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STRENGTHENING CLINICAL RESEARCH CAPACITY TO PREVENT EPIDEMICS

INTERNATIONAL VACCINES TASK FORCE

MAY 2018

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Statements, recommendations, and opinions expressed are those of the International Vaccines Task Force (IVTF).

The International Vaccines Task Force was supported by the World Bank Group and the Coalition for Epidemic Preparedness Innovations.

The World Bank served as Secretariat for the IVTF. The World Bank team was led by Mukesh Chawla and included (in alphabetical order, by last name) Erika Hartingh, Consultant; Nicole Lurie, Consultant; Adrienne McManus, Consultant; Micaela Mussini, Consultant; Rocio Schmunis, Senior Operations Officer, Health, Nutrition and Population; and Gabrielle Williams, Consultant. The World Bank team was supported by several colleagues from the Coalition for Epidemic Preparedness Innovations (CEPI), including Joseph Simmonds-Issler, Chief of Staff; Rebeka Yasmin, Executive Assistant to the CEO; Rachel Grant, Director of Communications and Advocacy; and Shanni Dhooper, Administrative Coordinator.

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1818 H Street NW
Washington DC 20433
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Internet: www.worldbank.org

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“Historically, we have had warriors who had spears to combat larger physical threats that could be easily seen (e.g., lions, snakes, tribal armies, etc.). We are now in an era where these threats cannot be seen with the naked eye or defended against with traditional weaponry. We are at war with things that we cannot see and we are losing many of the battles. In this era, it is the scientists who are the warriors and their weapons are micro- and nanoscopes. This change therefore demands that new policies and practices sufficiently fund these new warriors and equip them with the skills, knowledge, infrastructure and equipment to help address these serious health security hazards.”

Prof John David Kabasa

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Foreword

In 2014, the world watched in horror as the Ebola Crisis unfolded in West Africa. This outbreak, of unprecedented proportions, devastated the countries of Guinea, Sierra Leone, and Liberia and presented tremendous challenges to the global public health and emergency response communities. The inadequacy of the initial response demonstrated, if such demonstration were necessary, the world's lack of preparedness to respond to such events. More than any other recent outbreak—and there have been many—the Ebola Crisis has stimulated concerted efforts, from the frontlines of country health systems to the back offices of UN bureaucracies, to improve our readiness for epidemic and pandemic threats. Despite many promising developments, not least the establishment of the World Bank's Pandemic Emergency Financing Facility, there is still a long road ahead to achieving this goal.

The development of effective vaccines and other medical countermeasures would greatly reduce the risks the world faces from emerging infectious diseases, but the efficacy of such products can be demonstrated definitively only during outbreaks. Having research capacity that can be mobilized quickly and effectively in the countries where outbreaks are most likely to occur will be a prerequisite for the rapid deployment and testing of candidate products. The lack of such capacity will result in tragic delays, as in West Africa, where investigational Ebola vaccines and therapeutics were deployed far too late to impact the outcome of the epidemic.

The establishment in 2017 of the Coalition for Epidemic Preparedness Innovations (CEPI) and its subsequent investment in vaccines against high priority pathogens such as MERS, Lassa, and Nipah underscores the need to ensure that research capacity is in place during outbreaks. To advance this objective, the World Bank and CEPI supported the creation of an International Vaccines Task Force (IVTF) with the aim of producing actionable recommendations to secure essential national clinical research capacity in lower- and middle-income countries where such infrastructure is fragile or non-existent. Under the wise guidance of Co-chairs Marie-Paule Kieny and Richard Sezibera, the IVTF has, over the last 9 months, delved into this issue, consulting widely, deliberating deeply, and delivered the set of recommendations found in this report.

We are extremely grateful to the co-Chairs and all of the IVTF members for their efforts in this regard. We are also grateful to the leadership of Dr. Nicole Lurie who together with the World Bank team led by Mukesh Chawla helped not only to meet tight timelines but also surpass our high expectations.

There is no time to waste in implementing these recommendations. We look forward to doing our part, together with partners, to prepare for future outbreaks no matter where they may occur.

Tim Evans

*Senior Director, Health, Nutrition and
Population Global Practice, World Bank Group*

Richard Hatchett

*Chief Executive Officer, Coalition for Epidemic
Preparedness Innovations (CEPI)*

Preface

Lack of capacity kills. Literally. Epidemics are happening with increasing severity and frequency. An ever-growing army of new zoonotic infections descends on us each year. Older nemeses like Ebola and Lassa fever return more often and the outbreaks claim ever more lives. Clearly, the diseases are growing and adapting.

Yet the approach to them has, in many important aspects, remained unchanged. Certainly, we have increased surveillance efforts, and are doing better at recognizing emerging epidemics earlier before the outbreak spreads so far that containing it becomes a Herculean task, demanding mind-boggling amounts of human, technical and financial resources that we can ill afford. We have also stepped up our response efforts, and are improving our efficacy and capabilities as we race in each new epidemic to prevent new infections and to treat the infected.

These are admirable advances that we must strengthen even more as populations grow, live in ever closer contact with the zoonotic hosts, and the ability to travel far and quickly becomes a reality for more and more people—and pathogens as well. But at root our response to emerging epidemics remains just that: responsive. We remain in a seemingly unending game of “whack-a-mole”—the old carnival game in which players use a mallet to hit toy moles that pop up randomly from a “field” of holes before quickly disappearing again only to emerge from another hole over and over and over again. In short, we have been effectively giving these deadly enemies a pass, allowing them to control the parameters of the playing field while we remain focused on response, on defense.

It is time to stop giving these pathogens a pass. It is time to make a serious push to get ahead of them. It is time to find the pathogens before they find us and develop the tests, treatments and vaccines we may need before we actually need them.

Fortunately, people and institutions around the globe are already awakening to this challenge. Recent years have seen a wealth of new initiatives, new research and new funding efforts. For example, the World Health Organization (WHO) developed and is implementing a Research and Development (R&D) Blueprint for action to prevent epidemics by fast-tracking the availability of effective diagnostic tests, vaccines and medicines to save lives and avert large-scale crises. The Global Health Security Agenda (GHSA) is supporting an evaluation system to strengthen countries’ basic public health capacity and compliance with International Health Regulations for surveillance and reporting of outbreaks. And the Coalition for Epidemic Preparedness Innovations (CEPI), a novel global non-profit alliance that finances and coordinates partnerships for developing new vaccines to prevent and contain infectious disease epidemics is already funding vaccine development for three priority pathogens—Lassa, Nipah and MERS. Finally, the World Bank, with the support of Japan, Germany, WHO, and private sector partners, has developed the Pandemic Emergency Financing Facility (PEF), a quick-disbursing financing mechanism that provides a surge of funds to enable a rapid and effective response to a large-scale disease outbreak.

However, even as the battle has been joined, our ultimate goal remains out of reach. One important reason is that we haven't fully equipped ourselves with all the tools we need to succeed. In addition to all the impressive research advances in leading laboratories in the developed world, we need a world where those research and clinical capabilities are just as strong in the lower- and middle-income countries where epidemics often strike. Without those capabilities, promising new interventions cannot advance as quickly as we need.

Examples of this shortfall are sadly too easy to find. When the 2014-15 Ebola crisis first emerged, there were already candidate vaccines whose deployment could have been advanced by better preparedness. Lassa fever has been around for a long time, described first in 1969 from a case in the town of Lassa, in Borno State, Nigeria. Yet, our knowledge of its epidemiology and how to treat it has not evolved for decades. Identified by WHO as a likely cause of a future epidemic, Lassa virus has been listed for urgent R&D to develop new diagnostic tests, vaccines, and medicines.

But the situation is not entirely grim. Times of crisis present opportunities to focus capabilities and energy on solving important problems. Research during outbreak response is critical to the generation of new knowledge, especially for diseases like Ebola for which clinical trials must be conducted during outbreaks because the severity of illness and the frequency of fatal outcomes precludes using human experimental model infections for such studies. It is the only way to ensure that we don't face future outbreaks with the same knowledge gaps over and over again.

Research is so critical that WHO has now included research as a pillar in its incident management structure. Capabilities in low- and middle-income countries are also on the rise, with more robustly trained local researchers working in better equipped facilities, although their numbers remain far too limited. Moreover, during the recent epidemics of Ebola, plague, and Lassa fever, research groups from high-income countries have, with varying degrees of engagement of local partners, initiated important clinical research and trials in outbreak countries. Delays in implementing these efforts—well documented for the Ebola outbreak in West Africa by numerous reports, and continuing through the 2018 Lassa outbreak in Nigeria—have limited the potential to generate valuable information for clinical care on the one hand, and vaccine or drug treatment on the other. Yet, given the needs for country ownership and capacity-building, these and future outbreaks present important opportunities for gaining experience by doing clinical research.

The International Vaccines Task Force (IVTF) has been created to boost the national capacity of low- and middle-income countries to seize those opportunities and to create the clinical research capabilities necessary to surge activity during emergencies and sustain those efforts in times of calm. Founded by the World Bank and CEPI in October 2017, the goal of the Task Force is to produce a set of actionable recommendations that, when implemented, will ensure the existence of a minimal and sustainable clinical research capacity to enable low- and middle-income countries to collaborate and participate in late-stage clinical trials themselves or with regional or international partners in the event of an epidemic. The Task Force believes this goal can be reached through strengthening internal country capacity as well as by working with regional research networks.

The key takeaway message is that what needs to be done can be done. There are many promising efforts already underway, and with sufficient commitment, focus, and coordination, we can develop the capabilities and find the solutions we need to take the lead away from our pathogenic foes. We must, and we can, outsmart epidemics.

Marie-Paule Kieny

Co-chair, International Vaccines Task Force

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Acknowledgements

The International Vaccines Task Force (IVTF) deeply appreciates and would like to thank the individuals, organizations and institutions who took the time to provide their knowledge, experience and advice to the Task Force. However, the Task Force takes full responsibility for all facts, opinions and recommendations contained in this report.

We are deeply appreciative of the encouragement and advice from Tore Godal, Norway, who was instrumental in the establishment of the Task Force. We would not have come together—or worked as well—had it not been for his unwavering support.

We are especially grateful to the sponsors of the Task Force, the World Bank and the Coalition for Epidemic Preparedness Innovations (CEPI), for their technical and financial support throughout the course of the work. We are also particularly appreciative of the support of the World Bank team who comprised the Secretariat of the Task Force.

We owe special gratitude to the many health research leaders and experts who gave of their time and shared their experiences. We particularly thank Beyene Petros and Aster Tsegaye, Addis Ababa University; Afework Kassu, Ministry of Science and Technology, Ethiopia; Demissie Habte, Former Ethiopian Academy of Sciences; Taye Tolera, Armauer Hansen Research Institute; Alex Opio, Ministry of Health, Uganda; Cissy Kityo, Joint Clinical Research Center; Edward Mbidde, Former Uganda Virus Research Institute; John David Kabasa, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University and One Health Centre and Eastern Africa Network; Agnes Kahundha, One Health Centre and Eastern Africa Network; Leslie Nielsen, International AIDS Vaccine Initiative; Pontiano Kaleebu, Uganda Virus Research Institute and Medical Research Council/Uganda Virus Research Institute Research Unit; Richard Brough, Infectious Disease Institute, Makerere University; Fernando Polack, Vanderbilt Vaccine Center, Argentina; Miguel O’Ryan, Biomedical Sciences Institute, University of Chile; Xavier Sáez Llorens, Hospital del Niño; José Renán Esquivel, Panama City, Panama; Felix Espinosa, Universidad Nacional Autónoma de Nicaragua; Nirmal Ganguly, Indian Council of Medical Research, India; and Pyatat Tatsanavivat, MedResNet, Thailand.

We had several very insightful conversations with many key individuals knowledgeable about the health research environments. We gratefully acknowledge Ok Pannenberg, Council on Health Research for Development; Mike Ward and Abha Saxena, World Health Organization; Luis Gabriel Cuervo, Luis Alejandro Salicrup and Ian Stein, Pan American Health Organization; Mead Over and Jeremy Koyndyk, Center For Global Development; Keith McAdam, London School of Hygiene and Tropical Medicine; David Peters, John Hopkins Alliance for a Healthier World; Charles Holmes, Georgetown University; Simon Kay, Diogo Martins, Sophie Mathewson, and Alexis Gilbert, Wellcome Trust; Gail Carson and Peter Horby, University of Oxford; Ted Trimble and Doug Puricelli Perin, Center for Global Health, US National Cancer Institute; Jacques Demotes and Serena Battaglia, European Clinical Research Infrastructure Network; Øyvind Melien, Norwegian Directorate of Health, Norway;

Murray Lumpkin, Peter Dull, Scott Dowell, and Thy Pham, Bill & Melinda Gates Foundation; Jimmy Kolker, Former United States Department of Health and Human Services; Paul Stoffels, Johnson & Johnson; Christian Bréchet, Global Virus Network; Nadia Khelef, Institut Pasteur; Mike Strange and Agbor Ako, GlaxoSmithKline; Patience Kuruneri, African Development Bank; Lawrence Gostin, O’Neill Institute for National and Global Health Law; Jean Lang, Sanofi Pasteur; Dalvir Gill, TransCelerate BioPharma Inc.; Flora Katz, Fogarty International Center, NIH; Christine Pierre, Society of Clinical Research Sites; Robert Mallett and Suzanne Oguntoye, Africare; Dominika Jajkowicz, The European and Developing Countries Clinical Trials Partnership; and colleagues from the World Bank, Enis Baris, John Paul Clark, Mickey Chopra, Francisco Marmolejo and Andreas Blom.

We drew upon the related work of various organizations, and gratefully acknowledge their willingness to share their findings. These include Carel IJsselmuiden, Council on Health Research for Development; Martin Eigbike, Dalberg Associates (CARI/AAS initiative); Trudie Lang, The Global Health Network; and Michael Head, ResIn, University of Southampton, who allowed us benefit from the parallel work of their organizations.

Attendees at the workshop on Sustainable Clinical Research Capacity: Architecture, Governance and Indicators, organized jointly with WHO and the National Institute of Allergy and Infectious Disease (NIAID) and held at WHO Headquarters Geneva, provided valuable comments and suggestions. We especially acknowledge Sven Trelle, University of Bern; Alex London, Carnegie Mellon University; Moses Massaquoi, Clinton Health Access Initiative, Liberia; Jane Carter, African Medical and Research Foundation; Martin Veller, University of Witwatersrand; Alash’le Abimiku, University of Maryland; Philip Onyebujoh, Africa CDC; Rosanna Lagos, Centro para Vacunas en Desarrollo, Chile; Mosoka Fallah, National Public Health Institute of Liberia; Milagritos Tapia, University of Maryland; Martin Eigbike, Dalberg Associates; and colleagues at the World Health Organization: Emer Cooke, Laragh Golligly, Maria Van Kerkhove, Christian Lienhardt, Pascal Launois, Dermot Maher, Ahmed Mandil, Andreas Alois Reis, Martin Matthew Okechukwu Ota, and Abha Saxena.

And finally, we thank Erika Hartingh for successfully organizing the launch event of the report, Anugraha Palan for coordinating the release of the report to the public, and Sheryl Silverman for supporting our online communication efforts.

Acronyms and Abbreviations

AAS	African Academy of Sciences
AfDB	African Development Bank
BMGF	Bill & Melinda Gates Foundation
CARI	Coalition for African Research and Innovation
CDC	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
COHRED	Council on Health Research for Development
CRO	Clinical Research Organization
DRC	Democratic Republic of the Congo
DRM	Domestic Resource Mobilization
ECOWAS	Economic Community of West African States
EDCTP	The European and Developing Countries Clinical Trials Partnership
ESSENCE	Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts
FDA	Food and Drug Administration
FY	Financial Year
GCM	Global Coordination Mechanism
GDP	Gross Domestic Product
GFF	Global Financing Facility
GPMB	Global Preparedness Monitoring Board
GSK	GlaxoSmithKline
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
IBRD	International Bank for Reconstruction and Development
IAVI	International AIDS Vaccine Initiative
ICTRP	International Clinical Trials Registry Platform
IDA	International Development Association
IDA18/19	18th/19th Replenishment of International Development Association Funding
IDI	Infectious Diseases Institute
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IHR (2005)	International Health Regulations (2005)
INSERM	The Institut National de la Santé et de la Recherche Médicale
IVTF	International Vaccines Task Force
IWG	International Working Group on Financing Preparedness
LMIC(s)	Low- and Middle-Income Country(ies)

MENA	Middle East and North Africa
MERS-CoV	Middle East Respiratory Syndrome-Coronavirus
MTA	Material Transfer Agreement
MTR	Mid-Term Review
NASEM	National Academies of Sciences, Engineering and Medicine
NCD(s)	Non-Communicable Disease(s)
NCDC	Nigeria Centre for Disease Control
NHA	National Health Accounts
NIH	National Institutes of Health
ODA	Overseas Development Assistance
PAHO	Pan American Health Organization
PEF	Pandemic Emergency Financing Facility
PETS	Public Expenditure Tracking System
R&D	Research and Development
R&I	Research and Innovation
ResIn	Research Investments in Global Health
RFI	Research Fairness Initiative
RT	Rwanda's Resource Tracking Tool
S&P	Standard and Poor's
SADC	Southern African Development Community
SARS	Severe Acute Respiratory Syndrome
SCRS	Society of Clinical Research Sites
SDR	Special Drawing Right
SICA	Sistema de la Integracion Centroamericana
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
TGHN	The Global Health Network
UK	United Kingdom
UN	United Nations
US	United States of America
USAID	United States Agency for International Development
WBG	World Bank Group
WHO	World Health Organization



Executive Summary

In the last 5 years alone, the world has been tested with serious challenges from two viral diseases. The Ebola outbreak that unfolded between 2014 and 2016 devastated West Africa, and while its health and economic impacts beyond the continent were limited, it sent a loud message to the rest of the world about how vulnerable it was to the next epidemic. This was followed by the Zika Virus outbreak that began in early 2016, which also remained confined largely to Latin America, and served to remind the rest of the world that there was no room for complacency. Further warnings were not needed—but they nevertheless came in quick succession. In May 2017, the Democratic Republic of the Congo notified international public health agencies of a cluster of suspected cases of Ebola virus disease in the Likati health zone of the province of Bas Uélé. In October 2017, Madagascar reported an outbreak of the deadliest form of plague, pneumonic, which had hit its major cities and towns and was spreading fast. Around the same time, a Marburg virus disease outbreak was detected in the Kween district of eastern Uganda. And a few months later, Nigeria begun experiencing what would turn out to be its worst Lassa fever outbreak ever, recording more cases in January 2018 alone than during all of 2017.

