



Urgent lessons from COVID 19: why the world needs a standing, coordinated system and sustainable financing for global research and development

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The research and development (R&D) ecosystem has evolved over the past decade to include pandemic infectious diseases, building on experience from multiple recent outbreaks. Outcomes of this evolution have been particularly evident during the COVID-19 pandemic with accelerated development of vaccines and monoclonal antibodies, as well as novel clinical trial designs. These products were developed, trialled, manufactured, and authorised for use in several countries within a year of the pandemic's onset. Many gaps remain, however, that must be bridged to establish a truly efficient and effective end-to-end R&D preparedness and response ecosystem. Foremost among them is a global financing system. In addition, important changes are required for multiple aspects of enabling sciences and product development. For each of these elements we identify priorities for improved and faster functionality. There will be no better time than now to seriously address these needs, however difficult, as the ravages of COVID-19 continue to accelerate with devastating health, social, and economic consequences for the entire community of nations.

Introduction

2020 will long be remembered as the year of COVID-19, not only for its devastating health, social, and economic consequences around the world, but for forcing the world to consider the implications of the pandemic for solidarity and equity. It will be remembered as a year that exposed the fragility of our global system of preparedness and response to pandemics, and the fragmentation of our research and development (R&D) ecosystem. But it will also be remembered as a time of unprecedented innovation and scientific collaboration, in which the global R&D components came together and produced novel technologies and analytic tools, assessed treatments, and developed safe and effective vaccines in record time.¹ Yet, even with these achievements, R&D collaboration across the ecosystem fumbled and millions more could die before the essential products, such as new therapeutics or vaccines that are the fruits of the research and product development enterprise, become widely available everywhere. The successes have ignited a debate about global fairness and solidarity, and whether aspects of the R&D enterprise and its resultant products should be treated as global public goods, available and affordable in an equitable manner. To explore now what needs to be implemented for the future to achieve speed, coordination, and equity, we examine the evolution of the R&D ecosystem leading up to the COVID-19 pandemic (figure), describe important progress during the pandemic, and note crucial gaps that must be addressed for it to be better prepared and rapidly respond when the next pandemic arrives (table).^{4,5} Our perspective was enriched by insights from experts in different fields. A list of the individuals interviewed and their affiliations are available.⁴

The R&D ecosystem

The concept of a biomedical ecosystem emerged almost two decades ago, driven by the interests of the

pharmaceutical industry to expedite the translation of science into breakthrough therapies by enabling “all of us in the biomedical community to work together more effectively than ever before”.⁶ The idea soon evolved into one of an R&D ecosystem, to connect the talent and resources wherever they resided in academia, government, competitors in the biopharmaceutical industry, and patients or patient advocates in unique partnerships, including traditional competitive research and new

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Search strategy and selection criteria

We searched PubMed for peer-reviewed literature from Jan 1, 2000, to Jan 1, 2021, and medRxiv and bioRxiv from Jan 1, 2020, to Jan 1, 2021, focusing on the terms “pandemic disease”, “Ebola”, “SARS-CoV-2”, and “COVID-19”, linked to “research and development”, “product development”, and the various components of the end-to-end ecosystem, in particular “vaccines”, “therapeutics”, “diagnostics”, and “R&D ecosystem”. No language restrictions were applied. We also searched the internet for relevant grey literature and reviewed published and unpublished notes from numerous global meetings, especially those that we personally observed or participated in. In February and March, 2020, we interviewed 54 subject matter experts from basic and translational science, academic and private sector institutions, public health experts, epidemiologists and clinical trialists, vaccine and other product developers and producers, and high level staff in relevant government, industry, and multinational organisations, selected to cover each component of the end-to-end research and development ecosystem, with particular attention to representation from every continent across the globe. Interviews were recorded with permission and transcribed to identify key themes and insights relevant to the research and development preparedness and response ecosystem.

