it, and permit rigorous clinical research and trials to proceed. They facilitate timely public health actions (e.g. quarantine), or clinical interventions (proven treatment when available or emergency use of unproven or new and innovative approaches), and support decisions about how to pursue vaccine development strategies. To be maximally effective in a pandemic, tests need to be highly sensitive and specific, return results quickly, and be usable in a variety of settings as close to the patient as feasible. They must be available in the quantities needed for their purpose; in the case of a pandemic in massive quantities around the world and nearly simultaneously. The development of antigen-based platforms such as BioFire and GeneXPert represented a huge advance in diagnostic accuracy and ease of use and were essential to the recognition and control of the 2014 and 2018 DRC Ebola outbreaks. Easy to use point of care tests, such as the rapid antigen test for Ebola were transformative, enabling initial testing and isolation of people in remote areas while additional confirmation was pending. In theory, GeneXPert platforms can be configured to accommodate rapid detection cartridges for novel pathogens; however, funding to rapidly develop and produce

these at large-scale, and the relative lack of investment in point-of-care or point-of-patient tests, whether in a peripheral health post or home based, has been lacking. In the face of a novel pathogen, it is not clear that there is private sector willingness to invest, or who has the responsibility and financial resources to develop, validate, manufacture, procure or distribute them.

Preparedness to act early on in the current pandemic required a reliable, sensitive and specific detection system for coronavirus that could be modified to specifically detect CoV-2. PCR was fit for purpose and CoV-2 tests were rapidly developed, and in some countries scaled and used, but not everywhere. Two key issues emerge from this experience: 1) the lack of a global leadership and regulatory mechanism to insure that reliable and validated test kits can be made and made available everywhere they are required; 2) a coordinated global way to manage and assess the subsequent proliferation of test kits (The Foundation for Innovative New Diagnostics (FIND), currently lists 358 different CoV-2 PCR kits and 331 immunoassays available or in development[16]). The marketing and use of unvalidated or poorly performing tests, both for antigen and antibody, has led to important delays in the generation of reliable information, and there is currently no purchaser or market mechanism to ensure that quality low cost CoV-2 diagnostics will still be available as the pandemic wanes or potentially reappears. Further, funding and leadership are essential to stimulate innovation in the diagnostics arena, and to leverage outbreak situations for large step improvements in diagnostics, e.g. lower cost community-level testing (ideally with a centralized verification system) and with a simple rapid readout.

While the power of platform technologies to be transformative for epidemic response is obvious, there have not been significant advances in diagnostic test platforms for at least 5 years. COVID-19 has highlighted the desirability for point-of-patient rapid tests, as well as the significant challenges posed by pandemic-sized demand, with raw materials, reagents, and ancillaries as simple as optimized sampling swabs being unavailable in the supply chain. Validation for test kits is essential, but an additional bottleneck for rapid progress is the absence of global or regional entities charged with specimen collection needed to develop validation panels (see section 2. Science Networks). There is no global mechanism to oversee regulatory approval, manufacture and distribution wherever they are needed. Further, specimen collection and use depend on the ability to negotiate sample sharing, export and import regulations, material transfer agreements and royalty payments. Once again, which entity has the mandate, authority and budget to navigate this terrain? Is it and should it be WHO? In the post-Ebola rush to address emerging infectious diseases, the R&D focus has been mostly on therapeutics and vaccines, and not on innovation in the diagnostics arena. But development of novel platforms and technologies is clearly needed, together with a more streamlined system to build a distributed but connected global manufacturing capacity in LMICs to meet surge demands, and potentially stimulate economic development at the same time (see section 9. Financing). New concepts of diagnostics preparedness are also needed; for example, it may prove cost effective to maintain a stockpile of raw materials for some types of tests, so that supply chain shortages can be mitigated in a pandemic. It remains to find an entity with the responsibility for such action; if left to the private

[16] FIND Diagnostics Pipeline: https://www.finddx.org/covid-19/pipeline/?section=molecular-assays#diag_tab

sector alone, the result will be the sale of such materials to the highest bidder or there will be no test kit available at all.