Stunned by the scale of human and economic suffering caused by these large-scale disease outbreaks, many international expert panels examined what went wrong with the way that countries and international agencies addressed these outbreaks, and made several recommendations aimed at strengthening national public health systems, building resilience and enhancing global capabilities. Response has been strong, and in many ways, we are better prepared now than we were for previous pandemics. A large number of countries have voluntarily opened their gates to external evaluations of their state of preparedness. The World Health Organization (WHO) has rolled out its R&D Blueprint for

action to prevent epidemics. The Coalition for Epidemic Preparedness Innovation (CEPI) has launched a US\$1 billion effort to shorten the time it takes to develop new vaccines to protect against viruses that emerge suddenly as public health threats and has already targeted Lassa fever, Middle East Respiratory Syndrome (MERS-CoV) and Nipah, three of the R&D Blueprint priority diseases. In 2017, the World Bank launched the Pandemic Emergency Financing Facility (PEF), a mechanism to ensure low-income countries can receive timely, predictable and coordinated surge financing when affected by large-scale disease outbreaks (World Bank 2017a).

Despite the progress, however, there is still a lot more that needs to be done. One area in which there has been little progress relates to clinical research response, especially to our ability to conduct clinical trials during an outbreak. The most striking example of the critical need for clinical research response was witnessed during the 2014-15 Ebola outbreak. A recent report by the National Academies of Sciences, Medicine and Engineering (2017), which reviewed the response to the outbreak, concluded that it was “of unprecedented magnitude in a setting of limited capacity, with political systems that were fragile after many years of civil war, plagued by violence, and the virus itself killed health care workers, further decimating the indigenous capacity to care for patients and limit further dissemination of infection.” Although some promising results emerged from the vaccine trials conducted during the 2014-15 Ebola outbreak, there was an overall “thin scientific harvest” (Cohen and Enserink 2016). Further, as noted by WHO, “the only way of obtaining evidence on the safety and efficacy of any intervention in Ebola virus disease is during an outbreak” (WHO 2014). The NASEM report asserts that our ability to test and develop life-saving vaccines during an outbreak will depend on the progress we make in preparing during the inter-epidemic period.

Recognizing this challenge, the World Bank and CEPI established the International Vaccines Task Force on Strengthening Country Capacity for Vaccines Research and Development (Task Force) in October 2017 to develop a set of recommendations on strategic investments that can strengthen clinical research and clinical trial capacity in low- and middle-income countries. This report by the Task Force proposes ways in which national governments and development partners can finance investments in clinical research capacity and strengthen low- and middle-income countries capacity to conduct and participate in a late-stage vaccine trial during an outbreak.

Accelerating Commitment to Clinical Research

The first step for countries seeking to strengthen clinical research capacity, especially surge capacity to conduct clinical trials during an outbreak, is to make a political and policy commitment to developing this capacity during the inter-epidemic period. In the broadest sense, political commitment is the decision of leaders—including political and government leaders, parliamentarians, party leaders, civil and community leaders at all levels of society, private sector and business leaders, and so on—to use their power, influence, and personal involvement to ensure that strengthening clinical research receives the visibility, leadership, resources, and ongoing political support that is required to support effective action to build capacity for clinical trials during an outbreak.

RECOMMENDATION 1

By December 2018, in order to effectively respond to disease outbreaks, reduce preventable deaths, strengthen productivity and improve quality of life, countries should commit to strengthening capacity to conduct or participate in clinical research to address their public health needs.

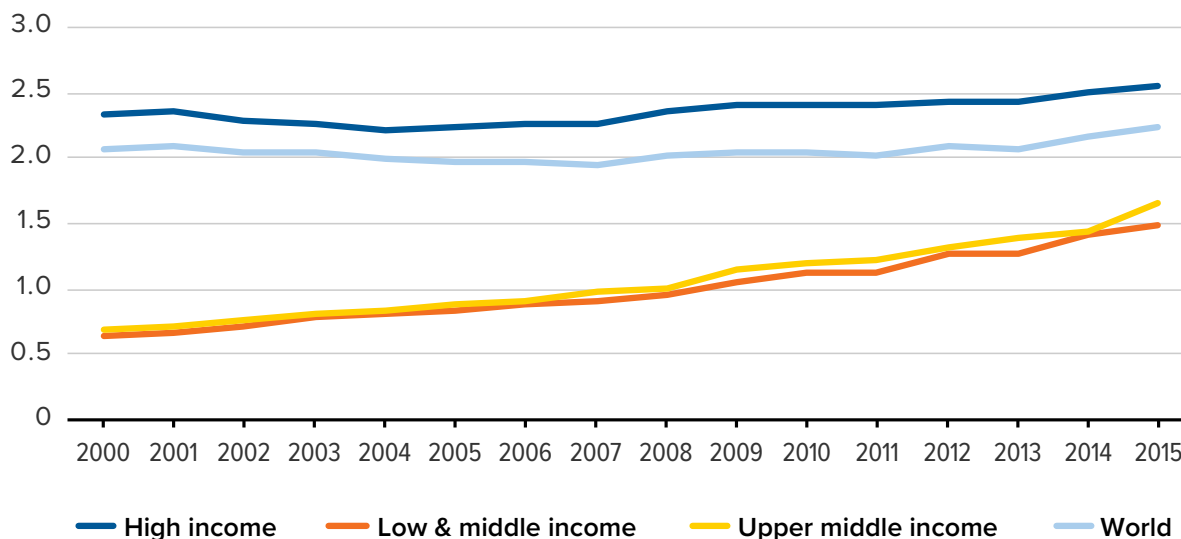
Framing Investments for Clinical Research

Low- and middle-income countries are increasingly spending more on all research and development (Figure 1). The limited data that are available on spending on health R&D suggests that only a small fraction of all R&D spending goes to health. At the same time, the investment case for clinical research is strong. A research study estimating the economic returns generated by public and charitable investments in medical research in the UK, using musculoskeletal disease research as an exemplar, finds that every UK£1 invested in musculoskeletal, cancer, cardiovascular and mental health research delivers a return equivalent to around UK£0.25 every year in perpetuity.¹ This suggests that investments in health research must be constrained by factors such as insufficient financing, lack of political support for investing in activities that do not necessarily yield returns in the present time, complexity in terms of implementation (that is, what to fund and how to maintain the investments over time), and so on. These challenges are further exacerbated in the context of resource-constrained economies, which use up all the scarce resources to take care of urgent needs today instead of worrying about the imperatives of tomorrow.

Every investor needs an investment framework that helps in improving decision-making outcomes. Likewise, countries seeking to invest scarce resources in clinical research would need to have clarity in understanding the different types of capacities and capabilities that they must develop, different financing sources available to them, trade-offs associated with investing in clinical research at the expense of other proximate demands, and so on. A strong investment framework for clinical research will help answer all these questions.

¹ The research study was produced by the Policy Institute at Kings College London, RAND Europe, and the Health Economic Research Group at Brunel University London, with funding from the Academy of Medical Sciences, Arthritis Research UK, the National Institute for Health Research, Medical Research Council, and Wellcome Trust. Wellcome Trust (2018) has the details.

FIGURE 1: SPENDING ON R&D AS A PERCENTAGE OF GDP



Source: World Bank 2018a

The World Bank, as part of its commitments under the 18th round of International Development Association funding (IDA18),² is helping at least 25 countries develop pandemic preparedness plans and strengthen their capacities to detect, prevent and respond to pandemics.³ The World Bank has begun working with many countries to develop comprehensive pandemic preparedness plans and make available financial support for strengthening clinical research capacity.

RECOMMENDATION 2

Recognizing the existing IDA18 commitment to strengthen preparedness in at least 25 countries, the World Bank Group should include, as a part of its IDA Mid-Term (December 2018) Review (MTR), an investment framework for national and regional clinical research capacities.

Developing Legal Frameworks for Clinical Research

A comprehensive legal framework is essential for creating a strong clinical research environment. Enabling legislation is needed in support of many areas related to clinical research and clinical trial capacities in a country, such as the capacity to transport equipment and specimens across borders, protect intellectual property rights and ensure proper ethical and regulatory oversight. While laws regarding clinical research, governance and regulation of research have become commonplace in Latin America over the past decade, they are less common in Africa. Indeed, there is no comprehensive repository or analysis of countries' laws appropriate to the conduct of clinical research.

Several organizations and partners have contributed to the development of the relevant health laws, and consolidating the laws and policies applicable to clinical research would enable countries to develop legislation more rapidly.

² The 18th round of IDA covers the period July 1, 2017 to June 30, 2020.

³ These include Afghanistan, Bangladesh, Benin, Burkina Faso, Cambodia, Cape Verde, Democratic Republic of the Congo, Ethiopia, Ghana, Guyana, Haiti, Kenya, Lao PDR, Liberia, Mali, Myanmar, Nepal, Niger, Nigeria, Papua New Guinea, Senegal, Sierra Leone, Sudan, Tanzania, and Uganda.

RECOMMENDATION 3

By end 2019, WHO should develop and disseminate examples of broadly applicable legislation and policies to support and enable efficient conduct of clinical research. This should include, at a minimum, model policies and laws that support the conduct of trials, enable timely ethics and regulatory review, address import/export of relevant commodities and bio-specimens, and address procurement and contracting systems. These policies should be a part of a broader governance architecture for clinical research.

Creating a Culture of Clinical Research

A supportive research culture is a sine qua non for strong clinical research capability, and there are several essential elements for such a supportive culture. First, increasing visibility and political support for clinical research, and ensuring that preparedness is a key foundation, is important. Second, support for careers in clinical research will motivate young investigators to pursue clinical research careers, and to choose to use those skills in-country. Third, a coordination mechanism that collects all funding and research proposals and places them on one platform would help researchers in low- and middle-income countries learn about the broad array of available opportunities. And finally, opportunities for fair and mutually beneficial research partnerships within and between countries help in nurturing an appropriate culture.

The Task Force believes that Academy of Sciences, national research committees and other similar research centers, such as the Council on Health Research and Development (COHRED), are strategically placed to communicate and prepare the necessary know-how for national governments on how to create an enabling environment and leverage existing initiatives.

RECOMMENDATION 4

By 2019, Research Forums/Institutions and/or Academies of Science in LMICs, drawing upon their experience and that of others, should synthesize best practices and develop guidance for consideration by countries on how to build a supportive research climate/culture.

Assessing Clinical Research Capacity

Figure 2 shows the number of clinical trials that have been conducted in different countries in recent years; however, since there is no widely accepted measure of assessing country-level capacities for clinical research, it is challenging to determine the depth of expertise and capability in conducting clinical trials in any particular country. There are some tools that measure specific research competencies, such as the TDR-TGHN Competency Wheel (TGHN 2018) that lists all the competencies that should be demonstrated by a research team to carry out a successful clinical study; the Mapping African Research Ethics Review and Medicines Regulatory Capacity initiative that maps health research oversight and regulatory activities in Africa; the Laboratory Network Scorecard that assesses national laboratory network functionality; the Research Fairness Initiative that creates a reporting system for governments, business, organizations and funders to describe the measures they take to create trusting partnerships in research and innovation; the WHO Global Benchmarking Tool for Regulatory Capacities that assesses and documents capacities of national regulatory agencies (PAHO 2017), including the capacity to provide informed no-objection to clinical trials, post marketing surveillance and oversight of research during outbreaks; and the Joint External Evaluation (JEE) that assesses, inter alia, lab and surveillance preparedness (WHO 2016).

The Task Force believes that an assessment tool that is evidence-based and widely accepted would help countries monitor and strengthen their research capacities and bring them up to international standards. It further believes that WHO is best placed to collate existing indicators and to take responsibility for creating a comprehensive assessment of clinical research capacity.

FIGURE 2: NUMBER OF CLINICAL TRIALS PER COUNTRY OF RECRUITMENT



Source: WHO ICTRP 2018

RECOMMENDATION 5

By end 2018, WHO should consolidate a robust set of indicators, to the extent possible building on indicators already used by countries, develop a tool for assessment of country-level capacities for clinical research, and propose a process to help countries rapidly conduct these assessments.

Committing Domestic Resources for Clinical Research Capacity

Despite numerous calls for higher domestic commitments to general health and health research (Abuja Declaration 2001; Mexico Ministerial Summit on Health Research 2004; Bamako Call for Action on Research for Health 2008) and for more effective mobilization of domestic resources (Addis Tax Initiative 2015), there is no systematic thinking about financing gaps in capacity-building for clinical research. It is widely agreed by most governments and donors that domestic resources should be deployed to fill the gaps. It is also widely

accepted that competing demands make preparedness investments somewhat unattractive for public budgets, and that it is unlikely that significant resources will be allocated in the absence of a clear and present danger. The Task Force believes that in order to generate and sustain improvements in clinical research capacity, governments must commit the needed resources to finance the associated capital and recurrent costs.

RECOMMENDATION 6

By end 2019, governments in IDA-eligible countries should commit short- and medium-term resources to address their clinical research capacity goals. These resources could potentially come from their IDA portfolios.

Buying Down Loans for Clinical Research Capacity

Buy-downs, which essentially bundle IDA interest-bearing loans and credits with donor-funded grants that are used to buy down the net present value of the loan or credit and reduce it to grant terms, are an innovative

financing mechanism that incentivize countries to borrow funds for investments in strengthening their clinical research capacity. Buy-downs represent a win-win-win approach for countries, the World Bank and the donors. Countries receive financing for a global public good if they meet the agreed performance targets; the World Bank can leverage the technical expertise of other partners; and the donors can leverage their funding. This mechanism has a lot of potential to support countries wishing to invest in clinical research capacity.

RECOMMENDATION 7

By end 2018, the World Bank Group should develop mechanisms to buy down IDA loans and convert them into grants for countries that have demonstrated development of research capacity based on agreed milestones.

Leveraging Regional Partnerships for Investments in Clinical Research Capacity

Infectious diseases do not respect national boundaries, and often the optimal response to an outbreak is one that comes from two or more adjoining countries and regional institutions. Two elements can greatly enhance the effectiveness of such a response. First, regional networks, if they exist, can greatly leverage the comparative advantages of the member partners, and facilitate sharing of critical infrastructure—such as laboratories—and distribute some of the fixed costs across the network partners. In inter-epidemic periods, regional networks can tackle health challenges common to partners, such as malaria, tuberculosis or meningitis, thus creating and strengthening their independent and collective research capacities. Many networks that support science and research in Africa already exist, including those supported by the African Academy of Sciences, the Bill & Melinda Gates Foundation, the European and Developing Countries Clinical Trials Partnership (EDCTP), New Partnership for Africa's Development (NEPAD), United States Health and Human Services (HSS), United States Department of Defense, Wellcome Trust, the World Bank, and other partners. Strong coordination across these networks would be beneficial.

Second, suitable mechanisms must exist to finance these partnerships. One such mechanism, offered by the World Bank, is the Program for Regional Projects (“Regional Program”) initiated under IDA in 2003. Financing provided by this program is added to funds already available in the regular country IDA allocation, and so acts as a strong incentive to applying for funds from this program. As part of the 18th replenishment of IDA's resources—which resulted in a record replenishment of US\$75 billion to finance projects over the three-year period ending June 30, 2020—resources allocated to the Regional Program were increased more than two-fold, from SDR2.2 billion⁴ in IDA17 to SDR5 billion in IDA18 (World Bank 2017b).

RECOMMENDATION 8

The World Bank Group should encourage IDA countries to establish or leverage existing regional partnerships for developing clinical research capacity, using the IDA Regional Window funds combined with domestic commitments. The World Bank Group should highlight progress and showcase strategic development outcomes of such regional partnerships in the IDA18 MTR (December 2018), and develop a robust case for inclusion of prioritized regional clinical research partnerships as a thematic area under IDA19 (January 2020).

Incentivizing Domestic Resource Mobilization

As noted previously, countries stand to gain substantially if they increase public spending for strengthening clinical research, and use their domestic budgets to ensure sustainable financing. However, inadequate domestic resource mobilization is a huge challenge in many low-income countries. The World Bank works closely with countries and development partners to incentivize domestic resource mobilization. Examples of these engagements include the application of behavioral insights to improve tax compliance and increase

4 SDRs (Special Drawing Rights) are an international reserve asset created by the International Monetary Fund (IMF) in 1969 to supplement its member countries' official reserves. The value of the SDR is currently based on four major currencies: the US dollar, euro, Japanese yen and British pound.

the tax base, providing technical assistance to evaluate fiscal space for health, supporting efforts to increase sector-specific revenues, etc. Another successful mechanism is that of matching grants, which are funds from the granting organization that are matched with funds from the beneficiary. Grant schemes generally stimulate new activities or induce particular processes, and usually enhance beneficiaries' economic activity.

Both country and regional development partners have played a critical role in research capacity strengthening, often through leveraging the domestic resource commitment. The African Development Bank (AfDB) includes research funding in each of its health system strengthening initiatives where feasible, re-affirming the recommendations of the WHO Consultative Expert Group on Research and Development.⁵ Like other funders, the World Bank has a long history of matching grants at the national level, having designed matching grant schemes in the agricultural sector in several countries including Nicaragua, Peru, India, Ghana, and Armenia (World Bank 2010).

RECOMMENDATION 9

By end 2018, the World Bank Group should collaborate with development partners and other research funders to incentivize domestic resource mobilization in developing countries for investment in clinical research capacity, including by such means as matching grants and other incentivizing mechanisms.

Gaining Clinical Research Experience from CEPI Investments

CEPI finances and coordinates the development of new vaccines to prevent and contain infectious disease epidemics. Its three initial target diseases—Lassa, Nipah and MERS-CoV—are endemic in Africa, Asia and the Middle East respectively, which account for 59 of the 75 countries currently eligible for IDA funds. In such resource-constrained settings, CEPI leverages its existing initiatives and works in-country to build clinical

research capacity in order to address critical knowledge gaps, such as better defining the epidemiology, reservoir and human host sites of viral persistence, and optimizing clinical care and immune responses to infection. These initiatives provide an opportunity for CEPI and its partners to leverage other capacity-building efforts, e.g., EDCTP- or NIH-funded networks, to strengthen research sites that enable researchers to be mentored in the conduct of clinical trials during the inter-epidemic period.