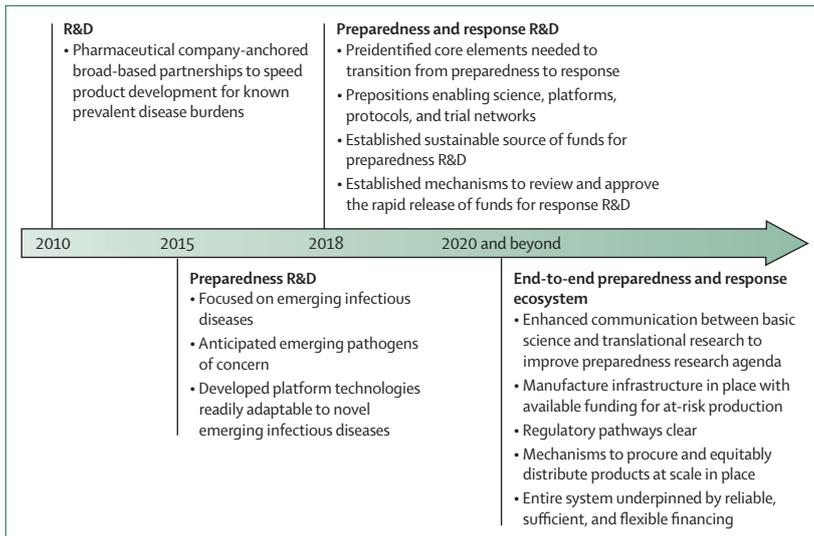


Figure: Evolution of the R&D ecosystem, 2010–20 and beyond
R&D=research and development.

creative collaborative R&D.^{7,8} The focus was primarily on known, prevalent chronic non-communicable diseases, not on emerging infectious disease threats. The 2009 H1N1 influenza pandemic and the later 2014–15 Ebola outbreak provided strong indications that the R&D ecosystem as envisioned could not move as fast as required during an outbreak in the absence of an earlier preparedness component. We know as well that this approach must build on a continuous investment in basic research on virulence, pathogenesis, immune response, and the identification of molecular and functional targets for diagnostics, drugs, and vaccines. Indeed, by 2014, earlier investments in Ebola vaccines and therapeutic monoclonal antibodies made it possible to bring products forward for clinical trials, albeit late in the outbreak when the decrease in cases made it difficult to reach trial endpoints.⁹ These experiences challenged the R&D community to conceptualise an R&D preparedness ecosystem for known and anticipated emerging epidemic threats while simultaneously setting the stage for product development geared to an unknown pathogen of the future—products whose characteristics and ultimate purpose are not known and might be developed for a market that never emerges.

The R&D preparedness ecosystem

Although it was clear that the world was unprepared for a rapidly spreading pandemic well before one became apparent in January, 2020, the lessons learned from the west Africa Ebola outbreak became an important turning point for new initiatives. WHO developed its R&D Blueprint for Action to Prevent Epidemics, a global strategy and preparedness plan to accelerate R&D activities during epidemics, reorganised its Health Emergencies Program to integrate research with

outbreak response,¹⁰ and identified a set of priority, high-consequence pathogens.¹¹ A novel international organisation, the Coalition for Epidemic Preparedness Innovations (CEPI), was designed and launched to expedite the development and delivery of vaccines for potentially epidemic diseases.¹² The Global Preparedness Monitoring Board (GPMB) was established, with the mandate to guide and monitor progress in the implementation of recommended improvements for preparedness and response.⁵ In addition, the Commission on a Global Health Risk Framework for the Future was convened by the US National Academy of Medicine, to provide guidelines for investments in pandemic preparedness and response and to accelerate R&D preparedness in advance of future global infectious disease emergencies.¹³ Research organisations also began to develop platform technologies for vaccines.¹⁴ For example, the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases (NIAID), using a prototype pathogen approach,¹⁵ studied how to stabilise the spike protein of coronaviruses and developed a platform strategy to rapidly prepare a vaccine candidate for any emerging novel coronavirus. NIAID also developed a public–private partnership (PPP) with Moderna Therapeutics to develop a candidate mRNA MERS coronavirus vaccine, and very soon after the genetic sequence of SARS-CoV-2 was posted a new mRNA construct targeting the new virus was sent to Moderna Therapeutics to engineer into their mRNA vaccine delivery platform. This preparedness R&D dramatically accelerated the initiation of a phase 1 study of this candidate SARS-CoV-2 vaccine.¹⁶ During January, 2020, BioNTech, a small German biotechnology company developing mRNA-based cancer immunotherapy, shifted its efforts to SARS-CoV-2 and formed a partnership with Pfizer. 11 months later, the Pfizer–BioNTech and Moderna Therapeutics vaccines both received authorisation for emergency use in the UK, Canada, the USA and subsequently in other countries. Approvals of vaccine candidates using other technologies are rapidly following with completion of phase 3 trials.