Recommendation 4. GPMB should identify innovation, development, manufacturing, distribution and use at scale of simple, sensitive and specific diagnostic test kits as a critical gap in the R&D preparedness ecosystem, and suggest how best to drive the agenda for efficient and flexible regulatory oversight, selection of a global set of high quality development, manufacture and distribution partners, preparedness and emergency funding mechanisms, and to leverage opportunities for innovation in design of new diagnostic platforms

5. Vaccines

The WHO R&D Blueprint for action to prevent epidemics, the development of R&D Roadmaps, and listing of priority pathogens have created new opportunities for better linked global collaboration for vaccine development. This effort has relied on WHO credibility to bring key players to convene, including LMIC's at high risk of potentially pandemic diseases. Convening, however, is only a necessary starter, and it is imperative to engage expertise in vaccine design, development, production, and preclinical and clinical research. This begins with basic research on pathogens, an extended translational R&D preparedness research and development effort to turn candidate formulations into candidate vaccines, and to scale up process engineering and, finally, to product manufacturing, primarily by the private sector. In a pandemic, these latter efforts need to be done in parallel and at risk, not in sequence because we can't wait. Such needs inspired the creation of CEPI, which has been at the center of R&D vaccine development both before and especially during the current CoV-2 pandemic.

Major research and research funding organizations have begun to change strategy for vaccine development by investing in vaccine platforms for particular virus families of concern, because the immune response may be similar across the family members and switching of the agent specific protective antigens may be sufficient to quickly obtain a candidate vaccine for a new emerging pathogen. An example is the mRNA vaccine platform developed for SARS and MERS[17] by the Vaccine Research Center at NIH, which was rapidly mobilized for SARS-CoV-2 when its genetic sequence was published. This approach has enabled rapid funding from BARDA[18] and CEPI to biotech companies working on mRNA vaccines and other platforms to prepare CoV-2 candidate vaccines. For one of these, phase 1 trials began within two months of public sequence availability. Better coordination among research funders and their grantees and with one another could increase the efficiency with which these virus families of interest are targeted, optimized expression platforms can be developed, and early human safety trials conducted prior to an outbreak. To date, full information exchange with China and coordination of efforts for vaccine development for CoV-2 has been problematic and needs resolution.

[17] MERS: Middle East Respiratory Syndrome

[18] BARDA: Biomedical Advanced Research and Development Authority, US Department of Health and Human Services

The creation of CEPI dramatically changed the global landscape for vaccine development. In its initial 5-year funding period, CEPI established a core portfolio of 17 vaccine candidates for 5 pathogens on the WHO priority list. At the time of the CoV-2 outbreak, CEPI was already supporting via contracts the development of 3 additional platform technologies at the proof of concept stage that can be adapted to outbreak situations, as well as to ensure equitable access. They rapidly engaged the MERS and platform developers and executed new contracts within 2 weeks of the release of the CoV-2 genetic sequence. CEPI is currently supporting 10 COVID vaccine candidates with a goal of advancing 3 and scaling to hundreds of millions of doses for introduction under regulatory emergency use authorizations. WHO maintains an inventory of COVID-19 vaccine candidates on its website, and as of April 20, 2020 there were 5 in clinical trials, 1 in Phase 2 and 4 in Phase 1, including 3 from Chinese companies. Some have or will shortly progress to Phase 3. In addition, 71 candidates in preclinical evaluation were listed. CEPI's emergence in the global R&D ecosystem has catalyzed critical conversation among ecosystem partners regarding regulatory collaboration, community involvement, equitable access and sustainable ready reserves of investigational vaccines when there is no business model for occasional manufacturing of such products.