RECOMMENDATION 10

By mid-2018, CEPI should commit resources to strengthening clinical research capacities in LMICs where clinical trials for vaccines against CEPI priority pathogens are likely to be conducted.

Leveraging the Private Sector for Clinical Research Capacity Development

Private sector activities, particularly those of pharmaceutical, biotechnology and clinical research companies, have led to the development of clinical research capacity across the globe simply through the conduct of clinical trials and in-country research. More recently, there are examples of private companies engaging in direct capacity-building efforts in LMICs, such as the EDCTP-TDR Clinical Research Development Fellowships in which international product development organizations, including major pharmaceutical companies are partnering with WHO and EDCTP to train their fellows to develop strong research capability in LMICs (IFPMA 2018).

One model that could potentially be scaled up to enhance capacity-building efforts in LMICs is TransCelerate, a non-profit organization in the biotechnology industry working to improve efficiencies and speed development in the clinical trial space. TransCelerate facilitates information-sharing on relevant subject matters across its member companies to enable faster and more efficient identification and recruitment of qualified investigators. This could strengthen capacity in LMICs, which could benefit from the associated cross-site learning.

⁵ Kuruneri, Patience (AfDB) Personal communication, email dated April 16, 2018.

RECOMMENDATION 11

By end 2019, the private sector pharmaceutical/biotech industry/clinical research organizations/other health sector businesses operating in LMICs should announce their commitment to maximize their contribution to clinical research capacity in LMICs. This includes transfer of skills and expertise and/or allocating a percentage of their spending to support the development of clinical research capacity in LMICs that is aligned with country public health needs and national research agenda.

Coordinating Investments in Clinical Research Capacity Building

Coordinating the many funders that are engaged in clinical research capacity-building can be a challenge. Research Investments in Global Health (ResIn) maps global research investments in infectious disease research awarded from public and philanthropic funders in the G20 nations. ResIn (2018) has generated a database of over 1,000 funders and approximately 80,000 discrete projects.⁶ However, the variety and number of funders, while offering more diversified funding flows, can pose difficulties if funding is duplicated or concentrated in select areas, to the detriment of research initiatives needed to generate evidence to inform urgent strategic policy questions.

Two initiatives have been established at WHO to address these issues. The first is the ESSENCE program, an initiative that allows funders to identify synergies, bring about coherence and increase the value of resources and actions for health research with a focus on LMICs (ESSENCE 2017). ESSENCE was created to respond to the sharp increase in uncoordinated and fragmented funding which has occurred over the past several decades. Its key areas of work include facilitating policy dialogue between funders of research for health; development of best practices documents for harmonization; and monitoring and evaluation of indicators to track input, process, outcomes and the impact

⁶ Head, Michael (ResIn, University of Southampton). Personal communication, email dated April 11, 2018.

of investment in capacity development. The second initiative is the Global Coordination Mechanism (GCM) of the R&D Blueprint at WHO, which focuses on coordinating countries' and partners' research activities for priority diseases both during the inter-epidemic period as part of research preparedness, and during outbreaks as part of the research response. Unlike ESSENCE, the R&D Blueprint GCM focuses on priority diseases with outbreak potential, including the three pathogens that constitute CEPI's initial vaccine focus. The GCM has worked with Nigerian Authorities to bring together relevant stakeholders and establish a research plan to be executed during the 2018 Lassa fever outbreak. Together, the objectives of the ESSENCE program and the GCM are complementary to achieving the goals of better coordination of funders for clinical research investments. ESSENCE draws on a decade of experience and the R&D Blueprint focuses on ensuring that clinical research is part of the outbreak preparedness response research architecture.

RECOMMENDATION 12

By end 2019, ESSENCE, in collaboration with the Global Coordination Mechanism and reinforced with additional LMIC representation, should articulate a mechanism that permits a thorough review of current and planned investments in research capacity strengthening. This should be done in consultation with major external funders of clinical research (including those involved in capacity strengthening of network, laboratory, ethics, and regulatory capability). This collaborative mechanism should ensure synergy at country and regional levels, and streamline the administrative burden experienced by institutions dealing with multiple research funders.

Surging Clinical Research Financing through Trust Fund Mechanisms

Clinical research surge capacity during an outbreak requires the ability to rapidly generate the funds required to support needed increases in researchers, mobile sites, medical and diagnostic equipment, and associated support. Trust Fund mechanisms can offer stable and predictable pools of financing to support

individual countries and global public goods. The Trust Funds held by the World Bank complement IDA financing and can act as a vehicle for supporting partnerships with other development actors.

Of the many Trust Funds at the World Bank, two that could potentially support the research agenda emerging from the WHO R&D Blueprint are the Pandemic Emergency Financing Facility (PEF) and CEPI Trust Funds. The PEF provides rapid surge financing in the initial stages of a severe outbreak before it becomes a pandemic. Financed through an insurance window that will make available up to US\$425 million for outbreaks of a group of diseases likely to cause major epidemics and a US\$61 million cash window, PEF funds can be used to finance the cost of response efforts during an outbreak, in line with what is described in the country response plan (World Bank 2017c). To the extent that response-related research could be leveraged for managing an outbreak, PEF funds may be used for strengthening research capacity and for improving the knowledge base to enable response to subsequent outbreaks of the same pathogen.

Likewise, the World Bank, which hosts CEPI funds for development of vaccines, can leverage the efforts of CEPI with its own initiatives to strengthen country-level preparedness. Drawing upon CEPI's support for preparatory actions needed to test the vaccines being developed, such as helping to improve regulatory capacity in low-income countries and preparing countries and sites to conduct clinical trials, the World Bank could complement support through IDA as well as through the PEF.

RECOMMENDATION 13

By the end of 2018, the World Bank Group, working through the PEF and CEPI Trust Fund mechanisms, should establish a rapid financing vehicle to support the priority outbreak-related research agenda emerging from the WHO R&D Blueprint, and to strengthen in-country capacity, including the conduct of clinical research as part of outbreak response.

Tracking National-Level Resources for Clinical Research Capacity

Governments and development partners need to monitor and track all funding that supports clinical research capacity-building activities within the country, not only for planning purposes, but also for monitoring and evaluation, and overseeing the performance of research partners. Of the many tools that are available for this purpose, two that can be relatively easily adapted to track spending on clinical research are National Health Accounts (NHA) and the Public Expenditure Tracking system (PETS). NHA provides a systematic framework for mapping expenditures by ordering all flows in sources-to-uses format, while PETS triangulates budget and financial records from different sources on the expenditure map and can uncover points of leakage in the expenditure chain. A widely available tool suitable for tracking clinical research capacity in a variety of LMICs would go a long way towards improving coordination and strengthening oversight and targeting of national health research priorities.

RECOMMENDATION 14

By June 2019, based on experience accumulated by countries, WHO and the World Bank Group should develop a resource tracking tool enabling governments to monitor and track, at a national level, all funding that supports clinical research capacity-building activities within the country and accounts for the multiplicity of funders involved.

Monitoring Implementation on the Task Force Goals

The Task Force has made a series of recommendations addressing a diverse set of requirements for developing and strengthening clinical research capacity. Success will depend on a coordinated series of actions targeting the entire spectrum of the clinical research ecosystem. Coordinating and tracking action in this complex space of pandemic preparedness will be challenging. The Task Force believes that a broad-based, scientifically qualified, and autonomous body, such as the

recently-announced Global Preparedness Monitoring Board, would be appropriate to coordinate and review progress on the implementation of the various recommendations of the Task Force.

RECOMMENDATION 15

Reviewing progress on the implementation of these recommendations should inform the agenda of the Global Preparedness Monitoring Board.

Conclusion

Infectious disease outbreaks are on the rise around the world. Severe Acute Respiratory Syndrome (SARS), MERS, avian influenza, Ebola, Zika, Lassa—these diseases hitherto restricted to the vocabulary of epidemiologists and medical professionals have now almost become household names. The number of new infectious diseases affecting humans has increased fourfold in the past 60 years, and the number of outbreaks per year has more than tripled. Most are just a blip in the news; but once in a while one or two slip through our containment defenses, and cause enormous harm. It is indeed only a matter of time before the next pandemic hits us.

The world is better prepared than before, of that there is no doubt. But knowing that it is not fully and adequately prepared, we asked what must be done to

ensure that that the next inevitable outbreak does not turn into an uncontrollable pandemic. We focused our attention on one gap—that of getting clinical research capacity in low- and middle-income countries to a level at which they can conduct or support needed clinical trials at the time of an epidemic. We realized right away that this is by no means an easy task, for it requires resource-challenged countries to have in place a strong, robust and functioning clinical research capacity that could be rapidly called upon in the heat of an outbreak. We are encouraged by the large number of ongoing initiatives that are contributing directly and indirectly to strengthening clinical research capacity in low-income countries. At the same time, we are sobered by the many challenges that governments and development partners must overcome to be ready the next time the world gets hit.

Our report outlines how low- and middle-income countries could secure the political commitment, raise necessary finances and leverage ongoing initiatives of development partners to enhance research and development capacity and strengthen outbreak preparedness. Our 15 recommendations define an integrated framework for action by countries, development partners, research funders, research organizations and the private sector, and suggests clear timelines. We are confident that if countries and all stakeholders adopt the suggested framework, the world will see huge improvements in its ability, at the national level and globally, to build clinical research capacity and strengthen universal health security.

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CHAPTER 1

Introduction



Recent outbreaks and emergencies with health consequences, including the Ebola outbreak in West Africa, Zika in Latin America and the ongoing Lassa fever in Nigeria, shed light on the major gaps in health systems throughout the world and the ever-present challenges to prevent, detect, and respond to health crises at country, regional and global levels. Recognizing the severe health and economic costs of failing to adequately manage outbreaks and health emergencies, multiple international expert panels have recommended specific reforms related to strengthening national public health systems, enhancing global and regional coordination and capabilities, and accelerating research and development (R&D).

There has already been a significant response to these recommendations. The World Health Organization (WHO) has established a new program combining all aspects of events-based surveillance, infectious disease expertise, response capacity, research and development, and country capacity-building. The World Bank, through its 18th replenishment of International Development Association (IDA18) funding, has prioritized country preparedness financing and established the Pandemic Emergency Financing Facility (PEF) as an innovative mechanism to accelerate response financing for outbreaks. Many other initiatives have been developed at national, regional and global levels to strengthen public health preparedness and response. Very importantly, the results are already being seen in more timely detection and response to major outbreaks around the world, such as the outbreak of Ebola in the Democratic Republic of the Congo (DRC) in 2017 or pneumonic plague in Madagascar in 2017, and in the widespread efforts towards more objective assessment and achievement of International Health Regulations (IHR) core capacities.

However, even as countries and global institutions are working on strengthening pandemic preparedness and enhancing the speed and effectiveness of public health response during outbreaks, the area of clinical research—and its connections with emergency outbreak response—continues to be challenging. Noting that the “mobilization of a rapid and robust research response during the next epidemic will depend not just on what happens during the epidemic, but on what happens before or between epidemics”, the National Academies of Sciences, Engineering, and Medicine (NASEM) (2017) suggests that “careful inter-epidemic planning and execution through a well-coordinated and collaborative effort from national, international, and local representatives can help ensure that the global community is prepared to answer challenging questions through the conduct of research.”

But this is by no means an easy exercise. First, it will require resource-constrained countries to take conscious decisions to move resources away from other urgent and key areas and increase investments in clinical research and development. Second, these investments will have to be sustained over time, which will require continuing budgetary allocations to clinical research and development. The implicit trade-offs in these allocations are bound to be difficult, and governments would need to be convinced that investing in clinical research and development is necessary despite the multitude of competing demands on their budgets. For some countries, development assistance may play an important role in financing clinical research—but the same questions and trade-offs will need to be resolved there as well.

Recognizing this challenge, the committee convened by the National Academies of Sciences, Engineering, and Medicine to analyze the experience of clinical trials

that were conducted during the Ebola epidemic recommended that “national governments should strengthen and incorporate research systems into their emergency preparedness and response systems for epidemic infectious diseases....multilateral institutions (WHO and The World Bank), and regional and international development agencies, and foundations working in global health, should support national efforts by providing expertise and financing.” Operationalizing this recommendation in practical terms for countries, development partners, research organizations, the private sector and others involved in funding or carrying out clinical research is the focus of this report.

The International Vaccines Task Force

The International Vaccines Task Force on Strengthening Country Capacity for Vaccines Research and Development (IVTF; henceforth referred to as the Task Force) was established by the World Bank and the Coalition for Epidemic Preparedness Innovations (CEPI) in October 2017 to develop a set of recommendations on strategic investments that can strengthen clinical research and clinical trial capacity in low- and middle-income countries (LMICs). It comprises subject-matter experts from around the globe, representing academia, development agencies, national governments and the private sector. In preparing its report and recommendations, the Task Force has drawn upon recommendations from numerous reports, including the Harvard-London School of Hygiene and Tropical Medicine (LSHTM) Independent Panel on the Global Response to Ebola (2015), United Nations High-level Panel on the Global Response to Health Crises (2016), International Working Group on Financing Preparedness (2017), and the National Academies of Sciences, Engineering and Medicine report (2017), with the goal of identifying mechanisms for investments in healthcare, public health, and health research capacity in resource-limited

countries at risk of emerging infectious disease outbreaks.

The Task Force held two face-to-face full membership meetings and a series of theme-specific discussions spread over seven months. Members used these meetings to share ideas, examine data and evidence, test hypotheses and form recommendations. The Task Force conducted literature reviews, key informant interviews, site visits and case studies to inform its deliberations. It made use of additional work that other organizations performed on its behalf or shared. This includes, *inter alia*, a survey undertaken by The Global Health Network, a digital platform managed by Oxford University for facilitating collaboration and resource sharing on global health research (TGHN 2018a); a workshop convened jointly by the World Bank, WHO and the National Institute of Allergy and Infectious Disease (NIAID); analyses of global funders of infectious disease research provided by the University of Southampton; inventory of clinical research and translation sites in Africa, compiled by Dalberg Associates under an initiative of African Academy of Sciences (AAS)/Coalition for African Research and Innovation (CARI); and an ethics review carried out by the Council of Health Research for Development (COHRED) for the Clinical Research Initiative in Global Health (CRIGH).

Overview of the Report

The remainder of this report is organized as follows. Chapter 2 makes a case for countries to commit to clinical research. Chapter 3 describes the enabling elements required for a strong clinical research environment. Chapter 4 discusses the need for clinical research capacity measures. Chapter 5 outlines various financing options for clinical research capacity building. Chapter 6 outlines mechanisms to better coordinate investments in clinical research capacity. Chapter 7 proposes an option for monitoring progress on the recommendations of the report. The report concludes in Chapter 8.

CHAPTER 2

Committing to Clinical Research

Clinical Research Response during Outbreaks

Clinical research, simply defined as “research in which people, or data or samples of tissue from people, are studied to understand health and disease” (National Cancer Institute 2018), has played a fundamental role in advancing medicine and health. There are countless examples demonstrating that clinical research has helped prevent or mitigate the impact of infectious diseases while simultaneously strengthening national health systems and changing clinical practices even in low-resource settings. Oral rehydration therapy for diarrheal diseases was first developed and tested in clinical trials in India and Bangladesh and, in the past three decades, has saved an estimated 50 million lives worldwide, mainly of children who are most at risk from fatal dehydrating diarrhea (The Lancet 2013). The International Center for Diarrheal Disease Research in Bangladesh had its roots in early programs developed to treat cholera and other diarrheal diseases. It has grown over time to become a global research and training center, branching out from its early work on cholera to make breakthroughs in areas such as maternal mortality, family planning and health system redesign (icddr,b 2018). HIV trials conducted in Africa have been central to reducing maternal-to-child transmission of HIV (NIH 2018) and to strengthening the clinical care system for women and children. The vaccine developed under the Meningitis A project in Africa, led by PATH and WHO with Serum Institute of India and supported by the Bill & Melinda Gates Foundation, has had a dramatic effect on the incidence of suspected and confirmed meningitis cases (Trotter et al 2017).

“Surging” research during an outbreak is a critical but neglected part of the research architecture. Arguably,

conducting good quality clinical research during an epidemic can reap even greater and more rapid dividends than many other investments. Often critical knowledge related to how best to respond both at an individual clinical level and societal public health level can only be generated by research conducted during an epidemic (Lurie et al 2013). Assessing the key characteristics of a new infectious disease outbreak—such as clinical severity, presentation, the course of the illness, and associated risk factors—is critical for decision-making (Williams et al 2013).

However, major epidemics are generally unpredictable and intermittent, and most often occur in settings with the least capacity. The logistical, technical, and regulatory requirements of clinical trials present a greater set of hurdles when time is limited. It is clear that to develop and be sustainable, clinical research and clinical trial systems must address routine health priorities of a country or region in the inter-epidemic period. To maximize the impact of these clinical research efforts, the core capabilities need to be just as strong in the lower- and middle-income countries where epidemics strike most.

The desired outcome of the collective recommendations of the Task Force is nationally-owned and/or regional clinical research response capacity that conducts quality research compliant with international standards on national health priorities in the inter-epidemic period and can pivot to a robust urgent research response during an outbreak. Achieving this requires a set of country commitments and activities, incentivized through financing and other arrangements by a range of development, research and private sector funders.

Following the Ebola epidemic in 2014-2015, the National Academies of Sciences, Engineering and Medicine reviewed the clinical research response during the outbreak, concluding that the capacity to conduct clinical

research was seriously lacking in a number of critical areas in Guinea, Liberia and Sierra Leone (NASEM 2017). More specifically, it highlighted three critical shortcomings that impeded establishment of clinical research during the outbreak and the disappointing results from research that was eventually conducted:

- i. The affected countries did not have the infrastructure, human resources, or experience to deal with the public health and health care demands of the epidemic, let alone to facilitate research;
- ii. Ethics review boards and regulatory authorities in the affected countries lacked the resources, experience, training, and information management systems that were needed to evaluate a sudden onslaught of clinical research proposals; and
- iii. The affected countries did not have experience and expertise in completing the various and complex legal and bureaucratic steps in clinical trial conduct, e.g., issues around data and sample-sharing.