The evolving R&D preparedness ecosystem also fuelled interest in replacing the classical randomised clinical trial with adaptive randomised trial platforms, which are especially useful in times of pandemic emergency to enable simultaneous, sequential evaluation of multiple candidate products, resulting in a shorter time to interpretable results.^{17,18} For example, an adaptive trial done during the 2018–19 Ebola outbreak in Democratic Republic of the Congo provided evidence for the efficacy of two of the four therapeutic candidates studied, and made it possible to deploy them during the outbreak.¹⁹ Notably, the UK National Institute for Health Research had previously organised a standing clinical research network to preposition clinical research sites within the National Health Service and speed up trial initiation. When COVID-19 reached the UK the network was

	Recognised responsible entity (USA)	Recognised responsible entity (global)	What happened during the COVID-19 pandemic?	Priorities for improved and faster functionality
Enabling science				
Posting and curating gene sequences over time	GenBank	None	Global Initiative on Sharing All Influenza Data became the de facto repository	Establish and fully fund global genetic sequence repository; broaden WHO Influenza Coordinating Centers to cover other respiratory pathogens
Receive, grow, and share virus samples	CDC and NIAID	None	Virus was shared by countries once the pandemic had spread beyond China	Pre-position globally funded networks on every continent able to receive, verify, store, and share virus isolates
Collection and sharing of biological reference material	NIAID or CDC	None	Multiple ad hoc, unstandardised efforts	Pre-position funded networks of investigators and laboratories on every continent to collect, store, and share clinical and biological samples
Develop animal models	NIAID	None	Multiple ad hoc, unstandardised efforts	Pre-position funded network of containment laboratories to validate animal models and make them available
Epidemiology and surveillance	CDC	Country public health agencies (eg, Global Outbreak Alert and Response Network, and WHO)	No standard procedures in place resulted in haphazard data collection, often lacking crucial information	Pre-identify validated protocols and data collection tools rapidly available from WHO; secure funding for capacity strengthening required under International Health Regulations (2005)
Product development				
Diagnostics	CDC and BARDA	None	Initial reverse transcriptase PCR rapidly created by German scientists and shared via WHO; limited oversight and validation of other platforms; very limited access to diagnostics in LMICs	Establish and operationalise a diagnostics development partnership to innovate, validate, produce, and disseminate diagnostic tests for the pathogen appropriate for the outbreak situation
Therapeutics	NIAID and BARDA	None	The RECOVERY trial ² in the UK provided early, actionable results regarding repurposed and new drugs using an adaptive platform design; similar effort launched by WHO (SOLIDARITY trial); ³ lack of a ready analogue in the USA early in outbreak led to site competition and trial delays	Ready network for high throughput screening and testing of small molecule libraries; set up standing clinical research networks with available adaptive trial designs appropriate for outbreak settings; establish a go-to and funded entity for therapeutics development
Vaccines	NIAID, BARDA, or DOD	CEPI	CEPI investment in a broad portfolio of candidates from the beginning of the pandemic; early Chinese, Russian, and UK investments using multiple pathogen-agnostic platforms; private sector and academic collaborations produce hundreds of candidates	Identify stable funding for CEPI and expand development support through licensure for emerging and potential pandemic pathogens
Manufacturing scale up and innovative practices	HHS or DOD	None	The USA supported at-risk product manufacturing before proof of safety and efficacy; lack of similar global funding delayed manufacture of vaccine doses	Global network of manufacturing facilities for diagnostics, therapeutics, and vaccines with surge capacity for pandemics; mechanism for coordination and manufacturing capability on each continent
Advance market commitments	BARDA	None	The USA made major advance market commitments for selected candidate vaccines; the EU, UK, and other countries also made bilateral advance market deals; the COVID-19 Vaccine Facility was created to obtain vaccines for LMICs, but suffered from delayed execution due to lack of funding and insufficient product availability	A global collaborative mechanism to finance at-risk manufacturing, tied to advance market purchase commitments and ultimately to procurement, in a fashion that ensures equitable allocation to LMICs driven by optimal public health principles
Allocation, distribution, and administration	CDC or state and local public health agencies	WHO, UNICEF, or GAVI, the Vaccine Alliance, responsible for allocation of outbreak vaccines (eg, yellow fever), but pandemic mandate not defined	US CDC is responsible domestically, but major problems developed early in allocation and roll-out; WHO, GAVI, or UNICEF responsible for developing allocation framework including for vaccines; successful applications to be decided	New global mechanism might be needed, building on experience during this pandemic
Personal protective equipment, ventilators, and other medical devices	HHS (ASPR), DOD, or SNS	None	SNS previously depleted inventory for pandemic response in favour of bioterror attack response principles for deployment to states and resupply mechanisms disputed and unclear; EU Emergency Support Instrument available to help Member States respond to COVID-19; European Commission strategic medical stockpile and distribution mechanism available under the Union Civil Protection Mechanism; most LMICs unable to access adequate supplies	Design and develop a global strategic emergency stockpile, especially for LMICs
<p>CDC=Centers for Disease Control. NIAID=National Institute of Allergy and Infectious Diseases. BARDA=Biomedical Advanced Research and Development Authority. LMICs=low-income and middle-income countries. DOD=Department of Defense. CEPI=Coalition for Epidemic Preparedness Innovations. HHS=Health and Human Services. ASPR=Assistant Secretary for Preparedness and Response. SNS=Strategic National Stockpile.</p>				
Table: Gaps in research and development preparedness and activities needed to address them				