As the COVID-19 pandemic has evolved, it has become clear that the development of effective vaccines alone will be insufficient for a robust global public health response. In April, the Access to COVID-19 Tools (ACT) Accelerator[19] was launched as a new global collaboration to speed the development and production of diagnostics, therapy and vaccines for COVID-19, and to insure equitable access to these essential products of R&D. The ACT Accelerator is a joint initiative of WHO, the Government of France, the European Commission, and the Bill and Melinda Gates Foundation, to bring governments, scientists, businesses, civil society, philanthropists and global health organizations such as the Wellcome Trust, CEPI, FIND, GAVI (the Global Alliance for Vaccines and Immunization), the Global Fund, Unitaid, the World Bank and its Global Financing Facility. With the creative leadership of GAVI, CEPI and WHO, another entity, COVAX, has emerged to shepherd the development and manufacture of vaccines and guarantee fair and equitable access for every country in the world. These represent major innovations, and an indication that with effective global leadership it is possible to support market commitments, procurements, and fair global allocation of vaccines.

CEPI was already prepared to launch a set of enabling science activities to support pre-clinical science needs for development of its pathogen specific portfolio and had begun to establish implementing partnerships to address the needs identified in section 2 (Science Networks) of this report. The existence of vaccine development partners for MERS and for platform technologies, combined with readily available funding, enabled the rapid roll out of vaccine development for COVID-19 when CoV-2 began to spread globally in January 2020, using an accelerated development paradigm to conduct development and scale up activities in parallel. Vaccine development has interdependencies with diagnostic test development to inform decisions about the need for vaccine development, obtain biological specimens for assay development as well as diagnostic test validations, and in epidemic control, in concert with public health and treatment

[19] https://www.who.int/initiatives/act-accelerator

options. There are additional overlaps with therapeutics development, particularly around antibody constructs including convalescent plasma and monoclonal antibodies that may afford at least short-term passive immunity as well as treatment benefits. How best to interface vaccine development with diagnostics and therapeutics development efforts remains critical and unresolved, but could be addressed and assessed by GPMB as CEPI develops its strategy around its financing replenishment.

Recommendation 5. GPMB should closely monitor the progress of CEPI and propose and promote greater funder coordination and acceleration of closer links between basic science and development of platform technologies for virus families, to enable CEPI and other vaccine development efforts to accelerate R&D preparedness for pandemic responses. GPMB can leverage lessons learned as CEPI makes progress, encounters and works to overcome barriers and bridge vaccine development from the upstream end of the R&D ecosystem to manufacture at scale and global access, and promote similar progress and preparedness for diagnostics, therapeutics and other essential products for epidemic and pandemic response. It is essential that vaccines (as with other types of products) are available everywhere needed and are not subject to export restrictions by countries in which they are produced. GPMB should advocate for global coordination of the different components of the R&D ecosystem for vaccines, including scale up, manufacturing at risk, allocation, delivery and deployment. This requires a clear and dependable financing mechanism for those activities, kept on track by GPMB assessments, and advocacy for the future support for CEPI beyond its first five years of funding, as well as secured funding for the long term.

6. Therapeutics

Therapeutics are needed to treat infected people in every emerging outbreak, both before a vaccine is available and widely accepted, as well as afterwards for those who develop the disease because they weren't immunized or because of vaccine failure in them. Effective therapeutics build on the value of quality clinical care, and rarely can dramatically alter progress of epidemics without an effective healthcare system. While not an R&D issue, preparedness to improve healthcare delivery prior to an outbreak will enable rapid assessment of the healthcare infrastructure and the articulation of a locally relevant optimized standard of care as the first step in delivering effective therapy during epidemic or pandemic responses. The development of novel therapeutics takes a two-pronged approach, with important preparedness aspects to each. First is identification of existing therapeutic candidates with a promising mechanism of action. The research strategy to screen for potentially protective licensed drugs for repurposing is the same for the use of small molecule libraries to search for new molecules. It is well described, from high-throughput screening in vitro, to animal models that provide sufficient information to proceed to Phase 1 safety studies in humans. Taking an organized, virus family/prototype pathogen preparedness approach has the potential to accelerate this work so that candidates further along the development pathway can be readily identified. However, who does this, how coordinated the research is, how rapidly studies can be funded and initiated early in an outbreak with pandemic potential, how private sector companies are involved, and how it can be supported as a global public good remain open questions.