Such capacity gaps are not unique to these three countries. One recent study examining the situation across the Economic Community of the West African States (ECOWAS) reported that just half of West African countries had established directorates for health research with defined terms of reference; that the existing funding mechanisms were inadequate to support the research structures within and outside the ministries or to improve the capacity of researchers; and that networking and monitoring activities were weak. Most countries had not even established national research priorities (Sombié et al 2013). A follow up survey reported that there was evidence of increased regional investment and some progress, but “high staff turnover, weak institutional capacities, and ineffective collaboration” remained significant challenges (Aidam and Sombié 2016). At a broader level, a mapping study of research ethics committees conducted by COHRED identified over 165 committees operating in 34 African countries, but concluded that there was great variability in skills, membership, capacity, and efficiency (Kasule et al 2016). Despite efforts to train many in research ethics and help promote the establishment of functional mechanisms for ethics review of clinical research, the lack of structural and institutional support continues to hamper the establishment of meaningful capacity in ethics as evidenced by the findings from Kasule et al (2016): “Many [ethics committee] administrators may not have defined roles and responsibilities, may lack adequate

training, and do not have efficient electronic information management systems to assist with their heavy and often complex workloads”.

Where to Start

While the field of clinical research is broad—encompassing epidemiologic, observational, cost effectiveness, operational and implementation research, and clinical trials (US FDA 2018)—this Task Force focuses primarily on clinical research capacities for epidemic response, including those ultimately needed to conduct clinical trials. In doing so, it recognizes that clinical research capacity is often built in a stepwise fashion and must encompass fundamental capacities required for surveillance, epidemiologic analysis, and reporting under IHR 2005 (WHO 2008).

The core capacities for conducting clinical trials are enabled by a national legal framework that permits and facilitates the conduct of this research, and includes an experienced clinical trial team, appropriate space in which to conduct clinical trials and maintain records, a capable laboratory system, biobanking, capacity for reliable data management, a functioning ethical review system, a capable regulatory authority, the capacity to fulfill responsibilities as a trusted institution, including through execution of administrative functions, such as contracting or accounting for funds, and the capacity to engage communities. Achieving these capacities requires not only physical infrastructure, but a human infrastructure consisting of a trained, capable, multi-disciplinary work force. In addition, the system must be sufficiently flexible to move from a fixed space for clinical research and trials during inter-epidemic periods to emergency units set up to provide care and isolation of subjects with an epidemic infectious disease, such as the Ebola Treatment Units set up during the outbreak in West Africa during 2014-2015.

To this end, in-country researchers will be best prepared to lead the response to an emerging infectious disease threat if they have broad capabilities, including epidemiology/surveillance, effective community connections, translational research capacity, clinical research capabilities, relevant laboratory capacity, international research partnerships, and so on. All these capacities need to be fostered in the right enabling environment. Research sites and researchers are at the heart of the research architecture, but they will not survive without

arteries to the government institutions (awareness and support) and to communities (empowerment and trust). These pathways must be created and maintained by strong research governance (Box 2.1).

BOX 2.1

BUILDING TRUST IN UGANDA

Institutions such as the Infectious Diseases Institute (IDI) in Uganda, have gone to great lengths to establish policies and mechanisms that showcase their commitment to transparency, high standards, fiscal management, measurable results, and zero tolerance for corruption and mismanagement of funds. This commitment, combined with efforts in community outreach, education and hiring has been central to building population-level trust as well. While sometimes uncomfortable, balancing a zero-tolerance policy with community engagement, including the willingness to take fair but definitive action in the face of inappropriate behavior, has led to broad sustained community engagement and trust. IDI leadership has also been clear that building this kind of capacity does not happen overnight; indeed, achieving this status has been a decade-long effort, marked by major challenges.

Source: Potter, Christopher and Brough, Richard (IDI). Personal communication, email dated April 13, 2018

Simultaneously, research institutions need to be dynamic and be ready to diversify their research agenda to increase their likelihood of funding sustainability. Most research institutions in LMICs developed from a single disease focus, and as a result, their funding can be at risk when the disease becomes controlled (e.g., polio, H5N1 avian influenza) or when research funders change their research emphasis. Even in developed countries, estimates indicate that over half of clinical trial sites fail to become sustainable because of their inability to attract a second trial.⁷ While the impetus to diversity can come from the country government, it also comes when investigators themselves recognize additional health challenges in their environment and garner resources to address them. The Fogarty International

⁷ Society for Clinical Research Sites (SCRS). Personal communication, email dated May 3, 2018.

Center at the National Institutes of Health (NIH) has dubbed the investigators who lead such efforts ‘research entrepreneurs’, highlighting many of them in their publications (Fogarty International Center, NIH 2009, 2012, 2017).

BOX 2.2

FOGARTY RESEARCHERS DIVERSIFYING FOCUS IN A CRISIS

As more and more babies in Brazil were born with microcephaly in 2015, Fogarty-supported scientists rapidly changed gears on work they’d been doing for years on Chagas disease and dengue, and shifted their focus to the Zika virus, which was suspected of causing the spate of birth defects. By the time researchers had confirmed the link between Zika and microcephaly in infants, scientists in Brazil who had been trained with Fogarty support were using the resources in place for Chagas disease brain research to better understand Zika, and collaborating with other groups to advance knowledge of the disease, said Dr. Jamily Oliveira-Filho of Brazil’s Federal University of Bahia. Meanwhile, in Mexico, two Fogarty-supported Ph.D. candidates who were researching different aspects of preventing and controlling dengue—transmitted by the same *Aedes Aegypti* mosquito as Zika—refocused their work on Zika.

Source: Fogarty International Center, NIH (2017)

Accelerating R&D during Emergencies: The Nigerian Experience

At the time of this writing, Nigeria is experiencing the worst Lassa fever outbreak on record, with the number of confirmed cases in January and February 2018 alone exceeding the total number reported in the whole of 2017. Between January 1 and April 22, 2018, a total of 1,865 cases (416 confirmed) have been reported from 20 states in Nigeria. Since the onset of the 2018 outbreak, there have been 105 deaths in confirmed cases, a Case Fatality Ratio in confirmed cases of 25.2 percent. Recent

weeks have seen a decline in the growth rate of new cases, but “We should interpret the recent declining trend in new cases with caution. The Lassa fever season is not yet over.”⁸

What has been remarkable about the response this time is the speed and the quality of research that has been launched to better understand the nature of the outbreak and obtain crucial insights which will help mitigate future Lassa fever outbreaks. At the onset of the current Lassa outbreak, the Nigeria Centre for Disease Control (NCDC), working with WHO and other partners, promptly developed a list of research priorities aimed at improving the ability of the response team to prevent, detect and control an outbreak in the future and to establish a national long-term capacity to conduct Lassa-related research, building on existing capacity. The research priorities and actions, which were initiated in record time as part of the Nigerian research plan, address:

- Harmonization of core clinical data variables and documentation of patterns of care for Lassa fever patients to improve support of care, aid interpretation of results from future studies on immune response to Lassa infection, and put in place an infrastructure for multi-site evaluations of therapeutics and vaccines;
- Testing of diagnostic assays to distinguish between acute illness, repeat or chronic infections, and response to vaccination that will permit improved management of cases and clinical research on promising Lassa fever treatments and vaccines;
- Strengthening of Lassa surveillance and laboratory capacity to enhance the understanding of disease incidence, prepare to respond to outbreaks and facilitate future vaccine trials;
- Strengthening infrastructure of critical health facilities, alongside supply-chain of essential medicines and equipment;
- Training of health and research workers on basic infection prevention and control measures and good clinical practices;
- Planning critical translational research to inform community engagement strategies and to further document risk factors for transmission of Lassa virus;

- Strengthening oversight by the Nigerian ethics and regulatory review bodies to evaluate a possible blitz of research protocols applications; and
- Mapping and coordination of the offers of support along the lines of the identified research priorities to develop a national research plan that addresses the Nigerian priorities.

Researchers at the Irrua Specialist Teaching Hospital—in collaboration with NCDC, the Bernhard-Nocht Institute for Tropical Medicine, Germany, WHO, and others—have conducted genome sequencing of the Lassa virus. As Dr Wondimagegnehu Alemu, WHO Representative to Nigeria, notes, “by conducting research as the Lassa fever outbreak unfolds, Nigeria is pioneering a new approach. Until now research in Africa has taken place much later in the response cycle. This is a new approach which opens the way to much more effective control of emerging and dangerous pathogens.”⁹

Not only has Nigeria responded quickly and adequately to the Lassa fever epidemic, it has also seized upon the opportunity provided by the outbreak to establish and initiate action on research priorities in parallel to managing the response. Despite a plethora of challenges—including lack of career paths, lack of awareness of research in their communities and instability in contracts/funding—this experience demonstrates that researchers and research institutions, in low-income countries, have the potential to produce life-saving innovations and improve quality of life for many. This leads us to our first recommendation, that governments commit to strengthening capacity to conduct or participate in clinical research to address their public health needs.

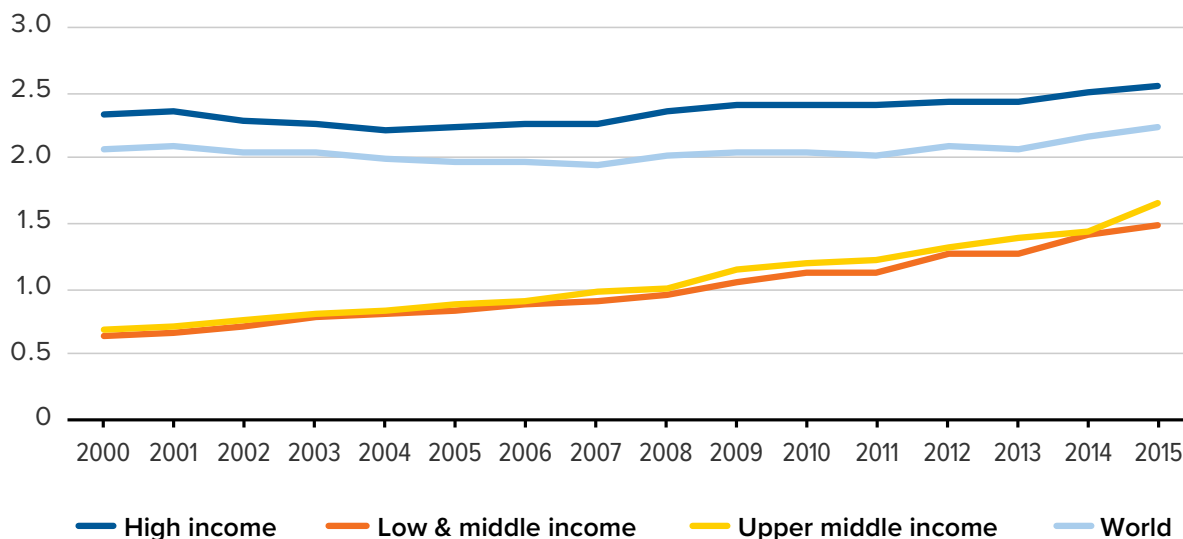
RECOMMENDATION 1

By December 2018, in order to effectively respond to disease outbreaks, reduce preventable deaths, strengthen productivity and improve quality of life, countries should commit to strengthening capacity to conduct or participate in clinical research to address their public health needs.

8 Dr Wondimagegnehu Alemu, WHO Representative to Nigeria, speaking on the Lassa fever outbreak in Nigeria, March 26th, 2018, Abuja, Nigeria. Accessed on April 26th, 2018 at 17:00 hrs. URL: <http://www.afro.who.int/news/who-nigerias-lassa-fever-outbreak-slowing-remains-concer>

9 Ibid

FIGURE 1: SPENDING ON R&D AS A PERCENTAGE OF GDP



Source: World Bank 2018a

Investment Framework

What clinical research capacities and capabilities must countries develop? What financing sources must countries tap, especially those that are already very stretched in terms of unmet demands? In an environment of constrained resources, what strategies must countries employ to prioritize investments in a subset of interventions? What strategies must countries put in place to sustain these investments over time? These are the kinds of questions that a strong investment framework for clinical research must help answer.

The world invested US\$1.67 trillion in all R&D, including health-specific R&D, in 2015, the latest year for which data are available, equivalent to 2.23 percent of global GDP (World Bank 2018a). The proportions varied considerably across countries, with high-income countries spending 2.56 percent of their gross domestic product (GDP) on all R&D in 2015, followed by upper-middle-income countries (1.66 percent) and low- and middle-income countries (1.49 percent). Between 2000 and 2015, global spending on all R&D as a percentage of GDP increased by only 0.56 percent annually on average. Encouragingly, R&D spending in low- and middle-income countries increased at an annual average rate of 8.8 percent during this period (Figure 1).

Comparable data on spending on health R&D is not readily available. The limited data available shows

that South Korea spent 0.21 percent of GDP on health R&D, which was under 5 percent of all R&D spending (UNESCO 2018). Likewise, Singapore and Netherlands spent 0.4 and 0.34 percent respectively of GDP on health R&D in 2014, equivalent to 18 and 17 percent of all R&D spending in these countries (WHO 2017).

The mix of arguments to be used to make the case for investing in clinical research will vary from country to country, depending on the scale of additional investment required and the broader socio-political and economic context. But one thing is certain: investing in health science research and research capacity yields positive economic benefits, and evidence suggests that the aggregate economic returns are large. The Fogarty International Centre, NIH (2017), the Wellcome Trust (2018), and the Global Health Technologies Coalition (2017) have all documented the economic returns of investing in health research. While estimates vary many fold, and are more often based on higher income countries experience, they demonstrate that every dollar invested in health research, or research more generally, returns far more than a dollar in return.

- The Fogarty International Center, NIH reports that each US\$1.00 increase in public basic research stimulated an additional \$8.38 of industry R&D investment after 8 years, and each US\$1.00 increase in public clinical research stimulated an additional US\$2.35 of industry R&D investment after 3 years (Toole 2007). In FY2017, US\$26.1 billion in NIH grants

led to US\$68.8 billion in economic activity nationwide. NIH grant funding in FY2017 created over 400,000 jobs in the United States. In California, the largest recipient of federal research funds, about US\$3.9 billion in NIH grants and contracts supported more than 62,000 jobs in the state in 2017. Another state receiving substantial NIH funds is New York, with US\$2.4 billion supporting more than 29,000 life sciences jobs in 2017 (United for Medical Research 2018). NIH research also helps to foster the creation of new biotechnology companies: one study by Kolympiris et al (2014) found that every US\$1 million in public R&D funding to universities over a 5-year period generated a 5.9 percent increase in the creation of location biotechnology firms in the nearby metropolitan area. Maryland, for example, contains 50 research-intensive federal institutes and centers that have helped foster about 500 bioscience companies.

- A research study produced by the Policy Institute at Kings College London, RAND Europe, and the Health Economic Research Group at Brunel University London,¹⁰ and reported by Wellcome Trust (2018) shows that for musculoskeletal, cancer, cardiovascular and mental health research, every UK£1 invested in medical research delivers a return equivalent to around UK£0.25 every year in perpetuity. It finds that research funding stimulates or ‘crowds in’ private investment, resulting in a boost to economic activity through industry commercializing new products or investing in further research.
- Global Health Technologies Coalition (2017) estimates that the US\$26 million invested in polio vaccine R&D resulted in treatment cost savings of US\$180 billion since the 1950s, and the US\$50 million that it cost to develop meningitis A vaccine is expected to have saved US\$9 billion in treatment costs by 2020.

Science Business (2017) puts these estimates in perspective. It notes that “the many economic measurements of returns on investment to publicly funded research and innovation (R&I) vary wildly in range, but seem to cluster at around a 20 percent annual return on investment. This can be compared to 6.8 percent for the past 10 years of the US stock market (S&P 500) or the 3.1 percent for 10-year Euro Area (19 countries)

¹⁰ Funding for this research was provided by the Academy of Medical Sciences, Arthritis Research UK, the National Institute for Health Research, and the UK Medical Research Council.

Government Bonds. In short, publicly funded R&I is a good investment” (Science Business 2017).

Although the investment case for clinical research is strong, mobilizing the necessary resources is constrained by a variety of factors, including insufficient financing, lack of political support for investing in activities that do not necessarily yield returns in the present time, and complexity in terms of implementation (that is, what to fund and how to maintain the investments over time). These challenges are further exacerbated in the context of resource-constrained economies, which use up all the scarce resources to take care of urgent needs today instead of worrying about the imperatives of tomorrow.

The World Bank is strategically placed to help countries develop investment frameworks for clinical research for low-income countries through its International Development Association (IDA) lending arm (Box 2.3). As part of commitments under IDA18, the World Bank Group is committed to helping at least 25 countries develop pandemic preparedness plans and strengthen their capacities to detect, prevent and respond to disease outbreaks. The World Bank Group has tentatively identified these countries and has begun working with them to develop, update, and/or review comprehensive pandemic preparedness plans. Strengthening clinical research capacity is an integral element of country preparedness for disease outbreaks, and the World Bank Group, through its IDA lending arm as well as its IDA18 commitments, can extend financial support to countries willing to invest in clinical research development. Although the commitments in the last round of IDA of developing preparedness plans are for 25 countries,¹¹ all IDA eligible countries have the potential to be supported under future commitments.

The World Bank Group carries out a detailed review of progress in all sectors midway through the IDA cycle. The review not only examines achievements and constraints within the IDA cycle under consideration, it also provides a strategic platform to explore new and innovative approaches that could potentially enhance IDA’s ability to respond to sustainable development goals (World Bank 2015a). The mid-term review of the ongoing IDA18 cycle is scheduled for December 2018. This would

¹¹ These include Afghanistan, Bangladesh, Benin, Burkina Faso, Cambodia, Cape Verde, Democratic Republic of the Congo, Ethiopia, Ghana, Guyana, Haiti, Kenya, Lao PDR, Liberia, Mali, Myanmar, Nepal, Niger, Nigeria, Papua New Guinea, Senegal, Sierra Leone, Sudan, Tanzania, and Uganda.