prepared to act, and a few months later the RECOVERY trial reported that dexamethasone significantly reduced mortality in patients with severe COVID-19 and, as importantly, identified therapies that offered no benefit but had potential adverse impacts, including lopinavir-ritonavir and hydroxychloroquine.² These results provided important clinical value in real time. Additional supportive data have come from a WHO organised global trials mechanism (SOLIDARITY)³ and from the US National Institutes of Health (NIH) programme, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership.²⁰

The end-to-end R&D preparedness and response ecosystem

The 2020 assessment of the R&D preparedness ecosystem for the GPMB,⁴ although noting substantial improvements in the R&D preparedness ecosystem, also identified the importance of seamlessly linking R&D preparedness to response when a new outbreak has occurred. The report found considerable gaps in the pre-COVID ecosystem and pointed to additional capabilities to ensure that the R&D ecosystem could rapidly manufacture and distribute needed medical countermeasures at pandemic scale to all nations affected by the outbreak. It also concluded that the usual linear model for R&D in the pharmaceutical sector, waiting for proof to invest and move from step to step, had to change to permit multiple steps to proceed in parallel to shorten the time not only to develop new products, but for them to be produced at scale and used throughout the world. Compared with parallel development models for private sector drug or vaccine development, for which the driver is efficiency and reduced cost of development,²¹ in this case the driver is increased speed to a usable product. In other words, a true, end-to-end R&D ecosystem must deliver needed products to people as rapidly as possible, and at scale in a globally fair and equitable fashion (figure). Although there has been progress towards realising that vision, the systems in the USA and elsewhere have evolved differently, highlighting gaps in each that must be bridged to realise the vision of a true end-to-end global capacity. Ideally, the USA will once again work effectively with partners around the world in this effort.

