

Advancing epidemics R&D to keep up with a changing world: progress, challenges and opportunities

Background

At the request of the Global Preparedness Monitoring Board (GPMB), the Wellcome Trust has developed this report as a contribution to the development of the Board's first annual report.

This paper examines the status, progress and challenges in research and development (R&D) for epidemics and cuts across the dimensions R&D governance and coordination, gaps and priorities in specific areas and how R&D is carried out. The report is intended for a wide audience including policy-makers, government officials, research organisations and the public. Findings of this paper were derived from a review of previous high-level panels and commissions¹, existing literature and expert stakeholder interviews.

The Global Preparedness Monitoring Board is an independent monitoring and advocacy body to ensure preparedness for global health emergencies. Comprised of political leaders, agency principals and world class experts, the Board provides an independent and comprehensive appraisal for policy makers and the world about progress towards increased preparedness and response capacity for disease outbreaks and other emergencies with health consequences.

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¹ Including but not limited to (i) Global Health Crisis Task Force; (ii) Commission on a Global Health Risk Framework for the Future; (iii) UN High-Level Panel on the Global Response to Health Crises; (iv) Harvard-LSHTM Independent Panel on the Global Response to Ebola; (v) National Academy of Medicine Report: The Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Crises (vi) International Working Group for Financing Pandemic Preparedness (vii) Money & Microbes: Strengthening Clinical Research Capacity to Prevent Epidemics.

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Executive Summary

Outbreaks of human infectious diseases have devastating consequences for lives and livelihoods around the world. A range of research and development (R&D)² activities are critical to understand, prevent and stop these infectious disease outbreaks. However, the window to study these diseases and develop approaches to tackle their spread can be short and infrequent, often happening in places that lack the infrastructure for R&D. Research during an emergency response is often the only opportunity for determining the safety and efficacy of interventions such as a diagnostic, therapeutic or vaccine. This relies on the work done in preparation, such as preclinical studies for a therapeutic, or the underlying anthropological or epidemiological knowledge for an intervention.

This paper examines the status, progress and challenges in R&D for epidemics, to inform the Global Preparedness Monitoring's Board (GPMB) first annual report and to ensure that R&D is better harnessed to address epidemics. Findings for this paper were derived from a review of previous high-level panels and commissions³, research and expert stakeholder interviews, that were used to focus on the key challenges. We have identified a number of topics that merit a more in-depth analysis than this paper allowed, including: preventing the rise of diseases; country capacity building for epidemics R&D; and market incentives and financing models. Annex I of the paper provides a list of the experts consulted and Annex II highlights the issues considered out of scope of this paper.

Key Findings, Gaps, Challenges

Progress

There has been some progress in a number of areas related to R&D for epidemics in recent years. First, there have been modest increases in public funding for neglected diseases R&D, reaching a 10 year high in 2017 and increased investment, if uneven, in R&D for epidemic risk diseases, such as CEPI for vaccine development. We have also seen a growth in international and regional programmes to support R&D for epidemics.

Research is also now widely accepted as an essential element of the response to epidemics and preparedness. There have been developments in the integration of research into response activities, demonstrated by the Ebola vaccine trials in Guinea, Sierra Leone and Liberia and the way the Ebola Response Anthropology Platform enabled social scientists and outbreak control teams to work together during the 2014-2016 West Africa Ebola epidemic.

² We define R&D as including fundamental scientific research, social sciences, ethics, epidemiology, product development, designing interventions, clinical research and adapting products and interventions before use in the field.

³ Including but not limited to (i) Global Health Crisis Task Force; (ii) Commission on a Global Health Risk Framework for the Future; (iii) UN High-Level Panel on the Global Response to Health Crises; (iv) Harvard-LSHTM Independent Panel on the Global Response to Ebola; (v) National Academy of Medicine Report: The Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Crises (vi) International Working Group for Financing Pandemic Preparedness (vii) Money & Microbes: Strengthening Clinical Research Capacity to Prevent Epidemics.

The World Health Organization (WHO) has been instrumental in this shift in how research is perceived in the context of response. A cornerstone was establishing the R&D Blueprint to prioritise, accelerate and coordinate product-related R&D for epidemic risk diseases with no existing treatments.

In the current Ebola outbreak in the Democratic Republic of Congo (DRC), the first multi-drug, multi-site, multi-country Ebola randomised controlled therapeutics trial is taking place, showing how new and innovative approaches are being used to collect the necessary data and evidence across outbreaks, countries and time, even in the midst of conflict. Innovative real time approaches to support and inform community engagement are also being used in the DRC using weekly social analytics and community dialogue.

Our changing world also offers new opportunities to accelerate progress for a world better prepared for epidemics. More connected societies can share information easily, and cheaper, and faster computational power allows us to analyse vast amounts of data more quickly. Developments in technologies such as genetic sequencing to be faster, more portable and easier to use mean that we can gain new insights into diseases in real time during epidemics. These examples demonstrate why now is the time to make progress on the key gaps in R&D, so we can stop infectious diseases in their tracks.

Gaps and challenges for future preparedness

Since research is increasingly being done in epidemic settings, there are new challenges for R&D in terms of speed, coordination and governance. Collaboration between a wide variety of actors becomes even more important. Some, such as research and humanitarian organisations, would not typically work closely together and have very different missions, so aligning them in support of a common goal is not always easy. Lack of consensus on the goals of research during epidemics has led to effort in different directions. Differing remits and the number of initiatives recently established to support, coordinate or carry out R&D related to health emergencies add complexity and can impede swift, decisive action.