BOX 2.3

INTERNATIONAL DEVELOPMENT ASSOCIATION (IDA)

The International Development Association (IDA) is the part of the World Bank that helps the world's poorest countries. Overseen by 173 shareholder nations, IDA aims to reduce poverty by providing loans (called "credits") and grants for programs that boost economic growth, reduce inequalities, and improve people's living conditions.

IDA complements the World Bank's original lending arm—the International Bank for Reconstruction and Development (IBRD). IBRD was established to function as a self-sustaining business and provides loans and advice to middle-income and credit-worthy poor countries. IBRD and IDA share the same staff and headquarters and evaluate projects with the same rigorous standards.

IDA is one of the largest sources of assistance for the world's 75 poorest countries, 39 of which are in Africa, and is the single largest source of donor funds for basic social services in these countries. IDA lends money on concessional terms. This means that IDA credits have a zero or very low interest charge and repayments are stretched over 25 to 40 years, including a 5- to 10-year grace period. IDA also provides grants to countries at risk of debt distress. In addition to concessional loans and grants, IDA provides significant levels of debt relief through the Heavily Indebted Poor Countries (HIPC) Initiative and the Multilateral Debt Relief Initiative (MDRI).

In the fiscal year ending June 30, 2017, IDA commitments totaled US\$19.5 billion, of which 17 percent was provided on grant terms. New commitments in FY17 comprised 261 new operations. Since 1960, IDA has provided US\$345 billion for investments in 113 countries. Annual commitments have increased steadily and averaged about US\$18 billion over the last three years.

Source: World Bank (2018b)

provide a good opportunity to consider which innovations implemented in IDA18 are ready to be scaled-up—and look ahead to what sort of next-generation innovations IDA can support going forward (World Bank 2015b). It thus provides a forum for proposing prioritization of a set of tailored investment frameworks for LMICs to develop clinical research capacity in the scope of the 19th replenishment of International Development Association funding (IDA19) commitments.

RECOMMENDATION 2

Recognizing the existing IDA18 commitment to strengthen preparedness in at least 25 countries, the World Bank Group should include, as a part of its IDA Mid-Term (December 2018) Review (MTR), an investment framework for national and regional clinical research capacities.

CHAPTER 3

Enabling Clinical Research



The capacity to conduct clinical research, including clinical trials, does not exist in a vacuum. Indeed, the capacity requires more than a few investigators to conduct a trial. Building capacity begins with a national commitment, which includes creating a comprehensive legal framework and nurturing a culture of conducting high-quality clinical research are essential elements for a more sustained capacity-building program.

Legal Frameworks

A legal framework and research governance system that supports and enables the conduct of clinical research and clinical trials is a prerequisite for building capacity. Laws are critical for authorizing a national entity to oversee a national research plan and priorities; a national regulatory and ethics review system; import, export and customs regulations related to research; and mechanisms for dispersing funds to support researchers and research institutions. Laws are also necessary to protect intellectual property rights.

While legislative frameworks and laws enabling a national health research system, clinical research and clinical trials are critical, the Task Force notes that there is uneven adoption of such laws. To illustrate, laws regarding clinical research, governance and regulation of research have become commonplace in Latin America over the past decade (for example, Peru, Argentina, Mexico, Ecuador, Paraguay, Brazil) (Motti 2008), but they are far less common on the African continent.

Legal and policy frameworks in other areas have been helpful in addressing these shortcomings to advance policy solutions. For example, a review of material transfer agreements (MTAs) of various countries was used by WHO to support efforts to develop and make a MTA template available for countries to use; these agreements set forth the conditions for sample sharing and specimen sharing outside of the country of origin. This analysis is being used by the Government of Nigeria to promote clinical research related to its Lassa outbreak.

Many countries, ranging from Singapore to Senegal have found that a governmental entity, such as a national health research institute, is key to working with its research institutions (both public and private). In a virtuous cycle, research conducted in national research institutions in turn provides evidence to strengthen country policies regarding not only health, but other sectors including education, animal and agriculture, science and technology, industrial/economic, and security.

The Pan American Health Organization (PAHO) has played a key role in promoting relevant laws in Latin America through its Policy on Research for Health (PAHO 2010), but a comprehensive repository or analysis of countries' laws appropriate to the conduct of clinical research appears to be non-existent. A synthesis of existing, broadly applicable laws and policies regarding clinical research would enable countries to more rapidly develop legislation, if needed, and assess whether their existing legal framework was sufficient to their needs.

RECOMMENDATION 3

By end 2019, WHO should develop and disseminate examples of broadly applicable legislation and policies to support and enable efficient conduct of clinical research. This should include, at a minimum, model policies and laws that support the conduct of trials, enable timely ethics and regulatory review, address import/export of relevant commodities and bio-specimens, and address procurement and contracting systems. These policies should be a part of a broader governance architecture for clinical research.

Culture of Clinical Research

Numerous interviews conducted for this Task Force, as well as a study of barriers and enablers to developing clinical research capacity conducted by Franzen et al (2017), identified the need for a supportive research culture if clinical research capability is to develop and thrive. The literature and the Task Force identified several elements that can create such a supportive culture. Some of these are highlighted below.

First, increasing visibility and political support for clinical research is important. Ensuring there are national research plans and priorities, with preparedness as a key element, is central to that effort. Even in the face of such plans, in many countries, the general public, students considering future careers, and government officials could benefit from increased information about nationally produced research and the role it can play in improving population health and economic development. At a recent workshop on strengthening clinical research in LMICs (organized by the UK Academy of Medical Sciences and the InterAcademy Partnership for Health), representatives of 25 LMICs reiterated the need for increased public interest, and noted that countries could benefit from increased awareness of what it takes to develop a research culture and that “the engagement of scientists with governments in order to raise awareness and advocate for policies supporting clinical research is a key step to addressing many of the issues faced by the [research] community” (Academy of Medical Sciences 2017).

Second, an environment that supports, promotes and publicizes careers in clinical research and role models for young investigators is a necessary element to support and motivate scientists to pursue clinical research careers, and to choose to use those skills in-country. While actions that a country might take to create such a culture may be clear to scientists themselves (e.g., adequate salaries, a career ladder) public understanding and appreciation, including that of government officials is usually limited.

Third, while well-resourced, research-intensive institutions have an infrastructure to compile and ‘push’ funding announcements to researchers, there does not appear to be any one-stop shop for researchers in LMICs to learn about a broader array of funding opportunities. One suggestion has been that Academies of Sciences fulfill such a role, although that may result in duplication of effort. The Council on Health Research for Development (COHRED) initiated a platform, Health Research Web (HRWeb), with the intent of gathering a range of research and management information, including funding opportunities, but funding to support it has not been maintained. It may be prudent for COHRED and others and global research funders to examine different models to support such a platform.

Finally, it is necessary to maximize opportunities for fair and mutually beneficial research partnerships within and across countries. COHRED has published guidelines on the Fair Research Contracting Program (COHRED 2013). Additionally, ensuring speedy ethical review is crucial to the conduct of trials in-country. RHInnO Ethics, an online review platform for research ethics committees, seeks to facilitate an efficient ethical review clearance of clinical research involving human subjects. In 2015, RHInnO Ethics was used by 25 research ethics committees in 8 African countries (Mokgatla et al 2017). These existing initiatives are just a few that can be supported and leveraged nationally to create an enabling environment.

In some industrialized countries, Academies of Sciences or other research institutes (e.g., the National Academies of Sciences in the US, or highly respected institutions such as the Royal Society and the Academy of Medical Sciences in the UK) are influential in-country, and often global health and research policy. In Africa, the African Academy of Sciences (AAS) is now playing a key role in coordinating clinical research development and funding in the creation of the Coalition for

African Research and Innovation (CARI), and is poised to become a catalyst and coordinator for clinical research activity. Similarly, in South Africa, the South African Medical Research Council is influential in research policy direction for the country. The Task Force found that such Academies, by nature of their stature, leadership, independence and growing influence, are well positioned to take charge over the immense knowledge transfer required between the decision-makers in governments, research capacity development experts, and the researchers themselves. As a pivotal group in this, the Academy of Sciences should be engaged by national

governments on the best way to strengthen enabling elements, culture and sustainability of clinical research.

RECOMMENDATION 4

By 2019, Research Forums/Institutions and/or Academies of Science in LMICs, drawing upon their experience and that of others, should synthesize best practices and develop guidance for consideration by countries on how to build a supportive research climate/culture.

CHAPTER 4

Assessing Clinical Research Capacity

There are no widely-accepted measures of assessing country-level capacities for clinical research, which makes it challenging to determine whether a country has the capability to participate in or conduct a clinical trial, including whether it has in place adequate regulatory and ethics frameworks necessary for the conduct of clinical research. It is also difficult to determine the extent of community engagement and the level of trust that would facilitate voluntary participation in randomized controlled trials. An evidence-based tool for assessing clinical research capacity would help governments identify the gaps and the needed investments to bring their research capacities up to international standards.

Existing approaches that track clinical trials in countries are indicative of the gaps in country capacities. WHO, for instance, maintains an International Clinical Trials Registry Platform (ICTRP),¹² which provides handy data on registered clinical trials in countries. According to this registry, 96 countries have registered vaccine trials in the last twenty years. Fifty-six out of these 96 countries have registered between 1 and 10 trials, followed by 13 countries that have registered between 10 and 20 trials, 3 between 20 and 30, 5 between 30 and 40, 4 between 40 and 50, and 11 countries over 50 trials. An additional 100 countries have registered non-vaccine related trials. Figures 2 and 3 show the world-wide spread.¹³

¹² The figures are made using ongoing and completed vaccine trials that were registered since 1999 regardless of recruitment status. Country of recruitment refers to the country "from which participants will be, are intended to be, or have been recruited at the time of registration". A trial may be counted more if participants are recruited from more than one country. Figure 2 data is as of April 6th, 2018; figure 3 data is as of April 4th, 2018. Source: International Clinical Trials Registry Platform (ICTRP). Available at: <http://www.who.int/ictrp/search/en/> Note: The ICTRP compiles trial records from 17 data providers, including ClinicalTrials.gov and EU Clinical Trials Register (EU-CTR). More information can be found at: http://www.who.int/ictrp/search/data_providers/en/.

¹³ In the absence of detailed information on who and how these trials were conducted, it is difficult to make a determination about the country's capacity and expertise to carry out clinical trials.

Some indicators that measure research competency at various levels are in use. These include:

- Global Health Observatory on Health R&D, which monitors the number of researchers in health and medical sciences, by country (WHO 2018a);
- The TDR-TGHN Competency Wheel (TGHN 2018), developed by the TDR (Special Programme for Research and Training in Tropical Diseases) at WHO in partnership with The Global Health Network which lists all the competencies that should be demonstrated by a research team to carry out a successful clinical study;
- The Mapping African Research Ethics Review and Medicines Regulatory Capacity (MARC) initiative, established by COHRED in partnership with the South African Research Ethics Training Initiative (SARETI) to map health research oversight and regulatory activities in Africa, which has collected information on over 150 African research ethics committees (COHRED 2018);
- The Laboratory Network Scorecard (LABNET) developed by the African Society for Laboratory Medicine (ASLM) and the Association of Public Health Laboratories for the assessment of national laboratory network functionality (Ondoa et al 2016);
- The Research Fairness Initiative (RFI), developed by COHRED and currently adopted by many countries and organizations, including the TDR at WHO, "to create a reporting system that encourages governments, business, organizations and funders to describe how they take measures to create trusting, lasting, transparent and effective partnerships in research and innovation" (RFI 2018).
- The WHO Global Benchmarking Tool for Regulatory Capacities, which assesses and documents capacities of national regulatory agencies (PAHO

FIGURE 2: NUMBER OF CLINICAL TRIALS PER COUNTRY OF RECRUITMENT



Source: WHO ICTRP 2018

2017), including the capacity to provide informed no-objection to clinical trials, post marketing surveillance and oversight of research during outbreaks; and

- The Joint External evaluation (JEE) that, inter alia, assesses laboratory and surveillance preparedness (WHO 2016).

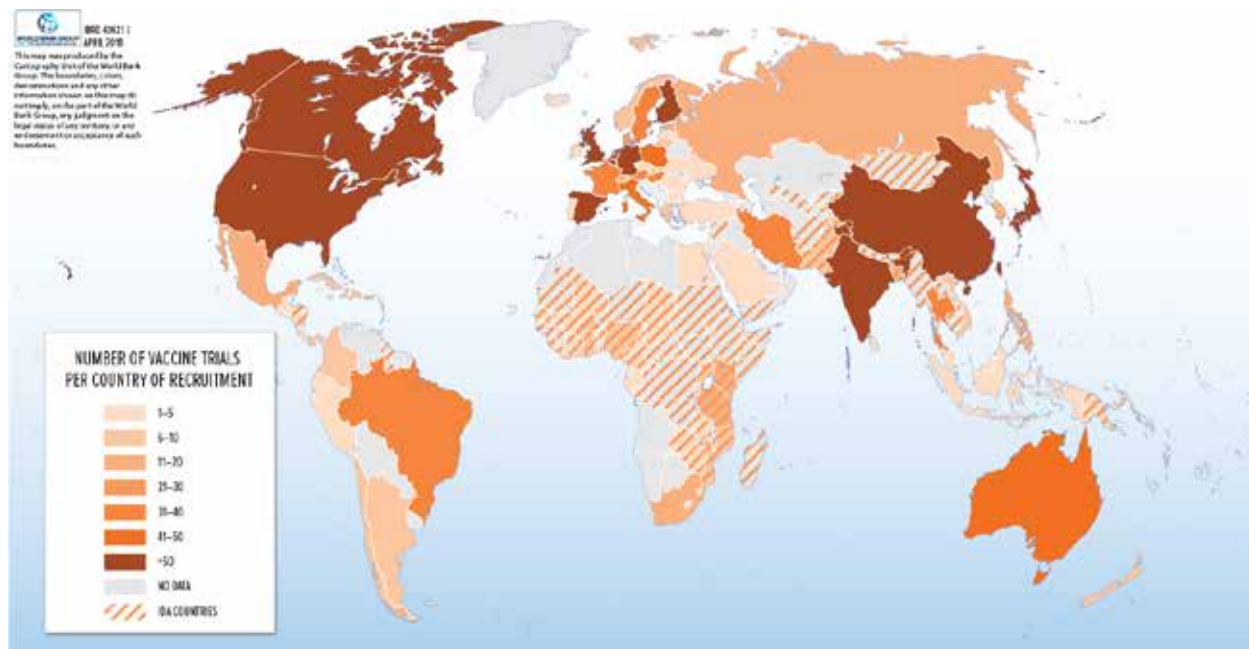
A critical but neglected part of the response architecture in the context of an outbreak is the ability to “surge” research to take advantage of the brief window of opportunity to better understand the nature of the outbreak and test new diagnostics, therapeutics and vaccines. This depends on the existence of a clinical research system and its agility and ability to shift priorities. Key constituent parts of this research system include appropriately trained researchers, including epidemiologists, anthropologists and clinical trialists; appropriate institutional conditions (jobs, salary, hardship supplements, personal protection precautions, etc.) to sustain researchers in the inter-epidemic period as well as during outbreaks; support for researchers to undertake research; ethics review boards (rapid but thorough); regulatory capacity for new diagnostics, treatments and vaccines; state-of-the-art methods for research

during crises; and standard operating procedures for operationalizing during different types of crises. It also requires the existence of an enabling environment with the necessary legal framework, professionally generated guidelines, and an atmosphere of trust and support, data management capacity and community participation. These elements, which comprise a multidimensional construct, have not yet been combined into a useful index, or developed into a standard that can be readily used at the country level.

Building upon the various existing indicators and ongoing work in this area, and developing a robust set of indicators to systematically assess country capacity for clinical research is a huge but necessary task. As a specialized agency of the United Nations, WHO is strategically and best placed to consolidate measures already in use and develop a tool for assessing clinical research capacity at the country level.¹⁴

¹⁴ This point was reinforced at a workshop co-organized by WHO, the National Institute of Allergy and Infectious Disease, and the World Bank in March 2018, and attended by low- and middle-income country representatives as well as the concerned international agencies.

FIGURE 3: NUMBER OF VACCINE TRIALS PER COUNTRY OF RECRUITMENT



Source: WHO ICTRP 2018

Given the urgent need to be better prepared to address outbreaks, countries need not wait for such a measure to be finalized before conducting their own assessment of research gaps. Key informant interviews as well as qualitative results from a TGHN survey of 5,000 individuals suggest that researchers are readily able to identify key capacity gaps. One interim suggestion is that governments encourage researchers, in both public and private institutions across their countries, to participate in a rapid assessment process, followed if needed by a more formal inventory of capacity gaps. COHRED typifies the organization that could facilitate these assessments, and has a track record of doing so. Such assessments could be facilitated by development of a relevant scenario-driven exercise to assess what would be required and is in place to participate in or conduct a relevant vaccine or therapeutics trial.

RECOMMENDATION 5

By end 2018, WHO should consolidate a robust set of indicators, to the extent possible building on indicators already used by countries, develop a tool for assessment of country-level capacities for clinical research, and propose a process to help countries rapidly conduct these assessments.

CHAPTER 5

Financing Clinical Research Capacity

We believe that countries seeking to step up investments in clinical research should raise and spend their own funds to provide for their people. We believe that “domestic resource mobilization not only provides governments with the funds needed to alleviate poverty and deliver public services, but is also a critical step on the path out of aid dependence” (USAID 2018). At the same time, we realize that despite recognition of the need for country investment and ownership, mobilizing domestic resources to support clinical research will be

challenging for most low-income countries. One issue is that domestic resource mobilization for clinical research in health must compete with other country priorities, such as building roads and bridges. When investments are likely to generate an immediate revenue stream, such as through power generation, the decision to fund is often easier. And, in part because the link between epidemic preparedness and clinical research is not well appreciated by policy-makers, it is neither widely known, nor clearly understood, that countries could choose to

BOX 5.1

DOMESTIC VS. INTERNATIONAL FUNDING: BASIC PRINCIPLES

As a fundamental principle, countries should aim to increase their domestic spend on development and specifically health, including preparedness, to maximize country ownership and self-reliance over time. This idea has been articulated in many settings: for example, the commitment of African Union countries to allocate at least 15 percent of their national budgets to improve the health sector (Abuja declaration 2001), and the partnership for improved domestic research mobilization (Addis Tax Initiative 2015).