Contrasting systems and their gaps

The USA, a large, wealthy, sovereign nation, has important advantages when it comes to its R&D preparedness and response ecosystem. Through its government agencies, including NIH, the US Centers for Disease Control and Prevention, Biomedical Advanced Research and Development Authority, US Food and Drug Administration, and Department of Defense, the USA has the resources, funding, and coordination necessary to sustain essential end-to-end R&D functions before and during a pandemic. The US Government supports basic and translational research, public and private sector development partnerships, and early and sustained development of products,

including clinical trials, manufacture, regulatory approval, procurement and, ultimately, distribution of products. It also has a strong private sector pharmaceutical and biotechnology sector able, if not necessarily always willing, to engage in pandemic disease research, manufacture, and distribution of new products. During the COVID-19 pandemic, many of these organisational roles have been taken on by ACTIV and Operation Warp Speed—emergency programmes to identify useful therapeutics and to fund at-risk vaccine development, production, and advanced purchase contracts.^{20,22} On Jan 15, 2021 the incoming Biden administration announced that Operation Warp Speed would be phased out and a new structure would be created within the White House Coronavirus office to focus on improving vaccine distribution under new leadership.²³ Although there were many shortcomings in the US response to the pandemic, vaccine R&D was not among them—witness the collaboration between NIAID and Moderna Therapeutics to develop its mRNA vaccine candidate and Operation Warp Speed to move vaccine production forward by funding development and manufacturing before proof of efficacy was available.^{15,22} However, the primary intent of this effort was to produce products explicitly for USA use; substantial public funding covered much or all of the cost of development and advanced purchase for some products, with a goal that they would be free to the USA public during the pandemic. Advance purchase commitments might not be sufficient, however, for companies to sell their products at a price affordable globally, especially to low-income countries.

In contrast, the global system, comprised of 195 member nations of the UN and its agencies, is fragmented, poorly coordinated, and under-resourced. Some of these countries (for example the UK, France, Germany, Russia, China, India, and a few others) have remarkable scientific expertise and financial and infrastructure resources, but only a few can support an end-to-end R&D system from basic research before a crisis to approved products during the response to an outbreak. Some countries, such as the USA or Russia, followed their own path without collaborating with any coordinated global effort. Although the R&D roles and responsibilities for the various components of the ecosystem might be apparent, it is at best uncertain which entities have the responsibility and resources to support a global system for the multitude of essential activities for development and deployment. Although recognising that the global system is comprised of the efforts of individual countries, as well as scientists and multinational companies and organisations, the table identifies the major R&D activities required for the emerging end-to-end R&D preparedness and response ecosystem, contrasts US and global capacity, highlights the gaps revealed during the COVID-19 pandemic in the USA and around the world, and indicates what needs to be created, developed, and financed.

CEPI had already recognised some of these needs for vaccine development, even before January, 2020;²⁴ however,

there were no global entities with a clear mandate, responsibility, or resources to initiate product development in a pandemic. There were also no recognised organisations to support a pathogen repository, host their sequence information, grow and share virus isolates for essential research, and organise and collect biological reference materials from patients to support product development and validation of new diagnostic tests. Fortunately, some organisations simply stood up and did the right thing using their existing resources, but the ability to support, let alone to coordinate, investigators around the world was inadequate.

In early January, 2020, as the first reports of the new outbreak in China became evident, CEPI mobilised the vaccine developers that it was already supporting to discuss how to pivot ongoing R&D to COVID-19. CEPI executed its first COVID-19 vaccine development agreements later that month.²⁴ In contrast, the lack of similar pre-existing go-to entities to activate development of diagnostics and therapeutics, or other essential products, soon became apparent. Had there been a CEPI-like entity for diagnostics or therapeutics could these essential products have been created more rapidly? What seems likely is that shortening deployment of diagnostics and therapeutics by a few weeks would have favourably and substantially altered the evolution of the pandemic and saved many lives.