The majority of R&D funding remains in high-income countries whose research agendas have not always connected to the needs in countries where outbreaks typically occur. This mismatch threatens research response capabilities and the long-term sustainability of R&D capacity building for epidemics which does not sufficiently build on national health R&D priorities. There is also a lack of systematic thinking that links R&D with other critical areas such as access and investment in research infrastructure in low- and middle-income countries (LMICs) and community engagement. To be sustainable and address the need for real-time research response, there needs to be better international effort to build research capacities at the country level, to ensure that research is driven by regional and national priorities and consider how these investments can be epidemic sensitive rather than epidemic specific.

While there has been progress in addressing key gaps in R&D, we have identified social science, diagnostics and therapeutics and Disease X as key priorities. Many social scientists lack the exposure to outbreak response training and biomedical concepts, while, those working in public health and humanitarian fields may have limited understanding of social science. This creates a significant gap in the ability to use and operationalise social science insights. Despite the notable progress in vaccines development for epidemics risk diseases,

therapeutics and, in particular, diagnostics are lagging behind. Diagnostics that do exist for the R&D Blueprint priority diseases are often not effective or usable in outbreak settings. The therapeutics pipeline is also heavily frontloaded at the preclinical stages, and in an ideal world have been through a phase I trial at a minimum. While there has been progress in accelerating disease specific R&D, the next epidemic could be caused by a pathogen not yet known to infect humans, a Disease X. There have been on average, two new human viral pathogens identified per year since 1901.

The way that R&D for epidemics is done and the regulatory environment that underpins this also poses challenges. While there have been efforts to fast track product assessment in epidemics and create pathways to licensure, there is still a lack of clarity about which approach is best suited for which circumstances. This lack of clarity is a particular challenge to investigators and small biotechnology or pharmaceutical companies with less capacity to navigate the regulatory options. As infectious diseases will continue to happen in new and different places, existing ways of doing R&D may not be effective or appropriate. The way clinical trials are designed and carried out has not changed much in the last 50 years and can be better adapted to accelerate progress for research on epidemic risk disease. For example, designing for more flexibility to adapt the trial design in ways that respond to the interim findings, or using a trial design that makes it feasible to carry out in a setting with diseases are endemic. While innovative trial designs such as the ring vaccination trial for Ebola vaccine in Guinea are being used to allow products to be tested in outbreak settings or where diseases are endemic, further work is needed to understand the ethical, social, scientific and regulatory aspects and how to best support the use of these approaches.

Suggestions/Recommendations. Based on our assessment of the challenges for R&D identified in this paper, we propose the following potential solutions for the GPMB and others to consider:

1. **Rationalise the system for coordinating R&D activities** to create more focused global leadership with respect to epidemics R&D, reduce fragmentation, recognise overlaps and accelerating innovation. As part of this, WHO's role needs to be further strengthened and resourced to provide leadership across preparedness and response.
2. **Develop norms**, ethics, and standards of behaviour for all actors including national governments, humanitarian organisations, international organisations, militaries, researchers, and communities.
3. **Develop multi-year plans** for R&D that move **beyond disease specific** approaches, to avoid cycles of panic and neglect.
 - a. These plans should reflect a sustained commitment to R&D **beyond immediate emergencies** and complement national research agendas and centres of research excellence, National Action Plans for Health Security and regional activities.
 - b. Efforts to strengthen in-country R&D capacity should be **more epidemic sensitive than epidemic specific**, addressing day-to-day issues and not focused on building capabilities that are only relevant in the event of an epidemic.
 - c. As long-term plans are developed, international and national research funders should **align their spending** on R&D for epidemics to these, such as R&D Blueprint roadmaps,

country-led research agendas for epidemic risk diseases and National Action Plans for Health Security (NAPHS).

4. Plans for R&D should address the following gaps:
 - a. **Systematic integration of social science into response programme** activities, and further training and collaboration opportunities for social scientists to work with response actors across the entire preparedness/response continuum. WHO and implementing agencies, such as UNICEF, need to build on existing efforts and further integrate social sciences into their programmes so that evidence shapes practice.
 - b. Accelerate development of **rapid diagnostics and therapeutics**. Building the foundations for this R&D should include biological reference materials and clinical care standards as well as basic biological understanding of diseases and the factors that affect emergence and transmission, as well as clinical research.
 - c. Expand **R&D for “Disease X”**, including investment in platform technologies for R&D on epidemic risk diseases and harnessing the potential of technological developments such as real-time genetic sequencing and geospatial mapping.
5. Improve the ability to do R&D on epidemic risk diseases
 - a. National regulatory authorities should develop and improve **pathways for emergency use** of products that are fit for purpose.
 - b. Work to expand the use of **adaptive clinical trial models** and other innovative approaches to R&D, that generate the most actionable findings and are appropriate for studying epidemic risk diseases, especially in the places where those diseases happen.
 - c. Significant **strengthening of country capacities**, especially those with few resources, including **ethics, regulatory capacity, and technical and clinical skills**, to ensure that innovative R&D approaches such as adaptive trials and human infection studies are ethical, rigorous and can take place when and where they are needed.
 - d. **Implementation research** should be integrated in the design and review of response activities, to ensure continual learning of what works, to inform future preparedness and response activities.

Introduction

Research and development (R&D) is essential for a prepared world. While there has been progress in responding to epidemics, recent analyses and panels have highlighted critical gaps that remain. The nature of R&D on epidemic risk infectious diseases is that there are few opportunities to study them as outbreaks are often short, sporadic and unpredictable. The majority of funding is concentrated in a small number of funders, typically from high income countries, with R&D not directed to those places that have the greatest need. There are challenges in incentivising R&D, due to the costs, high risk of failure and small markets. Epidemics can be seen as an issue that affects a subset of developing countries, which further constrains investment in R&D and helps to promote cycles of panic and neglect in line with major epidemics.