Whenever international development assistance is deployed, it should focus on “catalytic” activities or activities that have high global externalities and low domestic demand. Catalytic activities allow a step change in a country’s level of preparedness. These are expected to be mostly one-off costs—but can also be recurring costs, if these are critical to establish capacities in the countries, or if executing certain functions at a centralized level enables scale efficiencies. Activities with high global externalities and low domestic return are those that promise high impacts for global risk mitigation but may be deprioritized in countries without international support.

Regional entities and neighboring countries can play an important role in providing technical and financial support for preparedness activities in cases where they can add value through coordination (e.g., the establishment of the Mekong Basin Disease Surveillance Network and Africa CDC); economies of scale (e.g., joint drug procurement in Central America by SICA); or sharing expertise.

The private sector should also be included across the entire preparedness planning process, and its expertise should be leveraged in carrying out planning activities.

Source: IWG (2017); Phommasack et al (2013)

commit resources, such as those from their IDA allocations, to support clinical research capacity-building.

Costs incurred for clinical research capacity-building, as with other initiatives, include start-up costs, fixed costs and recurrent costs, all of which must be provisioned for in the development or expansion of clinical research capacities. Some of the enabling elements for strengthening a clinical research system, including establishing a legal framework, and country and institutional system for regulatory and ethics review, could be considered start-up costs. These costs would need to be funded early in the process. Further, countries setting up clinical research capabilities will face several fixed and recurrent costs. Fixed costs are typically large and lumpy capital costs, such as those that may be incurred in such areas as building a clinical trial facility, purchasing laboratory equipment, regional biobank/specimen storage, and establishing a data management infrastructure. Recurrent costs, on the other hand, must be borne on a regular basis year after year, and include salaries and wages, consumables, travel, training, and so on. Ethics and regulatory review systems, and running a laboratory or biobank may also generate considerable recurrent costs because of the human resource needs required for effective approval and oversight of clinical research.

The most problematic of all these costs are often recurrent costs, in that countries need to mobilize domestic resources and make specific budgetary allocations to pay salaries and wages, buy consumables, pay trainers, etc. While start-up costs may be borne from one-time grants from development partners, recurrent costs are incurred every year and must be provided for in every budget cycle. In contrast, financing for capital investments can be sourced by loans and credits, such as those from the World Bank Group's IDA.

RECOMMENDATION 6

By end 2019, governments in IDA-eligible countries should commit short- and medium-term resources to address their clinical research capacity goals. These resources could potentially come from their IDA portfolios.

Committing domestic resources for epidemic preparedness, and the clinical research needed to support it, can be a huge challenge for resource-constrained economies that struggle to meet more proximate and immediate demands. Countries also hesitate to borrow for investments in these areas, preferring to use external

loans and credits to finance what they see as more immediate needs. Financing mechanisms that offer soft terms may tilt the scales in favor of borrowing funds to strengthen their clinical research capacity. One such mechanism is the buy-down.

Buy-downs

One innovative solution used in some cases by the World Bank is 'buy-downs', which essentially bundle IDA interest-bearing loans and credits with donor-funded grants that are used to buy down the net present value of the loan or credit and reduce it to grant terms. This provides an attractive motivation to achieve the intended outcome, in that countries are incentivized to incur debt to undertake an activity that they might otherwise not have done, and to work toward successful completion of pre-defined targets so as to have the loan reduced to a grant (World Bank 2010a). Experience with pilot buy-downs suggests that they can help governments achieve purely national targets, creating internal incentives for improved monitoring and evaluation and more clearly defined accountability (World Bank 2010a), or they can be used to support regional activities that are considered global public goods.

One example of the successful use of buy-downs relates to financing of intensified polio-eradication activities in Pakistan in 2003. Developed in partnership with the Bill & Melinda Gates Foundation (BMGF), Rotary International (RI) and the UN Foundation, the World Bank set up a multi-donor Polio Eradication Trust Fund, which was used to pay the service fee for the IDA Credit to Pakistan¹⁵ during the implementation, and to buy down the Net Present Value of the IDA Credit and reduce it to grant terms upon successful completion of the project.¹⁶ This effectively translated the IDA Credit to Pakistan to a grant for polio eradication. The external partners bought the credit at the Net Present Value,

15 Other countries that benefited from this Trust Fund and buy-down were Afghanistan, Pakistan and India in South Asia and Nigeria and Angola in the Africa Region.

16 Two indicators were used to measure project performance: (i) Timely arrival of the Oral Polio Vaccine at the central stores of Pakistan's Expanded Program on Immunization (EPI) at least five weeks before each of the planned Supplemental Immunization Activities (SIAs); and (ii) SIA coverage of 80 percent achieved in the remaining endemic provinces during 2005. The timely arrival of the vaccine was measured through the EPI's vaccine arrival reports. SIA coverage was measured through a cluster sampling survey according to a WHO approved methodology. Achievement of these indicators constituted the trigger for the IDA buy-down.

which enabled them to leverage their funds for financing polio eradication in Pakistan with about a third of the funds they would otherwise have needed to finance the same goods and services. This partnership enabled the external partners to access the rigor of the World Bank's project preparation and supervision in support of their efforts for polio eradication. As of 2017, the Bill & Melinda Gates Foundation continues to support polio eradication in Pakistan through this mechanism.

Buy-downs represent a win-win-win approach for countries, the World Bank and the donors. Countries receive financing for a global public good if they meet the agreed performance targets; the World Bank can leverage the technical expertise of other partners; and the donors can leverage their funding (World Bank 2017a). This mechanism has a lot of potential to support countries wishing to invest in clinical research capacity, particularly when it also supports the global public good value of preparedness.

RECOMMENDATION 7

By end 2018, the World Bank Group should develop mechanisms to buy down IDA loans and convert them into grants for countries that have demonstrated development of research capacity based on agreed milestones.

Regional Financing

Infectious diseases know no borders, and move easily with travelers and trade. With porous boundaries, countries and regions need a borderless response. During the Ebola outbreak research groups in Liberia, Sierra Leone and Guinea began to organize into a research network to collaborate on Ebola research. If such a network were in place in early 2014 it is probable that clinical trials of Ebola diagnostics, therapeutics and vaccines would have been successfully completed sooner. Networks leverage the comparative advantages of the member partners, often with one goal that a center of excellence serves as an organizational and administrative anchor as well as a source of training and mentoring. Networks can facilitate sharing of critical infrastructure, such as high-level laboratory support, biobanking, gene sequencing and other resources, thereby distributing some of the fixed costs across the network partners. Critically important to preparedness and response, regional networks with government

collaboration can facilitate the organization and leadership of a coordinated research response in the region in the event of an outbreak. In inter-epidemic periods, regional networks can tackle health challenges common to partners such as malaria, tuberculosis, or meningitis, thus creating and strengthening their independent and collective research capacity. National support for regional collaboration facilitates translation of research results into policy as well.

Many networks have emerged in recent years to support science and research in Africa. These include the Joint West Africa Research Group (JWARG), supported by the US Department of Defense, and the East African Consortium for Clinical Research-2 (EACCR2), supported by EDCTP. EDCTP has recently funded the African coalition for Epidemic Research, Response and Training (ALERRT) and the Pan-African Network for Rapid Research, Response, Relief, and Preparedness for Infectious Diseases Epidemics (PANDORA-ID-NET), anchored by European institutions, to develop outbreak response capability. Building on prior investments from the World Bank (e.g., African Centers of Excellence (ACE)) and the Wellcome Trust (e.g., Developing Excellence in Leadership, Training and Science Initiative (DELTA) and Accelerating Excellence in Science in Africa (AESAI)), the Wellcome Trust, the Bill & Melinda Gates Foundation, NIH, NEPAD, and the African Academy of Sciences (AAS) are organizing CARI (the Coalition for African Research and Innovation) to serve as a hub for African-led research institutions. The West African Clinical Research Consortium (WAC) is a collaboration of researchers across Liberia, Sierra Leone, Guinea and Mali. Box 5.2 illustrates a regional network in Africa that began with a focus on HIV-AIDS and has continued to expand to address other diseases of regional significance.

Networks have their own challenges, however. Financing arrangements among partners can be complicated, as can ensuring that the developed country partner is focused on capacity-building, supporting 'learning by doing' and successively transferring responsibility, including fiscal and administrative arrangements and clinical trial execution, to network partners. Often such networks have overlapping agendas and pose a challenge to national authorities in terms of coordination or ensuring that nationally-relevant research is conducted. Ensuring financial sustainability over time is also challenging. The networks usually have earmarked resources with a medium-term outlook, and are often led by researchers from outside, which poses challenges for capacity-building and research leadership.

BOX 5.2

LEVERAGING AND SUSTAINING CLINICAL RESEARCH CAPACITY IN LMICS: THE IAVI-AFRICA CLINICAL RESEARCH NETWORK

Sustaining clinical research capacity is rooted in partnerships with in-country scientists, community leaders, governments, and policy-makers—stakeholders whose contributions are essential to developing effective and acceptable products, ensuring country ownership and enabling access to new biomedical innovations. In 1998, IAVI (the International AIDS Vaccine Initiative) established a clinical network in Kenya to provide IAVI and its scientific partners access to local populations for clinical trials of promising vaccine candidates. Since then, the network has grown to eight research centers in five countries in Eastern and Southern Africa that can recruit and retain study volunteers in both the general population and at-risk groups. The network includes sites in:

- Kenya: Kenya AIDS Vaccine Initiative-Institute for Clinical Research and the Kenya Medical Research Institute (KEMRI)/Wellcome Trust Centre for Geographic Medicine Research)
- Uganda: Medical Research Council/UVRI Uganda Research Unit on AIDS and the UVRI-IAVI HIV Vaccine Program
- South Africa: HIV Pathogenesis Program at the University of KwaZulu-Natal and the Aurum Institute
- Zambia: Zambia Emory HIV Research Project
- Rwanda: Projet San Francisco (PSF)

More than 100 clinical studies in vaccines, epidemiology, mucosal immunology, opportunistic infections and antiretroviral treatment have provided critical insights into global health challenges. Notably, the IAVI-Africa Clinical Research Network maintains (or exceeds) the clinical standards of networks in high income countries as evidenced by a 97 percent participant retention rate in HIV vaccine clinical trials.

In a long-standing partnership with the US Agency for International Development (USAID) now in its 17th year of financial and strategic support, IAVI has invested heavily in human and technical capacity-building for the network and has trained thousands of African healthcare workers, scientists, technicians, community advisory boards, regulatory agencies and other stakeholders in Good Clinical Practice (GCP), Good Clinical Laboratory Practice (GCLP) or Good Participatory Practice (GPP). Support for investigator-initiated research has nurtured the next generation of African scientists. These scientists have gone on to publish findings in peer reviewed journals, lead clinical trials and epidemiology protocols, generate additional funding for their research and become influential scientific leaders in their communities. Scientists in the network meet routinely to share progress, best practices and lessons learned. In addition, physical infrastructure improvements have included clinical space, immunological laboratories, intake facilities for participant recruitment, testing and counseling centers and administrative offices. These investments have enabled interventional trials for HIV, malaria and Ebola, influenced development of national and regional health policy guidelines, and facilitated plans for domestic financing for health R&D among policy-makers.

Source: Feinberg, Mark (IAVI). Personal communication, email dated April 13, 2018

Buy-down arrangements might help, as could ensuring that network partners communicate and collaborate on an ongoing basis, and work on day-to-day projects in the inter-epidemic period. If the networks are to be used in emergencies, pre-existing written agreements

will help avoid lengthy legal review and facilitate funding flows when they are needed. While this may present a challenge to countries, having research agreements in place is certainly preferable to having a lengthy delay in an outbreak.

BOX 5.3

ACCESSING IDA REGIONAL FUNDS

To be eligible for support under IDA's Regional Program, initiatives must (World Bank 2013):

- i. Involve three or more countries, all of which need to participate for the project's objectives to be achievable and at least one of which is an IDA country. The required minimum number of countries is reduced from three to two if at least one IDA Fragile and Conflict-affected State (FCS) participates in the regional project;
- ii. Have benefits that spill over country boundaries (e.g., generate positive externalities or mitigate negative ones across countries);
- iii. Have clear evidence of country or regional ownership (e.g., by ECOWAS or SADC) which demonstrates commitment of the majority of participating countries; and
- iv. Provide a platform for a high level of policy harmonization between countries and be part of a well-developed and broadly-supported regional strategy.

In addition to the regional project eligibility criteria described above, two additional criteria are applied to prioritize projects, including (World Bank 2013):

- v. Regional projects should avoid funding primarily national-level investments with regional resources. The specific investments proposed within a regional project should have clear externalities, not just the regional concept itself; and
- vi. Given the high demand for IDA regional project financing, IDA funding should be considered only once other options have been ruled out. Leveraging other resources and working with development partners are strongly encouraged.

IDA's Regional Program requires participating countries to contribute a third of the cost of their participation in regional projects from their IDA allocation. The co-financing ratio, however, depends on project design and resource availability. IDA18 introduced the following enhancements to the Regional Program: (i) the credit/grant distribution of Regional IDA financing will match that of concessional Core Financing for all beneficiary countries; (ii) the threshold for triggering the 20 percent cap under the Regional Program will be based on the definition of small states—i.e., countries with a population of 1.5 million or less;¹⁸ and (iii) the establishment of an SDR1.4 billion refugee sub-window under the regional program to finance projects benefitting refugees and their host communities (World Bank 2017b).

Source: World Bank (2013; 2017b)

IDA'S PROGRAM FOR REGIONAL PROJECTS

The Program for Regional Projects ("Regional Program") was initiated by IDA in 2003 in response to the increasing interest to establish regional cooperation and the acknowledgement that many development issues call for neighboring countries to work together. Through this program, countries may access extra financing above their regular IDA allocation for participation in a regional program (World Bank 2013). As part of the most recent replenishment of IDA's resources (IDA18)—which resulted in a record replenishment of US\$75 billion to finance projects over the three-year

period ending June 30, 2020, IDA resources allocated to the Regional Program were significantly increased from SDR2.2 billion¹⁷ in IDA17 to SDR5 billion in IDA18 (World Bank 2017b). Box 5.3 outlines the primary eligibility criteria for IDA's Regional Program.

17 SDRs (Special Drawing Rights) are an international reserve asset created by the International Monetary Fund (IMF) in 1969 to supplement its member countries' official reserves. The value of the SDR is currently based on four major currencies: the US dollar, euro, Japanese yen and British pound.

18 Given that regional integration is particularly important for countries with small allocations to overcome diseconomies of scale, for IDA-eligible small states, their contribution to a regional project is capped at 20 percent of their annual allocation.

BOX 5.4

EAST AFRICA PUBLIC HEALTH LABORATORY NETWORKING PROJECT

The World Bank has a track record of financing regional capacity-building initiatives in health. In 2010, the World Bank made financing available for the East Africa Public Health Laboratory Networking Project (EAPHLNP), with the goal of establishing a network of public health laboratories to enhance the diagnosis and surveillance of tuberculosis (TB) and other communicable diseases in the region. The US\$63.66 million project provides support to 25 satellite laboratories located in border areas of East Africa, specifically in Kenya, Rwanda, Tanzania, Uganda, and Burundi, with large numbers of vulnerable populations and high risk of disease outbreaks. Implementation is carried out by the EAC Partner States in collaboration with the East African Community Secretariat, the East Central and Southern Africa Health Community, the US Centers for Disease Prevention and Control and the World Health Organization.

The project includes three mutually reinforcing components, aimed at boosting the regional diagnostic and surveillance capacity through the development and operationalization of a regional diagnostic network among the project countries; supporting training and capacity-building for laboratory personnel to increase the pool of experts in the sub-region and to improve the effectiveness of public health laboratories; and financing of operational research and knowledge-sharing activities that aim to evaluate the impact of the new TB diagnostic technologies, assess drug-resistance patterns for endemic diseases, and ascertain feasibility of using mobile phone technologies for surveillance reporting; and support regional coordination and program management functions.

The project has already achieved multiple positive outcomes, including, inter alia, the introduction of a unique and cost-effective peer-review mechanism for cross country laboratory's performance assessment, the attainment of substantial gains in laboratory quality improvements and accreditation, the development of a regional framework for cross-border surveillance, the financing of the construction and equipment of state of the art laboratories in cross border areas, and expanding the pool of qualified personnel by providing training to over 7,000 professionals.

Source: World Bank (2015c)

Regional financing can leverage existing networks, such as IAVI or the many networks established by EDCTP, or develop new networks, such as a regional Lassa fever research network in West Africa; Middle East Respiratory Syndrome (MERS) network in MENA; and Nipah network in South Asia. The World Bank also has a track record of financing regional capacity-building initiatives in health. Box 5.4 provides an example of one such initiative.

RECOMMENDATION 8

The World Bank Group should encourage IDA countries to establish or leverage existing regional partnerships for developing clinical research capacity, using the IDA Regional Window funds combined with domestic commitments. The World Bank Group should highlight progress and showcase strategic development outcomes of such regional partnerships in the IDA18 MTR

(December 2018), and develop a robust case for inclusion of prioritized regional clinical research partnerships as a thematic area under IDA19 (January 2020).

Domestic Resource Mobilization

The importance of country ownership of its clinical research infrastructure has been highlighted throughout this work. Domestic Resource Mobilization (DRM)—increasing the flow of taxes and other income into government treasuries—is key to achieving the ambitious Sustainable Development Goals (SDGs) (World Bank 2016). To map their own futures and fund essential services such as healthcare, countries need to generate

additional fiscal space in ways that increase public spending in the desired areas of attention without jeopardizing the government's long-term financial sustainability. For most countries, the optimal source of finance for healthcare, including for strengthening clinical research, is the domestic budget, which is the best way to ensure sustainable financing and to facilitate seamless integration across the multiple initiatives. However, in many low-income countries, the challenge will be inadequate domestic resource mobilization (World Bank 2017).

The World Bank is strategically placed to engage with countries to strengthen their tax systems, improve the equity dimension of their overall fiscal systems, allocate a greater share to health, and promote public goods such as better public health, preparedness, and clinical research (World Bank 2016). Lending and advisory services for DRM are provided by the World Bank across the world. Examples include the application of behavioral insights to improve tax compliance and increase the tax base in Guatemala; fiscal technical assistance in China; tax incentives in Sri Lanka; equity aspects of tax reform in Colombia; and prevention of illegal transfer pricing in Kenya (World Bank 2016).