Unlike the USA and a few other countries, the rest of the world faced a resource and responsibility challenge because there were no global entities with a mandate, financing arrangements, or the ability to coordinate multiple independent actors to test, approve, manufacture, scale up, or ensure equitable global access to new products. Instead, advanced purchase commitments negotiated by high-income countries with major pharmaceutical and biotech companies for vaccines and diagnostics threatened to consume all the early supply. High-income countries, which account for 14% of the world's population, made deals during 2020 with manufacturers for over 50% of the anticipated supply of vaccines.²⁵ This competitive dynamic among wealthy nations, characterised as vaccine nationalism, served to drive up prices for everyone and leave out half of the world's population living in low-income and middle-income countries from timely access to the same products.²⁶

In response to the urgent need for global coordinated action, an unprecedented gathering of heads of governments, institutions, and industries took place in late April, 2020, to commit to work together to accelerate development, production, procurement, and delivery of COVID-19 health technologies that can control and end the pandemic. The Access to COVID Tools (ACT) Accelerator was formed as a 2-year, term limited, coalition of global health organisations including the Bill and Melinda Gates Foundation, CEPI, Gavi (the Vaccine Alliance), the Global Fund, UNITAID, Wellcome Trust, and WHO; private sector partners; and other stakeholders

to collaborate to accelerate the development and ensure the equitable distribution of COVID diagnostics, treatments, and vaccines.²⁷ The ACT Accelerator has made substantial strides towards these goals in its first 9 months, providing access to rapid diagnostic tests and treatments (eg, dexamethasone and oxygen), and by establishing the COVID-19 Vaccine Facility (COVAX), which is pooling global resources to expedite the development, manufacture, and procurement of vaccines to ensure global equitable access.²⁸

Although the ACT Accelerator and COVAX are promising initiatives, with 43 current donor governments, foundations, corporations and organisations listed on the Gavi COVAX hub²⁹ at the time of publication, a few countries with financial ability to support this effort initially refused to join, and current funding pledges remain grossly inadequate for the need. The gaps in manufacturing, procurement, and equitable access to diagnostics, therapeutics, and other essential products are even more striking than those related to vaccines, and mechanisms to address them have been slower to develop. In all these areas, inadequate financial support and major dependence on the private sector has been a substantial impediment for products developed through the R&D ecosystem to reach all who are in need. Financing of ACT Accelerator has depended primarily on donor funds designated for assistance to low-income countries; this is an inadequate model, either to meet global needs in a pandemic or to finance the type of global R&D infrastructure that is required for the future, particularly as pandemics impact the entire world. Furthermore, global financing instruments to support the ramp up of manufacturing at scale and, if necessary, at risk, and funding to procure products must be in place at the front end of the response to a pandemic. Fundraising during a pandemic cannot get the job done; in fact, it diverts attention from essential R&D and programme implementation and further delays equitable access.

Gaps in R&D preparedness and response

Previous efforts to do clinical research during emergencies had already documented the need for pre-positioned and rapidly available funding for an effective R&D response.³⁰ The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R),³¹ an organisation of global health research funders established in 2013 to fund research in pandemics, began to discuss the emerging COVID-19 outbreak by mid-January, 2020.³² GloPID-R and WHO convened a meeting soon afterwards to identify priorities for early research investments. This meeting was followed by a several month process in which various GloPID-R members issued calls for proposals, with each country and agency first needing to identify its source of funding and go through its own institutional processes. Simply put, although rapid funding was essential, existing procedural requirements substantially

slowed down the process. For future outbreaks and potential pandemics, it is crucial to identify key areas of research as quickly as possible, and have established mechanisms to rapidly release funds from a pre-positioned pool to jumpstart the R&D response. Although too complex to succinctly discuss in this paper, the rights to intellectual property and patents based on innovation in the academic and private pharmaceutical and biotechnology sectors remain a potential barrier to affordability and availability of needed products for low-income countries and impoverished people everywhere in the world. Efforts over the past 20 years to overcome these barriers and support and incentivise scientists and companies to develop global public goods have made slow but still inadequate progress.^{33,34}