Outbreaks of epidemic risk diseases often happen in challenging circumstances, such as countries with limited infrastructure for R&D and fragile health systems, and increasingly, further complexity caused by conflict and political instability. R&D and response are part of a continuum. Though this has improved since the 2014-2016 West Africa Ebola epidemic, we must avoid treating epidemics as discrete events, as we will fail to harness the knowledge, experience and resources which exist. As infectious diseases continue to evolve and the environment and social contexts in which they occur in change, we are likely to see more complex, multidimensional epidemics in the future and currently, we are not structured to prepare for and respond to these.

More systematic thinking and approaches are urgently needed, that move beyond disease specific approaches and link R&D with critical areas such as research infrastructure, community engagement, ethics, regulatory pathways and innovative approaches to research. While this paper cannot cover all the relevant issues, we will focus on urgent challenges which are addressable now, examining R&D funding and coordination, gaps and priorities in research, and how research is done and used.

Section 1 gives an overview of the status and progress of R&D funding, strategic initiatives and capacity building for epidemics, and innovative approaches to R&D focusing particularly on the 2015-2019 period. Section 2 highlights the challenges and opportunities that our changing world present to epidemics R&D. Section 3.1 outlines how R&D funding, activities and coordination need to change, in terms of R&D during outbreak response, leadership and coordination of R&D, funding capacity in countries and alignment of R&D funding with need. In this context, WHO's normative, technical and convening role needs to be reaffirmed and strengthened. Section 3.2 covers gaps and priorities for R&D. Therapeutic and diagnostic R&D remain gaps and social sciences are lagging behind the progress made in products. R&D on "Disease X" remains a critical gap in the world's ability to respond to emerging and as of yet unknown diseases. Section 3.3 outlines two key gaps in the way R&D is done and used, such as regulatory pathways for product authorisation for use and licensure, and approaches to doing R&D that fit the context, such as adaptive trials. Annex I of the paper provides a list of the experts consulted and Annex II highlights the issues considered out of scope of this paper.

Chapter 1: Status of R&D and progress so far

1.1 R&D for epidemics

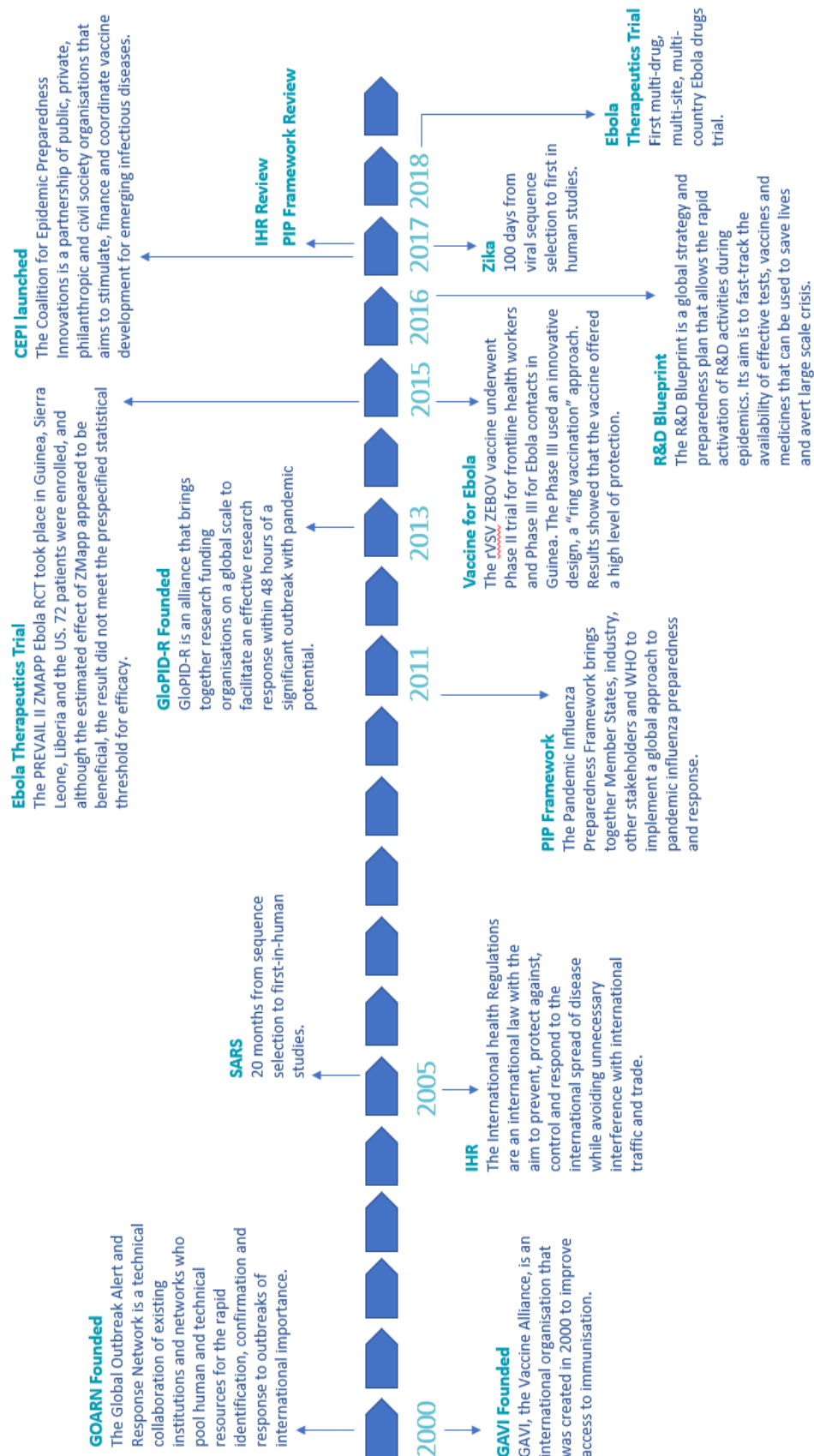
Outbreaks of human infectious diseases have devastating consequences for lives and livelihoods around the world. Research and development (R&D), including fundamental scientific research, social sciences, ethics, epidemiology, product development and clinical research, is critical to understand and stop these infectious disease outbreaks. However, the window to study these diseases and develop approaches to tackle their spread, can be short and infrequent, often happening in places that lack the infrastructure for R&D. Research during an emergency response is often the only or most effective opportunity for determining the safety and efficacy of interventions or products such as a diagnostic, therapeutic or vaccine.¹ This relies on the work done in preparation, such as the preclinical studies with preliminary safety and efficacy data for a therapeutic, or the underlying anthropological or epidemiological knowledge needed to develop an intervention for an outbreak. As a result, approaches to R&D have adapted to these different circumstances (Figure 1) and will need to continue to do so.