The Global Financing Facility (GFF) for women, children and adolescents' health and nutrition, launched in 2015, has supported multiple successful efforts to strengthen DRM. GFF support has focused on three mechanisms: (1) providing technical assistance to evaluate fiscal space for health in beneficiary countries (e.g., Cameroon and DRC) and to support more effective dialogue between the ministries of health and ministries of finance; (2) prioritizing health in the budget through country investment cases and health financing strategies, identifying high-impact interventions and efficient service modalities (e.g., Mozambique, Tanzania, Kenya, Guatemala, DRC, Senegal, Liberia); and (3) supporting efforts to increase sector-specific revenues by providing technical assistance to design and/or implement these taxes, particularly sin taxes (e.g., alcohol in Liberia, tobacco in Mozambique, Sierra Leone and Senegal) (World Bank 2018c).

Other efforts of the GFF evaluate the feasibility of earmarking taxes for health (e.g., Uganda, DRC), and provide technical assistance to develop or strengthen an equitable social health insurance scheme (e.g., Sierra Leone, DRC, Burkina Faso). The GFF is also exploring ways to leverage the capacity of the World Bank units that work directly with ministries of finance to strengthen overall domestic resource mobilization

BOX 5.5

MATCHING GRANTS

Matching grants are funds from the granting organization that are matched with funds from the beneficiary. Grant schemes generally stimulate new activities or induce particular processes, so they should give higher priority to investing in know-how rather than equipment (favoring expenditures on technical assistance, capacity-building, services, and studies, rather than on salaries, inputs, equipment's and infrastructure). These grants are more commonly used for demand-driven services and development subprojects (such as community-driven projects) or for enhancing private economic activity. For this reason, they often target select groups and industries and are expected to increase their incomes or profitability, improve their competitiveness, facilitate their access to finance, and strengthen collaboration and the development of partnerships.

When should they be used?

The rationale for providing grants is often associated with the public good nature of the investment; promotion of innovation, learning, or partnerships; or the reversal of market failures. Matching grants for enterprise development often take the form of a one-time subsidy for a concrete additional investment activity. Grants are generally considered justifiable, although not without further scrutiny, for particular innovation-related activities:

- Skills training, technology development, innovation, technical assistance, partnerships, interactive learning processes, and access to information (with an emphasis on know-how over equipment).
- Starting a business or facilitating private investment in local infrastructure or networks.
- Subproject preparation and participation in trade fairs.
- Lumpy capital investments with externalities.
- Investments of a public good nature (for example, investments that are expected to confer environmental and social benefits).
- Collective action for mutual benefit, with spillover effects.

Source: World Bank (2010b)

and public financial management in health to improve budget preparation, monitoring, and execution, and thus strengthen the argument for increasing domestic resources for health (World Bank 2018c).

Both country and regional development partners have played a critical role in research capacity strengthening, often leveraging the domestic resource commitment or through some type of matching mechanism. Regional development banks can also play a role; for example, the African Development Bank (AfDB) has included research funding in each of its recent health system strengthening initiatives as feasible, re-affirming the recommendations of the WHO Consultative Expert Group

on Research and Development.¹⁹ Like other funders, the World Bank has a long history of matching grants at the national level (Box 5.5), having designed matching grant schemes in the agricultural sector in several countries including Nicaragua, Peru, India, Ghana, and Armenia (World Bank 2010b).

The World Bank has the ability to convene development partners seeking to stimulate and assist government ownership in prioritizing health research and clinical research as part of its national agenda, and to facilitate

¹⁹ Kuruneri, Patience (AfDB). Personal communication, email dated April 16, 2018.

BOX 5.6

INNOVATE IN INDIA FOR INCLUSIVENESS

While India is recognized as a leading global manufacturer of high-quality generic drugs, industry gaps and market failures constrain its innovation capabilities, limiting its competitiveness and ability to address its disease burden. The Government of India has recognized, through initiatives such as the Make in India program, the need for strong innovation policies particularly in support of the biopharmaceutical sector that allow the country to successfully transition towards world-class innovation in biopharmaceuticals and medical devices.

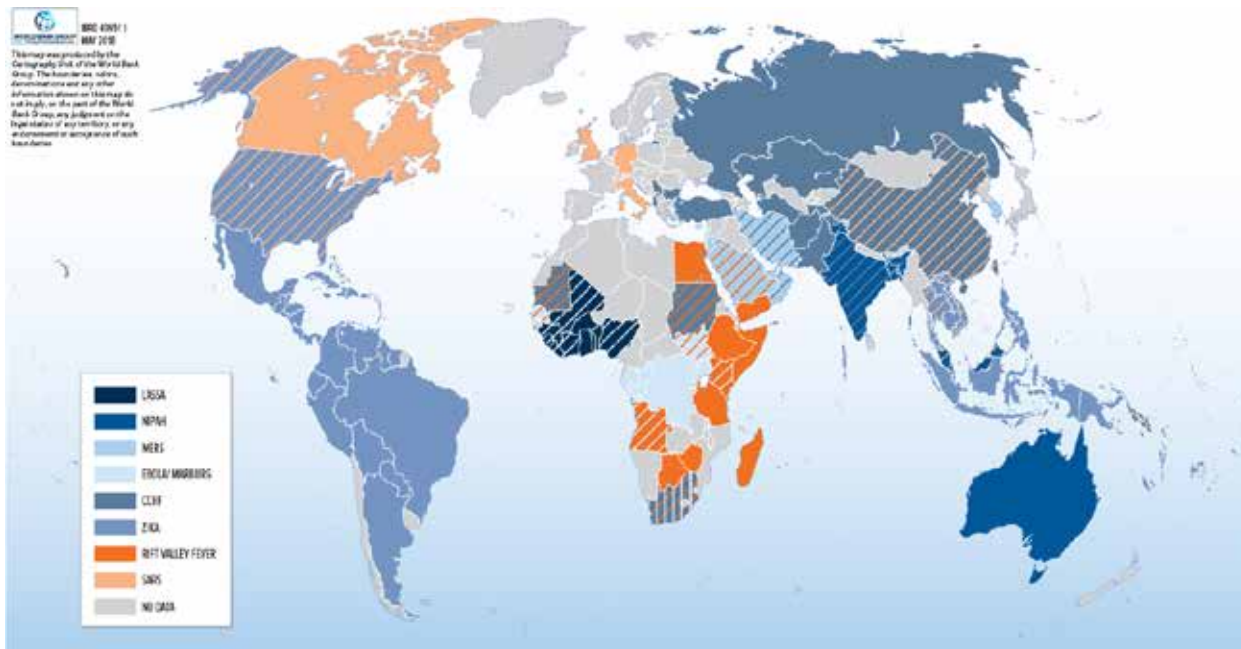
The *Innovate in India for Inclusiveness*, a World Bank financed US\$250 million project supports the Government of India in transforming the biopharmaceutical and medical devices industries in India and unlocking the country's potential for increased innovation. Drawing from global best practices adapted to the strategic and institutional context of India, the project focuses on select sections of the biotechnology value chain where critical gaps impede the development of the industry.

The project is implemented through two main components. The first component targets critical gaps in infrastructure, human capital, and technology transfer with the objective of strengthening the pilot-to-market innovation ecosystem. Grant funding is provided to support the creation of centers of excellence for validation, early stage bio-manufacturing, clinical development, training, and technology transfer. Grant recipients under this component are primarily private and autonomous public entities, selected through open and competitive calls for proposal with transparent selection criteria. Grantees are selected among top institutions from both the public and private sectors that already have a successful track record in the biotechnology space but lack specific capabilities required to enable faster, lower-cost validation, clinical development, and early stage manufacturing.

The second component aims at accelerating the pilot-to-market process for specific products. It provides grant funding to consortia of cutting-edge private, public, and academic institutions to accelerate the development of low-cost, select vaccines, biopharmaceuticals, diagnostics and medical devices that address public health priorities in India. By extending financing to consortia, the project seeks to foster a more collaborative R&D environment and supports the opportunity to link micro, small and medium enterprises in the field with larger companies. This funding covers the cost of critical aspects of the product development process, such as acquisition or licensing of proprietary technologies, equipment and specialized services as well conducting clinical trials and meeting other regulatory requirements.

Source: World Bank (2017c)

FIGURE 4: COUNTRIES WITH MORE THAN 5 REPORTED CASES OF WHO BLUEPRINT PRIORITY DISEASES



Source: WHO Personal Communication²⁰

and recommend matching funds in a way that best provides appropriate country incentives for investment. The “Innovate in India for Inclusiveness” is an example of one such engagement. Box 5.6 has the details.

RECOMMENDATION 9

By end 2018, the World Bank Group should collaborate with development partners and other research funders to incentivize domestic resource mobilization in developing countries for investment in clinical research capacity, including by such means as matching grants and other incentivizing mechanisms.

Coalition for Epidemic Preparedness Innovations (CEPI)

The task of increasing clinical trial capacity in-country does not fall only on development partners. There are other important ongoing and new initiatives by non-profits and private sector entities to contribute to capacity-building. Large research and research-funding institutions with an international presence—such as NIH, Wellcome Trust, the Bill & Melinda Gates Foundation (BMGF), Institut Pasteur, INSERM, Medical Research Council UK, Swiss Development Corporation, and USAID—have a long history of supporting clinical research platforms in LMICs, including those that address country needs.

CEPI, a co-sponsor of this Task Force, was specifically established in 2017 to “finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics...[and] ensure that the vaccines.... are available to populations with the most need” (CEPI 2018). Together with other public and private sector vaccine R&D entities, and drawing upon the WHO

²⁰ Henaó-Restrepo, Ana Maria (WHO). Personal communication, email dated May 4, 2018

R&D Blueprint's list of priority pathogens (see Figure 4 for countries affected by the priority pathogens), CEPI has selected priority emerging epidemic diseases in LMICs in Africa (Lassa fever virus), Asia (Nipah virus) and countries in the Middle East (MERS-CoV virus) as its initial vaccine development priorities, and intends to stimulate and coordinate activities from the discovery stage up to licensed vaccines to be stockpiled, allocated and distributed in the event they are needed.

However, as the previous Ebola and current Lassa experiences have highlighted, there are important gaps in knowledge that must be addressed on the critical path to vaccine development in addition to the essential capacities necessary to conduct clinical trials. These include better defining the epidemiology, reservoir and human host sites of viral persistence, and optimal clinical care and immune responses to infection, all of which require clinical research. Given the importance of 'learning by doing', CEPI and its partners intend to use the vaccine development process to help build clinical research capacity through addressing such critical knowledge gaps. Further, CEPI and partners can leverage other capacity-building efforts, e.g., EDCTP-funded networks, to strengthen research sites that enable researchers to be mentored in the conduct of clinical trials during the inter-epidemic period.

The Nigerian Lassa outbreak, which occurred before CEPI had signed its first vaccine development contract, has highlighted additional opportunities to simultaneously build clinical research capacity and speed vaccine development through supporting local researchers, with mentorship as needed to develop essential critical path knowledge. This may involve epidemiologic investigation, gene sequencing, development of immunologic assays, or other clinical trial protocols. CEPI has already taken steps to support such work as part of the Lassa outbreak response and has plans to work with partners to strengthen clinical trial capacity to conduct Phase 1 and 2 vaccine trials for its candidate vaccines.

RECOMMENDATION 10

By mid-2018, CEPI should commit resources to strengthening clinical research capacities in LMICs where clinical trials for vaccines against CEPI priority pathogens are likely to be conducted.

Private Sector Contributions

The private sector, particularly the biopharma industry, has played an important role in building research capacity in low- and middle-income countries. One of the ways in which the private sector can develop this capacity is through investments in research and development relating to infectious diseases. Drawing upon data on R&D funding flows for neglected diseases collected by the Policy Cures Research G-FINDER, the WHO Global Health Observatory on Health R&D shows that private sector investments in neglected diseases increased by 32 percent between 2012 and 2016, from US\$377.2 million to US\$496.5 million. In 2016, 44 percent of private sector investments in R&D for neglected diseases went into vaccines R&D. In the same year, most private sector investments in R&D for neglected diseases was spent on malaria (US\$137.3 million), tuberculosis (US\$96.6 million) and HIV/AIDS (US\$84.1 million) (WHO 2018b).²¹

In addition to investing directly in R&D, private funding has been instrumental in establishing sustainable independent research capacity. For example, the Infectious Diseases Institute (IDI) in Uganda was developed by the Academic Alliance for AIDS Care and Prevention (now Accordia Global Health Foundation), an initiative of university-based Ugandan and North American physicians, with the financial support from Pfizer Inc. in the form of unrestricted seed funding of US\$10 million over ten years. Support and mentoring from academic researchers at leading North American universities was also critical. Pfizer provided funding for building construction, start-up costs and for systems development that was integral to its evolution to a 'trusted institution'. When Pfizer discontinued funding as planned in 2012, IDI had already established other sources of funding, including from competitive research grants and sponsored trials. This is attributable to multiple factors, including the systems that had been put in place, the collaborations fostered, the deliberate diversification of their research scope to address country needs, and the demonstration that IDI could conduct high quality clinical research.²²

21 For 2016, funding data were collected from 187 private, public and philanthropic organizations, on all types of product-related R&D and basic research and platform technology investments covering 33 neglected diseases. Data are reported in US\$ 2016

22 Brough, Richard (IDI). Personal communication, email dated April 13, 2018

Pharma and biotech companies have initiated and sustained several significant capacity-building programs, returning benefits to countries, to researchers and research institutions and to science.

- GlaxoSmithKline, through the GSK Africa NCD Open Lab, is investing up to UK£25million in developing research capacity in 8 sub-Saharan African countries through funding investigator-initiated studies in non-communicable diseases (NCDs). In addition to these funds, GSK is leveraging its wider R&D expertise to provide scientific collaboration to strengthen projects and build capacity through skills and knowledge transfer.²³ In partnership with EDCTP, GSK NCD Open Lab supports capacity development of potential African research leaders using the train-the-trainer model (EDCTP 2018).
- Hilleman Laboratories, a joint-venture partnership between Merck and Wellcome Trust, based in New Delhi, India, supports the development of high impact, affordable vaccines for people in developing countries in a sustainable manner. It has built translational research capacity in India to address important issues around vaccine delivery, including thermostability, ease of use, and low-cost goods through core expertise and innovative partnership models with biotech companies, academia, and pharmaceutical manufacturers.
- Pharmaceutical companies such as Astellas, Bayer, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, and Sanofi have partnered with the BMGF, EDCTP, and WHO to develop strong research capability in LMICs. This partnership seeks to train researchers from LMICs involved in clinical research projects to acquire experience and develop skills for conducting clinical trials outside of an academic or public-sector setting. Between 2008 and 2014, the WHO-TDR program has trained 32 fellows, and this number is set to increase in coming years. These fellows have come from 19 African countries (Benin, Burkina Faso, Botswana, Cameroon, the Democratic Republic of the Congo, Ethiopia, Gabon, Ghana, Guinea, Kenya, The Gambia, Madagascar, Mali, Nigeria, Senegal, Swaziland, Tanzania, Uganda and Zimbabwe) and from China, Colombia, Peru and Vietnam. The host organizations trained fellows to develop specialist product development skills not readily taught in academic centers or public research institutions. On

returning home, the fellows are expected to become valuable resources for institutional capacity development to undertake and manage clinical research in accordance with international regulatory requirements and standards (IFPMA 2018).

Good clinical research capacity in LMICs may also attract more research funding and clinical trial activity from these companies. If done with appropriate balance and ongoing attention to country health needs, clinical research capacity can provide opportunities to sustain existing research platforms and increase the likelihood that they will be available when needed, for clinical trials of products such as vaccines, therapeutics, and diagnostics for epidemic infectious diseases. For this goal to be realized, it is critical that countries have a functional enabling infrastructure, legal system and regulatory and ethics review system. Indeed, companies continue to cite factors such as lengthy processing times for ethics committees, legal and regulatory agency review, and delays in getting material and equipment through a country customs process, as reasons why they do not move more clinical trial business to LMICs.

Country and investigator ownership of the research agenda, which this Task Force has identified as central to building and sustaining clinical research capacity, may encourage product development and subsequent trials germane to country health needs. While the GSK Open Lab is still relatively new, it provides a strong example of private sector funded research that is aligned with countries' national health needs. Box 5.7 has the details.

In addition to the capacity-strengthening associated with bringing clinical trial business to LMICs and more direct capacity-building partnerships, there may be opportunities for private sector companies, working alone or together, to facilitate clinical research capacity development modeled on existing work. One model which carries significant potential for working to enhance synergies between private and public actors in LMICs is TransCelerate, which is a member-based initiative of the biopharma industry collaborating around shared learnings and best practices related to processes critical to product development and clinical trials. TransCelerate's membership includes employees embedded in 19 large pharma and biotech companies where they work globally to adapt and implement integrated solutions for the conduct of clinical trials (TransCelerate 2017). Member companies can pool data from consenting investigators into a centralized, cloud-based resource to enable faster and more efficient identification, and prevent duplication

23 Strange, Mike and Ako, Agbor (GSK). Personal communication, email dated April 17, 2018

BOX 5.7

GSK OPEN LABS

Building on its Open Lab model in Tres Cantos, Spain, GlaxoSmithKline started the Africa NCD Open Lab in 2014. The impetus for this initiative was the recognition of the need for in-country scientists to address the burgeoning challenge of non-communicable disease on the African continent. Its aim is to stimulate scientific research to address NCDs in Africa, to identify ‘what is unique about NCDs in Africa,’ and to build a cadre of African scientists enabled to advocate for increased attention to these problems. This includes collecting data to better understand the scope and magnitude of the problems, and to elucidate the unique attributes of NCDs in the region such as disease etiology, clinical manifestations, complications and determinants of response to treatment, GSK began this initiative with a planned initial investment of UK£25 million, and established a small team of GSK scientists based in the UK to collaborate with African researchers, providing them access to experts across GSK R&D.