The second strategy is the development of platform technologies through which novel therapeutics can be developed. For example, the ability to generate human or humanized animal protective antibodies is increasingly efficient and scalable, and various antibody therapeutics have been proven safe and effective in recent Ebola outbreaks. Next generation platforms, some of which might simultaneously serve a short-term preventive as well as therapeutic function, are in the early development stage. As advances in immunology and structural biology continue, such platforms seem within reach. However, as is the case with other areas of R&D preparedness, apart from individual research activities, there is currently no global entity able to organize, lead and fund such development efforts for therapeutics among academic and private sector entities. The emergence of the Therapeutics Accelerator during the COVID-19 pandemic is encouraging, but such an effort needs to be sustained in order to be in place when needed during an outbreak, and not another one-off for CoV-2 which disappears when the outbreak recedes. As described in section 3 (Epidemiological and Clinical Research) above, use of a core protocol and multi-arm, adaptive randomized controlled trial design (with shared control groups) is a significant improvement in efficient and accepted mechanisms for clinical trials. WHO has a recognized role to convene the leading representatives of the essential sectors to promote collaborations to advance necessary research and development. What remains particularly vexing is to organize the governance of clinical trial initiatives and selecting which products enter into trial, including an agreed adaptive study design to sequentially remove poorly performing agents and add in others that may represent significant improvements. To play this role with least controversy WHO needs to partner more effectively with trial sponsors and executors, and refrain from directly sponsoring or leading clinical research going forward because of the essential requirement to avoid even the perception of conflict of interest with its normative, policy, and technical support roles. Maintaining standing clinical trial networks will facilitate this work. Going forward, it is conceivable that an entity charged with therapeutics development could directly or indirectly (e.g. through an implementing partner mechanism) sponsor critical clinical trials. Continuing capacity strengthening for clinical trials in LMIC's at greater risk of emerging outbreaks must continue and increase.

The creation of CEPI in the wake of failures to be prepared before and to efficiently move vaccine development forward during the Ebola outbreak in West Africa in 2014-2015 has highlighted the need for similar mechanisms for therapeutics. This must also build on continuing basic research traditionally funded by science agencies, and collegial collaboration with industry to study repurposing of already licensed drugs for new uses, screening of compound libraries, or enhanced evaluation of platform technologies such as human monoclonal antibodies. Improving R&D preparedness for therapeutics requires a similar mechanism. Whether the COVID-19 Therapeutics Accelerator will evolve to fulfill this need for future pandemic preparedness or whether existing structures can be configured to advance R&D preparedness for other essential countermeasures and products remains to be seen.

Recommendation 6. GPMB should closely monitor the impact of the COVID-19 Therapeutics Accelerator and consider whether it can be expanded to serve as the model for R&D preparedness for therapeutics, how to encourage collaboration and coordination among research

funders to support therapeutics research across the ecosystem, and how to create synergies with similar efforts for vaccine development. An important role for GPMB will be to catalyze discussions regarding a financing mechanism for surge manufacturing for therapeutics as well as development of a global purchasing pool to facilitate fair access for LMICs facing an outbreak of serious magnitude.