Research is now widely accepted as a key component of the response to epidemics following progress in recent years. Take Ebola viruses, first identified in 1976 and emerging periodically in Central African countries over the next few decades. Efforts to develop vaccines against these viruses remained stuck in the early stages of R&D for years, with no human safety studies either between or during outbreaks. This changed in the 2014-2016 West Africa Ebola epidemic, which demonstrated the ability to do research in outbreaks, and the role of countries where research is conducted. Increased efforts to accelerate R&D for preparedness have paid off by creating the tools needed to respond to outbreaks, such as the portfolio of Ebola vaccines in late stage development. The Ebola vaccine rVSV-ZEBOV and the cAd3 vaccine were trialled in Liberia, with rVSV-ZEBOV also trialled in Sierra Leone followed by a phase II trial in Guinea in 2015. rVSV ZEBOV was then used in the DRC to control a relatively small outbreak in the west of the country in May 2018.

The vaccination strategy using rVSV ZEBOV in the much larger epidemic in the DRC's North Kivu/Ituri region since August 2018 shows the benefits of preparedness and international collaboration (Box 1). The availability of the protocol and swift deployment of trained personnel and equipment meant that the vaccination strategy started seven days after the declaration of the outbreak. Over 180,000 people in DRC⁴ have been vaccinated since², in an effort that has helped manage the spread of the disease in an extremely challenging situation amid security issues, conflict and other humanitarian needs. Preliminary analysis indicates high vaccine efficacy and that the vaccination strategy is a highly efficient delivery method³, although there are methodological limitations with the data. Serious difficulties with contact tracing due to conflict and displacement of people are posing significant challenges in getting the epidemic under control, but we assume it would have been worse without the vaccine. However, the vaccine is still unlicensed and the path to bringing other vaccine candidates forward has been slow.

⁴ Correct as of 29 August 2019

Figure 1:
Milestones in R&D related to epidemics



Box 1:

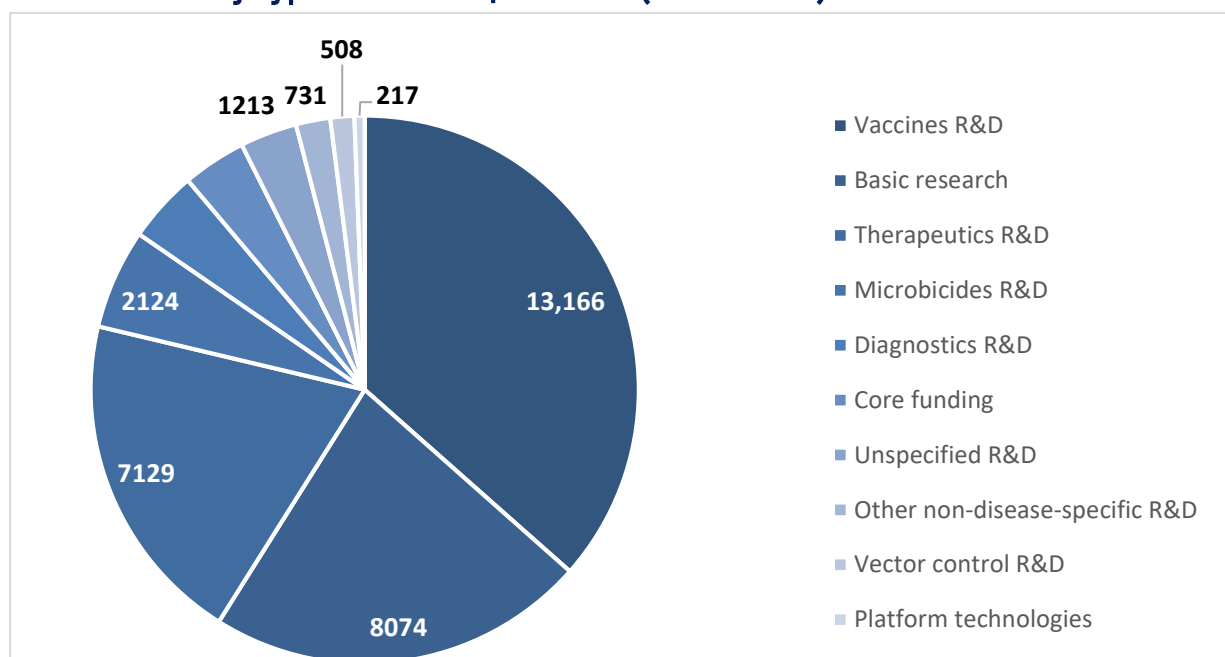
rVSV ZEBOV Ebola vaccine– journey from bench to field