Through a landscape analysis, GSK identified where science infrastructure was already in place, ‘building on the infectious disease heritage.’ They convened a scientific advisory board composed of leading African researchers to identify critical problems, and have subsequently funded and are collaborating on 11 projects with African researchers/institutions led from 4 main countries: Uganda, Nigeria, Malawi and South Africa. However, many of these projects involve collaboration between institutions from multiple African countries and these include Cameroon, Kenya and Mozambique. Projects focus on asthma, diabetes, hypertension, chronic renal disease, cardiovascular disease and cancers as well as the relationship between locally-prevalent infectious diseases and NCDs.

Subsequently, a critical gap was identified where early career researchers lacked mentoring, support and funds to undertake research that would enable them to transition into more established researchers whilst generating valuable preliminary data to compete for major funding. Through an open call for proposals, GSK has further identified 10 early career researchers from Tanzania, Nigeria, Kenya, Ethiopia, Uganda, and Malawi with projects covering the NCDs of focus. After completing due diligence, these researchers will be provided full funding and scientific support to undertake and successfully deliver their projects.

Through an extensive multi-stakeholder engagement process, including an external scientific advisory board, GSK ensures that funded projects are aligned with the national health plan and priorities in the country in which the principal investigator is located, and that the bulk of the funding stays in the country to build expertise, rather than being used to sub-contract out research components (e.g., outsourcing advanced technologies such as gene sequencing) to developed countries. GSK views this and other investments in human research capacity are in the ‘pre-competitive space’ and anticipates that engagement with other stakeholders will provide a coordinated structure and additional support for ongoing NCD clinical research that can be sustained and translated into improved outcomes for the African patient.

Source: Strange, Mike and Ako, Agbor (GSK). Personal communication, email dated April 17, 2018

of site-qualification activities. For LMICs, the model could reduce administrative and record-keeping burden on research sites, and provide important opportunities for cross-site learning and rapid initiation of clinical trials during public health emergencies.

In addition to private research institutions and pharma companies, both for-profit and not-for-profit clinical research organizations (CROs) continuously conduct

and/or support clinical trials in some LMICs. For example, ClinWin, a medium sized contract research organization based in Kenya “provides clinical development services for poverty-related diseases. It has partnered with industry, not-for-profits and academic sponsors to provide a suite of trial and site management, and sponsor oversight services to local clinical research programs. These services include: training, trial monitoring, quality assurance, ethical and regulatory expertise;

contract negotiation and trial coordination among others. Leveraging its indigenous knowledge of the clinical trial landscape in the region, it has developed a database of potential and current local investigators capable of conducting registration trials. The lessons learnt in each project are documented and shared with investigator staff at new sites” (Onyango 2016). In general, CROs can play a key role in strengthening capacity-building and provide opportunities to local research staff by hiring and training them, offering fellowships, and by partnering with them to provide operational and logistical support to investigators and sites lacking those capabilities.

RECOMMENDATION 11

By end 2019, the private sector pharmaceutical/ biotech industry/clinical research organizations/ other health sector businesses operating in LMICs should announce their commitment to maximize their contribution to clinical research capacity in LMICs. This includes transfer of skills and expertise and/or allocating a percentage of their spending to support the development of clinical research capacity in LMICs that is aligned with country public health needs and research agenda.

CHAPTER 6

Coordinating Investments in Clinical Research

Mechanisms to Coordinate Investments

The magnitude of resources and the volume of initiatives, networks and funders involved in research capacity-building, especially in Africa, is dizzying, and pose their own unique opportunities and challenges. Key benefits of having many initiatives is that they generate large amounts of funding for clinical research and help develop core research capacities. A major challenge is that the scope and distribution of funding is often not well coordinated. Key informant interviews conducted by the Task Force show that large funders are often unaware of one another's efforts and plans, and therefore miss opportunities to realize potential synergies. The interviews also show that recipients often receive funding from multiple funders for related efforts.

Two existing mechanisms housed at WHO offer the potential to better coordinate donor and funder capacity-building activities. The first is the ESSENCE program housed within TDR, which brings together funders for information-sharing and to increase coordination related to investments. One of its stated goals is to promote harmonization and optimization of resources (ESSENCE 2017). Organizationally, it is well placed, not only to share best practices, but to address the types of administrative issues and needs for harmonization raised by the research community.

The second mechanism is the Global Coordination Mechanism of the R&D Blueprint, which was established in 2017 to improve coordination and to foster an enabling environment for research and development

to prevent and respond to epidemics. Its intent is to bring together major stakeholders of research on the Blueprint priority pathogens in order to better plan research initiatives during an outbreak and avoid many of the problems that affected the ability to launch clinical trials during the 2014-2015 West Africa Ebola outbreak. One helpful activity undertaken under the aegis of the Blueprint is a mapping of funders and research groups involved with the priority pathogens. This not only has the potential to set the stage for greater collaboration, but also for enhancing speed during response. The research response coordination mechanism of the GCM was used during the 2018 Nigeria Lassa outbreak. The GCM Secretariat at WHO worked with the Government of Nigeria to identify priorities for research, and communicated them to the community of research funders.

These two mechanisms are well-suited to facilitate enhanced coordination of capacity-strengthening activities during inter-epidemic periods and more rapid planning and implementation of research during an outbreak. Bringing together the partners that focus on capacity-building more broadly through ESSENCE, with the R&D-focused coordinating function of the GCM, offers promise for acting with urgency when new events are detected and identified. Together with ESSENCE, it could serve as a powerful forum for information-sharing and coordination, including about research and capacity-building for addressing outbreak pathogens.

Two interesting models supporting better coordination are the Strategic Coherence of ODA-funded Research (SCOR) Board, launched by the UK "to better coordinate government operations, eliminate duplication, and prevent waste" (Devex 2017); and the Research Investments in Global Health (ResIn) study, housed

at the University of Southampton. Since 2015 ResIn researchers report that their database currently includes over 1,000 funders and approximately 80,000 discrete projects. Staggeringly, the bulk of this research funding, roughly 85 percent, is generated by approximately 10 funders, with the US NIH providing roughly half of the resources.²⁴

RECOMMENDATION 12

By end 2019, ESSENCE, in collaboration with the Global Coordination Mechanism and reinforced with additional LMIC representation, should articulate a mechanism that permits a thorough review of current and planned investments in research capacity strengthening. This should be done in consultation with major external funders of clinical research (including those involved in capacity strengthening of network, laboratory, ethics, and regulatory capability). This collaborative mechanism should ensure synergy at country and regional levels, and streamline the administrative burden experienced by institutions dealing with multiple research funders.

Trust Fund Mechanisms

A Trust Fund is a financing arrangement established with contributions from one or more external development partner(s), including multinational agencies, non-governmental organizations, foundations, and other private organizations, and in some cases, from the World Bank, to support development-related activities. The World Bank uses Trust Funds as a complement to IDA and IBRD financing to mobilize and direct concessional resources to its strategic development priorities, and as a vehicle for supporting partnerships with other development actors. Trust Funds may be country-specific, regional, or global in their geographical scope, and can finance recipient activities (i.e., of governmental, non-governmental or other external entities), World Bank activities, partnership activities, or a combination of these. Trust Funds play a pivotal role in strengthening institutional and knowledge capabilities in previously under-addressed areas like gender, climate change, and fragility, etc., and help expand the scope and scale of annual flagship funding programs (World Bank 2017d).

²⁴ Head, Michael (ResIn, University of Southampton). Personal communication; email dated April 11, 2018.

As a distinctive aid vehicle, they add value by providing coordinated financing and grant resources for individual countries, targeting development issues and providing global public goods (World Bank 2011). Two Trust Fund mechanisms at the World Bank that are aligned with the goals of strengthening clinical research capacity in low income countries are the PEF and the CEPI. These are discussed below.

PEF TRUST FUND

The Pandemic Emergency Financing Facility (PEF) provides rapid surge financing in the initial stages of a severe outbreak before it becomes a pandemic. The funds are paid out through two windows: insurance and cash. For the next three years, the insurance window will make available up to US\$425 million for outbreaks of a group of diseases likely to cause major epidemics. And it will pay out quickly, within days of the outbreak reaching a defined level of severity, to the eligible-countries and/or designated responding agency. Insurance premiums have already been paid for the next three years by donor contributions, including by Japan and Germany.

The PEF also has a US\$61 million cash window it can use to make resources available for outbreaks that have not or will not meet the criteria of the insurance window. This window will be operational and available to countries in 2018, and can be used to finance the cost of response efforts during an outbreak, in line with what is described in the country response plan (World Bank 2017e). With some forethought, the opportunity exists to consider how response-related research could be 'surged' with the triple aim of managing an outbreak, strengthening research capacity, and ensuring that the knowledge base for responding to subsequent outbreaks of the same pathogen is better.

CEPI TRUST FUND

In hosting CEPI funds for development of vaccines and ensuring that vaccine candidates are advanced past the Phase 2 stage of clinical development, the World Bank is ideally positioned to coordinate its own initiatives with CEPI's to strengthen country-level preparedness. The World Bank's emergency response and lending instruments strategically complement vaccine development and deployment objectives, and provide opportunities for robust, sustainable, and effective action at all levels of development, deployment, and response.

The opportunity of accelerating vaccine development against pathogens with pandemic potential is a critical part of pandemic risk management, and actually conducting a pivotal, regulatory trial in an outbreak is part of that, as it enables a safe and effective vaccine to be deployed as soon as is feasible. CEPI's support for preparatory actions needed to test the vaccines it is developing, such as collaborating with others to help improve regulatory capacity in low-income countries and prepare countries and sites to conduct clinical trials could complement support provided through IDA as well as the PEF. Ultimately, the intent is that vaccines developed through CEPI support could help to ensure that low-income countries rapidly and effectively have access to life-saving vaccines.

RECOMMENDATION 13

By the end of 2018, the World Bank Group, working through the PEF and CEPI Trust Fund mechanisms, should establish a rapid financing vehicle to support the priority outbreak-related research agenda emerging from the WHO R&D Blueprint, and to strengthen in-country capacity, including the conduct of clinical research as part of outbreak response.

National-Level Resource Tracking

It is important that governments and development partners monitor and track all funding that supports clinical research capacity-building activities within the country. This essential element of housekeeping is important, not only for planning purposes, but also for regular, systematic monitoring and evaluation. It further assists in accounting for the multiplicity of funders involved and in oversight of their performance of research and its outcomes.

The case of Rwanda, elaborated in Box 6.1, shows that it is not easy for governments to have ready access to information and be fully aware of the range of research or capacity-building funds that flow into their country. This makes it challenging for countries to own the research and focus on country-specific priorities.

Although the case of Rwanda is related to overall health spending flows, it depicts the characteristic issues and

opportunities for other countries to utilize a resource tracking tool. In addition to a custom tool—as chosen by Rwanda—there are several tools and instruments that countries and development partners use to track expenditures and any of them can be readily adapted to track flow of funds that support clinical research. Two tools that deserve mention are National Health Accounts (NHA) and the Public Expenditure Tracking system (PETS).

National Health Accounts provides a systematic framework for mapping expenditure levels in a country's health system both for decision-making and accountability. It identifies all goods and services that relate to health care and organizes the flow of funds to finance these goods and services in a sources-to-uses framework. Organized in ways compatible with the national income and product accounts, the NHA method orders health expenditures and use of funds in a format that provides an analytical base for accountability and policy development, and is flexible enough to adapt to the evolving features of health systems. WHO has provided expertise and technical advice to a very large number of countries that have developed and institutionalized NHAs over time.

Public Expenditure Tracking Surveys (PETS) is a set of tools developed in 1996 to uncover points of leakage in the expenditure chain for particular programs or line items. While PETS has become an umbrella term for wider budget tracking, traditional PETS involves the triangulation of budget and financial records from different sources on the expenditure map. Implementing a PETS search tracks the flow of resources through the various layers of government bureaucracy, down to the service facilities to determine how much of the originally allocated resources reach each level, and how long they take to get there. It can help identify the location and extent of impediments to resource flows (financial, staff, equipment), and therefore evaluate the mechanisms and incentives responsible for leakages, capture and deployment impediments. PETS became a popular tool for the World Bank and other international and multilateral organizations, due in part to its potential to identify hard-to-uncover problems with spending. It is axiomatic that funding allocated but not delivered cannot accomplish what it has been provided to do.

Finally, The University of Southampton and the EDGE program are working with partner countries including the Philippines, Sri Lanka, Indonesia, Ethiopia and Jamaica, and with the Asian eHealth Information

BOX 6.1

RWANDA'S EXPERIENCE WITH HEALTH RESOURCE TRACKING

It is vital for effective policy-making that decision-makers have access to essential information on health expenditure in a timely manner. Such information includes the share of health expenditure within an economy, the financial burden of health spending on households, the magnitude of external financing in health expenditure, and the share of spending on primary care. From these patterns of spending the policy-makers and funders are able to determine coverage and equity and the breadth and scope of services covered. They are normally two ways of determining such metrics either through routine and continuous resource tracking or through ad hoc periodic surveys, the most prevalent method in LMICs. By 2009, the Rwanda Health Sector was conducting seven separate periodic data collection surveys. These activities were placing an enormous burden on health care providers. Additionally, results from such surveys are retrospective and too late for planning cycles. They can also be full of errors in terms of misclassification, recall bias and completeness.

The Ministry of Health teamed up with the Clinton Health Access Initiative to institutionalize data collection through the Resource Tracking Tool (RT) that harmonizes and standardizes data collection, making it routine, timely, complete and comprehensive. Because the RT was being populated annually and alongside implementation, data became available and in sync with the annual planning cycle.

The RT produced many benefits: including reducing costs, making information available on a timely basis, identifying significant gaps in per capita spending between regions and discovering misalignment of resources with national priorities. The RT also allowed the government to develop three critical policies: Human Resources for Health Plan; District Health Strengthening System; and Division of Labor.

Source: Sezibera, Richard. Personal communication, email dated April 3, 2018

Network (AeHIN), Canadian and Belgian Health to develop a resource tracking tool, with the goal of being able to monitor and capture all external funding, including private sector sponsored research or training. However, a widely available tool suitable for use in a variety of LMICs would go a long way towards improving coordination and strengthening oversight and targeting of national health research priorities.

RECOMMENDATION 14

By June 2019, based on experience accumulated by countries, WHO and the World Bank Group should develop a resource tracking tool enabling governments to monitor and track, at a national level, all funding that supports clinical research capacity-building activities within the country and accounts for the multiplicity of funders involved.

CHAPTER 7

Monitoring Progress



Development and strengthening of clinical research capacity will depend on a coordinated series of actions targeting the entire spectrum of the clinical research ecosystem. The recommendations in this report address a diverse set of requirements for a successful outcome, including country ownership and strategic alignment of the research infrastructure and country health goals; a climate and culture in which clinical research can thrive; shared investment in the clinical research system between countries themselves and development partners, research funders and the private sector; a value of public-private partnerships; and coordination between funders, and between research institutions themselves.

Governance and coordination of the complex space of pandemic preparedness, including research, is challenging. Therefore, the Task Force believes that a broad-based, scientifically qualified, and autonomous body is necessary to monitor and evaluate the implementation of the recommendations contained in this report. The Global Preparedness Monitoring Board (GPMB), announced at the 2018 IMF-World Bank Spring Meetings, is emerging as the platform of choice for coordinating and reviewing progress on the implementation of various aspects of preparedness, including of the recommendations of this Task Force.

The GPMB is a new initiative co-convened by WHO and the World Bank Group in follow-up to the UN Secretary General's Global Health Crises Task Force (2017), which recommended in its final report the development and

implementation of an “independent mechanism for reporting on the status of the world’s preparedness through (i) monitoring system-wide progress towards increased health crises preparedness and response; (ii) helping to ensure political visibility and accountability for efforts at country, regional and global levels; and (iii) providing an alert to the Secretary-General and other key stakeholders if the system is not functioning adequately.” Located at WHO Headquarters in Geneva, GPMB is an independent, comprehensive, and inclusive global mechanism that will monitor systems-wide progress towards increased preparedness and response capacity for health crises, including outbreaks and emergencies with health consequences. Comprised of political leaders, agency principals and world-class experts (in the process of being identified), the GPMB will play a critical role in ensuring system-wide accountability for preparedness efforts at community, country, regional and global levels. It will provide an annual overview of the state of the world’s preparedness, and report on the adequacy of financing, monitor the progress of relevant research and development, make specific recommendations, and engage in communications and advocacy, as required.

RECOMMENDATION 15

Reviewing progress on the implementation of these recommendations should inform the agenda of the Global Preparedness Monitoring Board.

CHAPTER 8

Conclusion

Infectious disease outbreaks are on the rise around the world. Severe Acute Respiratory Syndrome (SARS), MERS, avian influenza, Ebola, Zika, Lassa—these diseases hitherto restricted to the vocabulary of epidemiologists and medical professionals have now almost become household names. The number of new infectious diseases affecting humans has increased fourfold in the past 60 years, and the number of outbreaks per year has more than tripled. Most are just a blip in the news; but once in a while one or two slip through our containment defenses, and cause enormous harm. It is indeed only a matter of time before the next pandemic hits us.

The world is better prepared than before, of that there is no doubt. But knowing that it is not fully and adequately prepared, we asked what must be done to ensure that the next inevitable outbreak does not turn into an uncontrollable pandemic. We focused our attention on one gap—that of getting clinical research capacity in low- and middle-income countries to a level at which they can conduct or support needed clinical trials at the time of an epidemic. We realized right away that this is by no means an easy task, for it requires resource-challenged

countries to have in place a strong, robust and functioning clinical research capacity that could be rapidly called upon in the heat of an outbreak. We are encouraged by the large number of ongoing initiatives that are contributing directly and indirectly to strengthening clinical research capacity in low-income countries. At the same time, we are sobered by the many challenges that governments and development partners must overcome to be ready the next time the world gets hit.

Our report outlines how low- and middle-income countries could secure the political commitment, raise necessary finances and leverage ongoing initiatives of development partners to enhance research and development capacity and strengthen outbreak preparedness. Our 15 recommendations define an integrated framework for action by countries, development partners, research funders, research organizations and the private sector, and suggests clear timelines. We are confident that if countries and all stakeholders adopt the suggested framework, the world will see huge improvements in its ability, at the national level and globally, to build clinical research capacity and strengthen universal health security.



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