7. PPE, ventilators, and other necessary commodities

Personal protective equipment (PPE) is an essential commodity to protect front-line health workers from high-risk exposures, including first responders and caregivers with direct contact with patients on one end, to safe burial teams on the other end, and everything in between. The current COVID-19 pandemic has demonstrated the need for appropriate PPE for other categories of society, including essential non-healthcare workers and the public when they must venture out of self or mandated isolation at home. What has been made eminently clear is that PPE for CoV-2 is not the same as PPE for Ebola. We are unprepared with designs for updated low cost, safe, innovative potentially reusable PPE, easily and safely donned and doffed, that allow clinicians sufficient comfort and mobility to readily carry out patient care tasks and be compatible with use in extreme climates, and do not dehumanize the wearer by obscuring their face. The lack of standardized "fit-for-purpose" PPE, whether for a filovirus or a coronavirus or the next 'disease X', that can be rapidly produced when surge conditions require it must be overcome. Appropriate PPE is an essential component of preparedness, and too little attention has been given to this, or to an R&D preparedness agenda to develop the next generations of these essential supplies.

Manufacturing, and regulatory approval including certification of adherence to international quality standards must be addressed in addition to cost and distribution. Research gaps exist to inform 1) what types of PPE are needed for different pathogens in different environments, 2) human centered design to inform the R&D, and 3) process engineering to enable globally distributed manufacture of high quality at required scale. The extent of the current outbreak and the number of critically ill patients with progressive life systems failure has also pointed out the shortage of intensive care support of respiratory and renal function, including ventilators and dialysis equipment and supplies. While other outbreaks and agents, including the possibility or likelihood of future annual/seasonal return of CoV-2 outbreaks, may not be at the same global scale as at present, R&D for innovations leading to lower cost, less complex support technology but functional to meet the essential clinical needs for critical care remains to be created. This requires advocacy and financing, and when better product designs emerge there must be global action to make them and make them available when needed. One strategy to consider for some of the necessary equipment may be to produce and store the parts around the globe for later assembly when there is a surge in needs. Alternatively, proven innovative manufacturing processes – for example 3-D printing – that can be very quickly mobilized to meet acute needs around the globe is also feasible. This gap in R&D for innovative design does not end with ventilators or dialysis equipment. For example, point of care ultrasound to assess pulmonary involvement in COVID-19 is being increasingly used in LMICs in a variety of settings in which more expensive imaging technologies are not available or, frankly, not necessary. They are also useful for other non-pandemic health concerns.

Recommendation 7. GPMB should stimulate an assessment of supplies and technologies that might be in short supply in a pandemic, and consider where R&D could play a role in improving designs that enhance preparedness for a serious outbreak, and monitor the adequacy of the global response.

8. Manufacturing

Once effective and usable diagnostics, vaccines and therapeutics (and other necessary products) are developed they need to be accessible during a pandemic or large epidemic to very large populations quickly, on the order of billions of doses in the case of vaccines. Rapid manufacturing requires repurposing and scale up of systems and facilities that are already in place, building new manufacturing capacity, or maintaining a sufficient 'warm base' of manufacturing capacity for whatever types of products may need to be made quickly. Our interviews identified five key themes for improving manufacturing capacity.

First, in some cases, because manufacturing processes are slow, often antiquated, and not necessarily well matched to the newer products being developed, research investments in engineering science are necessary to ensure there is a good match between current or future products and the ability to make massive quantities quickly. For example, biomanufacturing processes may offer potential to speed up manufacture of some products, in comparison to traditional processing methods. Ideally, manufacturing facilities for diagnostics, vaccines and therapeutics will be aligned with the most-promising platforms under development, e.g. innovative rapid point of care diagnostics, nucleic acid vaccines, and monoclonal antibodies. Second, in a pandemic situation, products will most likely need to be considered as global public goods, and both demand and development of a commercial market will be uncertain. The lack of a specific global entity responsible for either identifying or financing the capacity to produce these products for a pandemic, in many cases at financial or liability risk, is of particular concern. Third, even if this is solved there is no clear purchaser for these products, so most private sector manufacturers are unlikely to fully engage. This is especially so if they must make massive investments to manufacture products before it is clear that they work, and if there is no clear future market for their products, but that is precisely when those products need to be made. Fourth, novel therapeutics and vaccines are increasingly developed in academic institutions or small biotech companies, and it is unusual for them to identify and complete tech transfer to a large-scale manufacturing partner until development is complete, products are licensed, and a market need is established. Tech transfer is typically a lengthy process, not suitable for pandemic response, and better more efficient mechanisms must be in place in advance.