- 2003. rVSV ZEBOV created by researchers at the Public Health Agency of Canada (PHAC) National Microbiology Laboratory and patented⁴.
- 2005-2009. Three animal studies published, including in non-human primates.
- 2010. Vaccine licensed to a small biotechnology company (NewLink Genetics), that continues preclinical development of the vaccine.
- 2013. PHAC, backed by the US Department of National Defence, spends \$887,000 to have IDT Biologika manufacture 1,500 vials of the vaccine candidate suitable for human trial.⁵
- 2014. Newlink, agrees to accelerated clinical development pathway, which was designed and implemented by interested parties, including PHAC, the US National Institutes of Health, the WHO led consortium (VEBCON).
rVSV ZEBOV licensed to Merck & Co.
Phase I trials in Gabon, Kenya, Germany, Switzerland (four VEBCON partners), the US, and Canada.
- 2015. Placebo-controlled randomised Phase II trial in Liberia (with US-NIH and Phase II trial in Sierra Leone in Health care workers (with US-CDC).
Phase II trial for frontline health workers and Phase III for Ebola contacts in Guinea (with WHO, MSF, Governments of Norway, Canada and UK, Wellcome Trust).
The Phase III trial used an innovative design, a “ring vaccination” approach. For the 11,841 people in the trial, 5,837 people who received the vaccine had no Ebola cases recorded 10 days or more after vaccination. In comparison, there were 23 cases in those who did not receive the vaccine⁶. This showed that the vaccine offered a high level of protection.
- 2017. The ring vaccination study design was reviewed by the DRC, allowing the country to be better prepared for the 2018 outbreak.
- 2018. Vaccine used to successfully control outbreak in Equateur province, DRC. Vaccine used in separate outbreak in North Kivu and Ituri provinces, DRC. To implement the protocol in North Kivu, 45 trained Guinean and Niger researchers worked under the leadership of Professor Jean-Jacques Muyembe, Director of the DRC's Institut National de Recherche Biomédicale (INRB), in South-South collaboration which built on previous WHO experience in West Africa. Guinean teams also used their clinical trial experience to train over 300 Congolese colleagues⁷.
- 2019. Preliminary results show the vaccine is highly effective at stopping Ebola transmission relative to no vaccination.⁸

1.2 Funding for R&D – lack of data on epidemics R&D

It is challenging to find good data on the levels of investment in R&D related to epidemic risk diseases. We need better monitoring and reporting of these investments in order to more accurately track progress in preparedness. Over recent years, spending on R&D for neglected diseases as a whole has increased above inflation⁹. Figure 2 provides a breakdown of the areas in which these investments have been made over 10 years, with the vast majority going towards vaccines, basic research and therapeutics, representing 36%, 22% and 20% respectively. Between 2008-2017, public funding from LMICs increased, reaching US\$105m (up \$17m) in 2017, its highest share of public funding (4.5%) since 2013. India was responsible for over 70% of the total LMIC public funding and was largely responsible for this increase in LMIC public funding compared with 2016. South Africa also provided its highest ever level of government funding (\$14m).

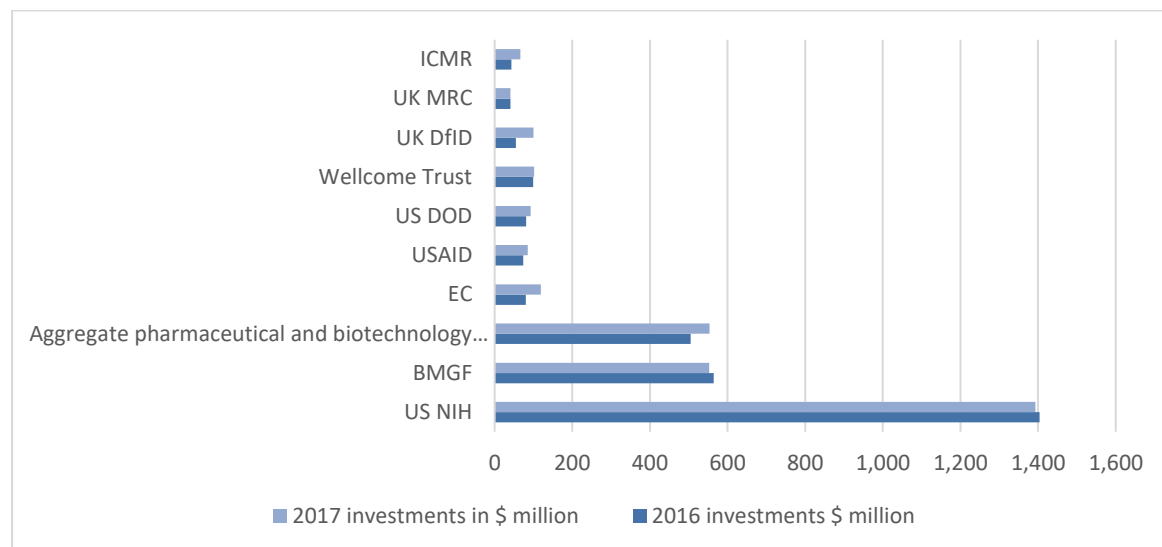
Figure 2:
Investments by type of R&D in \$ millions (2008-2017)



Significant investment from public funding for neglected diseases R&D

R&D investments for neglected diseases are up 7% from 2016 to 2017, totalling US\$3,566 million¹⁰. The top ten funders and their investment in neglected diseases R&D is shown in Figure 3. As in previous years, HIV/AIDS, malaria and tuberculosis (TB) collectively received more than two thirds of funding, \$2,496m¹¹. Note that neglected diseases included in the G-FINDER data do not include those on the WHO R&D Blueprint priority list. This data is lacking for investment in R&D for epidemic risk diseases, however data on neglected diseases shows relevant trends in major funders and investment in R&D.