Building on the model of the WHO Influenza Collaborating Centers, pre-positioning science hubs on each continent should be a high priority. Such a distributed network could then be close to where the next outbreak occurs, contribute to closing the R&D equity gap, and ultimately involve local scientists and populations in clinical trials, facilitating not only the understanding of the diseases and needed public health measures, but also promoting public trust in the countermeasures required for disease mitigation. These hubs should be capable of executing crucial preparedness science activities on pathogens of regional relevance, which also means that they must be nimble and leveraged to respond to a new outbreak. They are essential to link preparedness and response; to systematically isolate, sequence, culture, and share pathogen samples; quickly examine the One Health nexus; and collect crucial relevant biological specimens.

R&D preparedness is needed in several key clinical areas in the USA as well as elsewhere. As new diseases emerge, understanding their natural history and clinical course underlies efforts to interrupt transmission in the community, mitigate progression to illness, and improve care for the seriously ill. The COVID-19 pandemic has emphasised how important established mechanisms are to bring front-line clinicians together, not only to share observations, but to turn observations into reliable evidence and widely disseminate this information. A prototype for this, the International Severe Acute Respiratory and Emerging Infection Consortium, a constellation of global research networks to collect standardised information about emerging respiratory infections and rapidly activate clinical research, was able to shift attention to COVID-19 and provide online clinical research resources.³⁵ The Extension for Community Healthcare Outcomes (ECHO), a global peer-to-peer networking platform, is another useful model to share information and promote learning through telementoring that brings health-care providers and subject matter experts together in virtual communities of learners to promote an “all learn, all teach” approach.³⁶ Although project ECHO was ultimately asked to serve as a platform

for US clinicians to share observations and ideas about treatment, there was no pre-positioned mechanism to identify the most pressing clinical research questions or to test various treatment modalities in a nationally coordinated way. In contrast, the RECOVERY trial mechanism in the UK took advantage of the existing UK-wide clinical research network to rapidly initiate trials of potential therapeutic interventions within the National Health Service. Ensuring such standing preparedness capacity globally could have additional multiple uses between outbreaks.

For the future, it is crucially important to recognise the essential role for the seamless transition from preparedness R&D to response R&D, and the ability to operate within an end-to-end ecosystem from clinical observation and care, through basic and translational research, to an adequate supply of necessary products widely delivered across the world to diagnose, treat, control, and prevent the disease and bring the outbreak, whatever the cause, to an end.

Financing a system of R&D preparedness and response

It is now clear that current financing models, both for preparedness and response, cannot simply depend on traditional and willing donor assistance. Although this approach might have been adequate for outbreaks in a small number of countries, it is not fit for global pandemic preparedness, prevention, or response. The ACT Accelerator, which is serving as the current model for bringing together all the components of an end-to-end system, has suffered from insufficient funding and a structure in which each component (diagnostics, therapeutics, and vaccines) competes for funding with the others. Although research and development has moved at an impressive speed, it is evident that the inadequate dedicated ACT Accelerator funds for manufacturing and rapid pooled procurement have impaired and delayed equitable distribution and its potential to save more lives.

The world needs a reliable and sustainable financing mechanism to ensure that the global public goods essential for pandemic preparedness, prevention, and response are developed, ready, and responsive in the next pandemic.¹ Although PPPs, including product-development partnerships targeting known diseases of poverty have been successful, particularly when linked to access-PPPs to purchase and deliver products to the populations in need, they are not expected to anticipate the unknown challenges of the future and begin R&D before they are identified. To deliver the required resources for pre-competitive R&D preparedness, including enabling science all the way to administering products to people, a technology push from basic research to generate new knowledge linked with a technology pull to develop necessary products is required, whether or not profit is part of the equation. Generating sufficient resources means calling on the global financial system, including national whole-of-government treasuries going beyond