Fifth, realizing the goal that pandemic products are global public goods will likely require distributed manufacturing in multiple countries, so that no single country can seize products made within its borders for itself. This need for redundancy carries with it additional costs, financing, and more complex standardization and quality control considerations. In response to new emerging pathogens or in pandemic outbreaks, siting this capacity in small population countries, or in developing countries through the growing network of the Developing Country Vaccine

Manufacturers Network, whose members manufacture numerous vaccines of public health importance, can help ensure a distributed global capability to manufacture affordable high quality vaccines and potentially other products when confronted with global needs.

Recommendation 8: To be effective in pandemic response, R&D preparedness requires investments in manufacturing science, technology, engineering, and available capacity when needed to make large volumes of necessary products quickly. A global mechanism for financing the manufacture (and ultimately for purchase) of products that will satisfy the global public goods needs for equitable distribution must be identified and in place prior to the next pandemic to avoid bottlenecks and delays in production and distribution. A more dispersed supply chain may also be essential, not only for diagnostics, vaccines and therapeutics, but for PPE and other commodities such as ventilators, in order to get them to populations when they need them. Leveraging the network of DCVMNs for vaccines, and considering analog partners for other products, and providing needed financing to ensure surge capacity during pandemics can meet the need, facilitate global equitable access, and also be an economic benefit for the countries involved.

9. Financing the R&D ecosystem

Preparedness requires a commitment to invest. The only pertinent questions are what should the investment include, how much is required, and who pays. Investments are needed in several upstream research domains: 1) to better characterize viral families, 2) understand their basic biology, immunology and pathogenic factors, 3) and identify molecular targets for diagnostics, vaccines and antiviral therapy, as well as immunotherapy options to enhance immune protection. There are also limits to investments, and the preparedness strategy will need to focus first on virus families most likely to cause the next new pandemic while maintaining attention to known outbreak viruses that can readily mutate and evolve, to fund research to identify prototypes or platforms in advance of an outbreak, and more rapidly initiate R&D for the emerging new or new variant pathogen. The research must become less competitive and more coordinated and collaborative. Focusing and coordinating research to inform R&D preparedness makes both scientific and financial sense. There are additional needs across the translational R&D agenda as well, for example: 1) capacity to identify and sequence pathogens, 2) to curate and share sequence, 3) to archive all emerging viruses, and 4) provide strains for research to pre-approved laboratories and investigators. A formal mechanism and commitment to finance these activities is critical to effective global collaboration.

Once an outbreak begins, though, funding must be rapidly released to kick start the next phase science to find specific products tailored to the outbreak pathogen. GloPID-R was established in 2013 to facilitate an “effective research response of a new or re-emerging infectious disease with epidemic and pandemic potential.” Advance planning before the onset of an outbreak is the only way to identify the additional funds needed to fuel the acute R&D needs during an outbreak and to ensure they are rapidly released. While CEPI was formed to develop vaccines for potentially epidemic diseases, it has found that its funding was insufficient for a pandemic response, both because so many aspects of development needed to be done in parallel, and because there is

no global entity responsible for financing scale up development or for making a sufficient advanced purchase commitment for private sector manufacturing to occur. The implication is that the usual mission related replenishment funding for an entity charged with development may not be sufficient to cover future unanticipated challenges, and therefore financing mechanisms to respond to a pandemic-sized event should be thought through and put in place as part of a global preparedness strategy. The World Bank may be particularly suited to support such financing mechanisms. If the Bank were to play such a role, it would be particularly well served and understood were there a Senior Health Scientist reporting to the highest levels of Bank leadership.