Figure 3:
Neglected disease R&D investment by funder (2016 and 2017)



Progress has been made in recognising the valuable role that social and behavioural sciences play in research response to epidemics. Even though social and behavioural sciences have been involved in outbreaks and epidemics risk R&D for years, there has recently been much greater visibility of this work. The Ebola Response Anthropology Platform, as part of the Scientific Advisory Group for Emergencies (SAGE), helped to shape UK policy in Sierra Leone and has received attention for its efforts in the West Africa Ebola epidemic^{12 13}. The Ebola Response Anthropology Platform enabled social scientists and outbreak control teams to interact and develop a coordinated, adaptive and iterative response to the Ebola outbreak. The core activity was providing rapid response by email, conference call and online dialogue to operational questions raised by those working for NGOs, government and international agencies to contain the epidemic or care for those affected. Social science has demonstrated its potential to save lives, humanise outbreak responses, and mitigate the disruptive socio-economic and psychosocial burdens associated with outbreaks. Despite this development in the profile and relevance of social and behavioural sciences research related to epidemics, there is a lack of data on funding at an international level.

Funding for the pipeline of R&D Products

While there are a number of long-standing programmes to fund epidemics related R&D, a few are worth noting. The European Union provides financial support for relevant projects through their Horizon 2020 programme as well as through the European and Developing Countries Clinical Trials Partnership (EDCTP), which invested €652.5 million in 442 projects between 2003 and 2018¹⁴. The European Union funded Innovative Medicines Initiative (IMI) has also funded product development for epidemic risk diseases, notably Ebola and zoonotic diseases. The US Biomedical Advanced Research and Development Authority (BARDA) and US National Institutes for Health (NIH) have invested significantly in pandemic influenza products, including diagnostics, therapeutics and vaccines, as well as epidemics R&D more broadly.

In 2017, the African Union established the Africa Centre for Disease Control and Prevention (CDC), a significant demonstration of political support and investment for improved surveillance, emergency response and prevention of infectious diseases.

There has also been greater investment in epidemics related R&D since 2014. Established in 2017, the Coalition for Epidemic Preparedness Innovations (CEPI), is a partnership of public, private, philanthropic and civil society organisations that aims to stimulate, finance and coordinate vaccine development for emerging infectious diseases. CEPI brings together often-siloed aspects of R&D for vaccines and has committed to investing a total of \$370 million in 13 candidate vaccines for diseases on the R&D Blueprint priority list as well as vaccine platform technologies for Disease X (Table 1). CEPI has received multi-year funding from Norway, Germany, Japan, Canada, Australia, the Bill & Melinda Gates Foundation, and Wellcome Trust, reaching over US\$ 750 million of its \$1 billion funding target. CEPI has also received single-year investments from the governments of Belgium and the United Kingdom.

There has also been significant investment into the antimicrobial drug development pipeline in the form of CARB-X, which will invest US\$550 million. \$300 million of this commitment is from the US Government, and although not an epidemic-specific initiative, it demonstrates that there is appetite for pooling public and private funds to address global health challenges like antimicrobial resistance. The large public investments in CEPI demonstrate that the political will and support that exists for R&D for epidemic risk diseases has moved up the agenda in several countries.

Table 1:
CEPI vaccine development activities as of July 2019

Focus	Vaccine development activity
Lassa	5 active vaccine candidates in CEPI portfolio (IAVI rVSVΔ G, Emergent rVSVNC4G, Themis measles vector, UOXF/J ChAdOx1, Inovio DNA) – one is in phase I trial (Inovio DNA) and one due to begin clinical trials shortly
Nipah	3 active candidates for Nipah (UOXF/J ChAdOx1, U. of Tokyo measles vector, Profectus subunit)
MERS CoV	3 phase I candidates projects fully funded (Inovio DNA, IDT MVA, UOXF/J ChAdOx1, one for preclinical work (Themis measles vector)
Chikungunya and Rift Valley fever	One CHIKV project (Themis measles vector) in phase I trial and several others in due diligence. One RVF project in preclinical stage.
Platform technologies for vaccine development	3 projects preparing material for preclinical proof of concept -9 vaccine candidates

1.3 Leadership, coordination and strategies

Global coordination: WHO and the R&D Blueprint

The WHO has been instrumental in shifting the perception of research in the context of epidemic response, as demonstrated by their leadership of the Ebola vaccine trial in Guinea¹⁵. A cornerstone of WHO's efforts was establishing the R&D Blueprint strategy in 2016 to prioritise, accelerate and coordinate product-related R&D for epidemic risk diseases, with efforts on both research preparedness and research during outbreak response¹⁶. Preparedness activities are organised into three approaches: improving coordination and fostering an enabling environment, accelerating R&D processes and expanding research capacity. The R&D Blueprint has a list of priority diseases which present an epidemic threat and where R&D has been neglected so far¹⁷ (Box 2). As part of the R&D Blueprint, WHO has also developed Good Participatory guidelines for the design and conduct of trials of emerging (and re-emerging) diseases that are likely to cause severe outbreaks¹⁸ and convened experts to support the development of innovative study designs.