development assistance and foreign aid, private industry, all of the financial resources of the World Bank Group, regional and central banks, and major private international banks, as well as a consortium of global scientific agencies and research funders, and independent foundations. Although the proliferation of potential funding entities creates a governance challenge, it is necessary to create a sufficient and sustainable financing mechanism enabled to be quickly activated in an emergency situation.⁴ If the need for available pooled pandemic financing were realised, it would be wise to ensure a portion of such funding is used to preposition the enabling science capabilities described above, with the flexibility and authority to release the funds when needed. For such a system to produce global public goods and serve the pre-competitive space for R&D, private sector pharmaceutical and biotechnology companies must be engaged and committed, both to the science, and to funding such an effort.

Realising such a vision requires a standing end-to-end coordinated mechanism that aligns R&D with manufacturing, procurement, distribution, and delivery to people. It will need a more agile and harmonised structure for regulatory action, whether during emergencies or for licensing.³⁷ The ACT Accelerator might be a good foundation from which to build, but it is itself limited in scope. There is also a need for an operational, expert research coordinating entity, modelled after Glpid-R but with broader representation and leadership from other key stakeholders including national governments, mandates for co-funding, a commitment to equity of opportunity, the ability to fund quickly, and with the responsibility for identifying and pre-positioning implementing preparedness partnerships. It must also leverage WHO's unique role in establishing norms for global behaviour (eg, data sharing, material transfer agreements, common protocols, and ethics reviews) but as WHO is not an operational body and is responsible to its member states, we believe the management of this complex R&D organisation should be independent of WHO. Care is required to be certain the weight of the multiple responsibilities does not crush the structures assigned to bear it.

The system which links R&D preparedness and response will require a framework and threshold for activation as this transformation must take place during the initial response to a new outbreak. There will, of necessity, be occasions when the global system and its rapid expenditure mechanisms are activated but are then quickly dialled down because the outbreak is effectively contained with minimal new investment needed. Rapid activation is a clear global good, and initial response funding should be viewed as both an exercise for the ecosystem and a cost of preparedness. Such expenditures could be considered as the payment of an insurance premium, but even better because it also builds capacity and represents real-world practice for future and more

challenging events. To succeed, a research preparedness-response fund would need a no regret annual budget to be confident those resources are always available and can be rapidly released when appropriate.

The World Bank's 2018 report, *Money and Microbes*,³⁸ was prescient in suggesting that a multi-donor fund held at the World Bank could support such activities for pandemic vaccine development, since the institution itself typically supports country needs and does not usually finance R&D activities. But the world needs a reliable financing system for the end-to-end preparedness and response ecosystem of the future. The GPMB and other initiatives such as the G20 High Level Independent Panel on Financing the Global Commons for Pandemic Preparedness and Response, an international committee of eminent economists and financing experts, with the US National Academy of Medicine and the UK Wellcome Trust as the Administrative Secretariat for the Panel, are currently re-evaluating how such activities might be financed in the future.³⁹

Conclusion: seizing the current momentum

The opportunity to structure an ambitious global mechanism has never been more possible than now. The International Monetary Fund had estimated that COVID-19 would result in a US\$3.86 trillion annual loss⁴⁰ of global gross domestic product in 2020. Rather than take such risks with the global economy of the future, a crucial step in preparedness is surely to create and maintain a system of global financing enabled to step in quickly to help finance the end-to-end components of the R&D ecosystem and ensure global equitable access to these products. Although this financial mechanism will surely be politically challenging, the time to start building such a system is now, with the ongoing experience with COVID-19 as a daily reminder of the needs going forward. Determining what scientific advances are required, as well as how these elements will be mobilised, funded, and orchestrated, is work that must and can be done now, before the world moves on to its next crisis, still suffering from the impacts of COVID-19.

Contributors

NL, GTK, and VJD conceptualised the article and its format. NL and GTK researched and prepared the draft manuscript. NL, GTK, and VJD edited the final version and responded to reviewer comments.

Declaration of interests

We declare no competing interests.

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