Without such mechanisms, and without liability protection and indemnification, large manufacturers cannot and will not fully take on the financial and liability risks involved. There are examples where shared financing by private sector and public and/or philanthropic funding meets the need, for example current support for some of the CoV-2 vaccines. Some high-income countries, notably the US, have mechanisms to address financial and liability risks, but that leaves most LMIC's without the necessary resources and makes it more difficult for them to be engaged as R&D partners.

Recommendation 9: GPMB should call on the major national research organizations and their governments to identify and/or develop funding sources for collaborative R&D preparedness. CEPI-like mechanisms for diagnostics and therapeutics, with funding commensurate with the mission, would jump start the process for these essential products. The GPMB should consider whether to recommend building this into the current CEPI structure, or to create new or use other existing entities for this work. Additionally, the GPMB should call on research funders to pre-position funds, perhaps through a multi-donor trust fund held at the World Bank, that can be released, perhaps to Glopid-R or a similarly structured entity, within days to kickstart essential research when an outbreak occurs. It should also recommend an amount of 'no regret' funding that would be reasonable to have spent in the event that such an outbreak does not expand to a major epidemic or pandemic. This funding should always be available, with the intent that some resources would be expended well before a PHEIC is declared. Additionally, GPMB should catalyze the development of the remaining needed financing structures so that the essential products that come as the result of R&D can be manufactured at scale and made available through a fair allocation system to populations and countries in need. The GPMB might also suggest that the World Bank consider changes to its own structure, in part by adding a Senior Health Scientist to its senior leadership. That individual would be ideally positioned to lead Bank initiatives to strengthen R&D preparedness in the interpandemic period, perhaps with a focus on human capital development, as well as to develop and participate in the governance of other acute pandemic financing efforts, ensuring they are in place and rapidly deployable when the next pandemic emerges.

Conclusions and related concerns

The global architecture and its capacity to respond to new and recurrent threats is complex and multi-faceted, continually facing new challenges requiring adaptations in real time. There have been improvements in many aspects of the global R&D mechanisms, but some lag behind and

unaddressed gaps are continually revealed. As is clear from COVID-19, the agreements embodied in the IHR and the PIP framework are insufficient for pandemic response; it may be time to consider a new treaty on pandemic threats that not only strengthens surveillance and, equally as important, reporting, but also virus sequence and isolate sharing, and puts in place agreements and funding structures for key R&D activities that need to occur both regionally and globally.

WHO has critical roles to play in developing and securing such a global treaty. It is also critical to recognize its essential role in global public health crises such as COVID-19, leading some initiatives, and at the table when others take the lead. This is important considering the vast stretch of the R&D preparedness ecosystem and the real limitations in WHO staffing and financial resources. It is counter-productive to expect WHO to flawlessly engage in every aspect of R&D preparedness and outbreak response without the necessary people, tools and finances, and then criticize WHO when it does not perform to expectations. It is both easy to criticize and oxymoronic to do so; it is more relevant to recognize the roles WHO should and can undertake, and be sure the organization can deliver, often what only WHO can do, both before and during an outbreak.

GPMB itself has an important role to play to monitor progress and improvement and to keep the global enterprise focused on continuous quality improvement. There is no other independent expert body to take on this critical role, and as GPMB itself matures it needs to become more proactive, constructively critical, and willing to hold various players and partners accountable, including in the midst of important outbreaks. The destructive nature of the COVID-19 pandemic has highlighted the health, social, economic, and political consequences of persistent gaps in R&D preparedness, particularly with regard to the organization and speed of mobilization of R&D efforts. The R&D ecosystem as described in this report is vast. To address every aspect of it at once is an unrealistic expectation. This report will hopefully make clear what ultimately is needed; GPMB will need to determine what are the short, medium, and longer term priorities to tackle. From our perspective, these fall into four categories: 1) defining the R&D ecosystem and recommending an approach to its governance, when it comes to pandemic preparedness, 2) studying and recommending a global financing system that addresses the situation of the entire world having needs for diagnostics, therapeutics, vaccines and PPE. This should focus particularly on assuming the financial risks for scale up, manufacturing at risk, purchasing commitments in support of a globally fair allocation system. Forming a time-limited, high level commission under the GPMB umbrella might be a useful way for this work to proceed, 3) monitoring R&D preparedness efforts, and 4) taking on a new mission, to start immediately, to monitor critical activities during a pandemic or an outbreak with pandemic potential, with the goal of helping global stakeholders to rapidly see and address bottlenecks to progress.