Box 2: 2018 R&D Blueprint priority diseases

Given their potential to cause a public health emergency and the absence of efficacious drugs, vaccines, or both, there is an urgent need for accelerated research and development for the following diseases:

Crimean–Congo haemorrhagic fever (CCHF) *

Ebola virus disease * and Marburg virus disease

Lassa fever *

Middle East respiratory syndrome coronavirus (MERS-CoV) * and severe acute respiratory syndrome (SARS) coronavirus

Nipah * and henipaviral diseases

Rift Valley fever (RVF)

Severe Fever with Thrombocytopenia Syndrome (SFTS)

Zika

Disease X (*a serious international epidemic that could be caused by a pathogen currently unknown to cause human disease*)

One part of R&D Blueprint activities is the creation of roadmaps for diagnostics, therapeutics and vaccines development, bringing together key actors for each disease to review the evidence and develop priorities and a way forward to accelerate R&D. As of May 2019, roadmaps for CCHF, MERS-CoV, Lassa fever, Ebola/Marburg and Nipah viruses have been developed, and a roadmap for Disease X is underway. This focus on a product approach may overlook a broader public health perspective, which would seek to mitigate the risks to communities and how to integrate tools into an effective response, rather than assessing the

effectiveness of an individual tool. Moving away from disease specific approaches towards a public health approach and platforms for diagnostics and therapeutics would be a significant step forward. Related to this, one gap that remains is support to make sure the roadmaps are acted upon, including available funding, and how the resulting R&D and tools are used.

There have also been a number of changes in WHO's Health Emergencies programme to integrate research into outbreak response. This includes the use of Strategic Response Frameworks during outbreaks, that include three pillars: surveillance, response and research. For example, the strategic response framework for Zika¹⁹ aimed to provide support to affected countries, build capacity to prevent further outbreaks, and to facilitate research that will better understand Zika and its effect. As well as the R&D Roadmaps the WHO has also developed Target Product Profiles for the priority diseases, which define a set of key attributes, such as target population and safety and efficacy requirements to provide early technical guidance for products²⁰.

The path to aligning national strategies and international funding

WHO has been supporting countries to develop research agendas for R&D Blueprint diseases (Box 3). Countries have used the product roadmaps to inform their own research agendas and strategies for priority diseases, such as Nigeria's Lassa fever research agenda and India's for Nipah virus. Once countries have developed national research agendas or strategies there is a gap in ensuring the alignment of international funding with these activities as much as possible, recognising that the majority of current R&D funding for epidemic risk diseases come from a small number of funders based in high income countries (HICs).

Box 3:

Nigeria's Lassa Fever National Research Plan

Nigeria developed Lassa Fever National Research Plan in 2018 to gain a better understanding of the disease and enable research to be fully integrated into outbreak response. Several research institutions offered to support Nigeria, and the Nigeria Centre for Disease Control (CDC) requested assistance from the WHO to map and coordinate the numerous offers of support and identify potential for overlaps.

At the onset of the 2018 outbreak, the Nigeria CDC, working closely with WHO and partners, developed a list of research priorities to improve the ability to prevent, detect and respond to Lassa fever. Key objectives were to²¹:

- Set in place a mechanism in Nigeria to facilitate the coordination of all research efforts related to Lassa Fever, and to prioritise and facilitate multiple local and international partner requests based on local needs.
- Provide answers to unanswered questions and increase knowledge about the disease, such as 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 and research to inform community engagement strategies and to further document risk factors for transmission of Lassa virus.
- Expand existing research capacity in Nigeria.

1.4 Regional and national domestic R&D capacities

Health R&D capacity is largely concentrated in HIC, supported by a small number of funders. This has impacted not just where R&D takes place but also decisions about which ideas to explore. This imbalance persists despite the recent upwards trend in investment in neglected disease R&D from LMICs, including public investment. Tools and interventions should be effective in the places most likely to be affected by outbreaks, but in practice little of the relevant R&D involves communities in the areas at most risk. This poses a challenge due to the short time frame and other constraints under which action is taken to manage the spread of a disease, as well as issues of access, ethics and equity.

R&D doesn't happen in a vacuum. As well as trained people, research infrastructure and equipment and a supportive regulatory environment, R&D for epidemics also depends on the wider health system and public health functions like disease surveillance, reporting and reference laboratories. The International Vaccine Task Force report on clinical research capacity for epidemics provides an overview of the clinical research capacities in various countries²². Since the 2014-2016 West Africa Ebola epidemic, several regional programmes to support research and science capacity development in Africa have been established.

These include:

- International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), builds capacity for clinical research for epidemics, since 2011
- Joint West Africa Research Group (JWARG), supported by the US Department of Defense since 2015
- Global Health Security Agenda (GHSA), which has supported efforts to strengthen countries' basic public health capacity, laboratory capacity, surveillance and reporting of outbreaks internationally since 2015²³
- The EDCTP Regional African Network of Excellence: a) East African Consortium for Clinical Research-2 (EACCR2), b) The Trials of Excellence for Southern Africa (TESA2), c) Central African Network (CANTAM2) and d) the West African Network (WANETAM2), all renewed by the European and Developing Countries Clinical Trials Partnership (EDCTP) in 2016
- African coalition for Epidemic Research, Response and Training (ALERT) network, funded by EDCTP since 2018, is a multidisciplinary consortium for building a patient-centered clinical research network to respond to epidemics across sub-Saharan Africa
- Pan-African Network for Rapid Research, Response, Relief, and Preparedness for Infectious Diseases Epidemics (PANDORA-ID-NET) network, funded by EDCTP since 2018 to strengthen pan-African capacities and networks and enable locally led robust 'ready to go' joint human and animal outbreak response teams during outbreaks
- Regional Lassa fever research network in West Africa²⁴

Initiatives in other regions include the Indo-Pacific Health Security Initiative, established by the Australian government in 2017 to invest in national R&D and capacity building to strengthen health systems and preparedness. While it is too early to assess the impact of these new initiatives, it is promising to see recent commitments, including political attention and financing, for research for preparedness.