This is a very challenging agenda for GPMB with its own limitations in staff and resources. It may not be implementable across all of its dimensions at the same time. But to make a start towards realization the broad R&D preparedness agenda must be identified and the need to move forward recognized. This will not be easy. But without a doubt, unless this is begun and pursued under watchful monitoring and assessment of progress, the world will experience another COVID-19-like pandemic in the forseeable future, with equal or perhaps greater consequences to life,

economic growth, and political stability that will threaten the world order for all nations and all populations.

Appendix: List of interviewees and affiliations

No.	First Name	Last Name	Affiliation
1	Sarah	Austin	NIAID
2	Sulzhan	Bali	World Bank
3	Catharina	Boehme	FINDDX
4	Dennis	Carroll	USAID
5	Gail	Carson	Nuffield Department of Medicine
6	Mukesh	Chawla	World Bank
7	John Paul	Clark	World Bank
8	Beth-Ann	Coller	Merck
9	Peter	Daszak	EcoHealth Alliance
10	Annette	Dixon	World Bank
11	Althea	Dopart	World Bank
12	Ruxandra	Draghia-Akli	Johnson & Johnson
13	Victor	Dzau	NAM
14	Tim	Evans	Former World Bank, McGill University
15	Patricia	Geli	World Bank
16	Josie	Golding	Wellcome Trust
17	Barney	Graham	NIAID
18	Rebecca	Grais	Epicentre
19	Margaret	Hamburg	AAAS
20	Richard	Hatchett	CEPI
21	Sara	Hersey	World Bank
22	David	Heymann	Chatham House
23	Elizabeth	Higgs	NIAID
24	Alice	Jamieson	Wellcome Trust
25	Rebecca	Katz	Georgetown University Medical Center
26	Marie-Paule	Kieny	Former WHO, INSERM
27	Jerome	Kim	International Vaccine Institute
28	Gary	Kobinger	University of Laval
29	Christos	Kyratsous	Regeneron
30	Cliff	Lane	NIAID
31	Mark	Lim	ASMUSA
32	John	Markels	Merck
33	Hilary	Marston	NIAID
34	John	Mascola	NIAID
35	Tarik	Mohammed	NCDC
36	Suerie	Moon	Graduate Institute of International/Development Studies
37	Carlos	Morel	Fiocruz
38	Michael	Nally	Merck
39	Mike	Osterholm	University of Minnesota CIDRAP
40	Toomas	Palu	World Bank
41	Charles Ok	Pannenborg	World Bank (Retired)

42	Muhammad	Pate	World Bank
43	Alexandra	Phalen	Georgetown University Medical Center
44	Ranga	Sampath	FINDDX
45	Richard	Seifman	Former World Bank, UN Associations of DC Area
46	Anant	Shah	Merck
47	Armand	Sprecher	MSF
48	Paul	Stoffels	Johnson & Johnoson
49	Walter	Straus	Merck
50	Soumya	Swaminathan	WHO
51	Wendy	Taylor	Rockefeller Foundation Fellow
52	Andrew	Trister	Gates Foundation
53	Linfa	Wang	Duke Global Health Institute, SIngapore
54	Yazdan	Yazdanpanah	Bichet Claude Bernard Hospital