These and other new initiatives should build on prior investment in research capacity building and long-standing public health capacity building efforts such as:

- Africa CDC, established by the African Union in 2017 to improve surveillance and prevention of infectious disease as well as emergency response
- West Africa Regional Disease Surveillance Systems Enhancement (REDISSE) Programme, established in 2016 to support 11 West African countries to increase capacity for disease surveillance and response
- ASLM, established in 2018, galvanises local, national and international stakeholders to improve local access to world-class diagnostic services and leads the Pan African Consortium for Laboratory strengthening
- RISLNET, Regional Integrated Surveillance and Laboratory Networks, established in 2018
- AFENET, established in 2005 to expand applied epidemiology and laboratory capacity in Africa²⁵
- TEPHINET, a global network that has facilitated the training of thousands of public health professionals since 1997²⁶
- International Association of National Public Health Institutes (IANPHI) network, which works to link and strengthen government agencies responsible for public health in over 45 countries since 2016

The African Vaccine Regulatory Forum (AVAREF) was established in 2006 by WHO to build capacity of regulatory and ethics agencies and to improve harmonisation of practices in support of product development. AVAREF has played a crucial role in the successful development of several vaccines and Ebola virus therapies²⁷. Another positive development is that in 2016 AVAREF agreed new terms of reference to cover medicines and diagnostics as well as vaccines across all African Union countries²⁸.

Capacity building efforts in line with the International Health Regulations (IHR) and assessments such as the Joint External Evaluation tool (JEE) have been taking place through numerous programmes to attempt to tackle these weaknesses. These efforts are providing useful direction for activities in countries. In the 2018 outbreak of Nipah virus in Kerala, India, capacity building as part of the GHSA directly improved the abilities to detect and respond to the outbreak, as well as care for the people affected (Box 4). Although over 100 countries have completed JEEs, the challenge lies in prioritising the actions needed to address the gaps highlighted and access to funding for these activities from both domestic and international sources.

Box 4:**Nipah virus outbreak in India– the benefits of capacity building in action**

The 2018 Nipah outbreak was the third in India but the first in Kerala. A year before, the US Centers for Disease Control (CDC) had provided in-country wet laboratory training to the Manipal Centre for Virus Research (MCRV) and the National Institute of Virology (NIV). This training helped increase diagnostic capacity, and included sharing technical expertise, reagents and training for diagnosis of viruses, including Nipah and Crimean-Congo²⁹.

During the outbreak MCRV and NIV teams were able to rapidly sequence the virus's RNA genome and found that it was similar to the virus previously detected in West Bengal. This informed clinical care of affected people. Because next generation sequencing analysis could be done without the sample leaving India, the turnaround time for lab confirmation of Nipah virus was around 12 hours.

In response to the outbreak, the Indian Council of Medical Research collaborated with the WHO R&D Therapeutics Working Group and others to develop a multinational, multi-outbreak, adaptive clinical trial “A Randomized Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Nipah Virus Infection”. The protocol was developed in a week, and built off the existing work on the Nipah R&D Blueprint roadmap and the Partnership for Research on Ebola Virus in Liberia II (PREVAIL II) master protocol³⁰.

There has been progress in developing a one health approach to zoonotic disease outbreaks. ‘One Health’ is about the relationship and interconnections between humans, animals and the environment, and recognises that the health and wellbeing of people is intimately connected to the health of animals. Initiatives are being built across regions for rapid and innovative investigation of the zoonotic and human elements of outbreaks, and there have been a number of examples where a One Health approach had enabled a better understanding about zoonotic spread, and allowed more effective monitoring and response to outbreaks (Box 5).

Box 5:**Chikungunya in the Republic of Congo and a one-health approach**

On February 9th, 2019 the Republic of Congo declared a Chikungunya outbreak which rapidly spread to 24 health districts.

An ecological, epidemiological, and public health investigation was conducted between March 22nd and 27th 2019, in collaboration with the Congolese Department of Health, and the US NIH, the National Institute for Medical Research in Tanzania, and the UK Royal Veterinary College³¹. This was coordinated by PANDORA-NET-ID, a multidisciplinary One Health, South-North research consortium established in 2018. A multidisciplinary team of local and international epidemiologists, physicians, entomologists, virologists and vector-borne disease modellers, was deployed, allowing a rapid and functional investigation of the animal and human element of outbreak. Their investigations led to insights into the outbreak dynamics in a matter of days, which were also shared with the communities affected.

1.5 Innovative approaches to R&D

Outbreaks in complex environments have required new and innovative approaches to research, while recognising that scientific standards and rigour are still paramount. For example, randomised controlled trials (RCTs) are typically planned at the outset and do not allow deviations from the original plans. Using more “traditional” trial designs can be a challenge in research on epidemic risk diseases, where there may not be existing treatments to compare to, or uncertainty on the numbers of people that can be recruited to take part. Innovative approaches to trials and RCTs, where trial design allows for flexibility for adapting dosages, sample size, or stopping early for futility can accelerate progress in epidemics R&D. Alternative trial designs include cluster randomised trials and stepped wedge trials. During the West Africa Ebola epidemic, the EMA supported alternative trial designs and concluded “adaptive design would be best utilised as a tool for planning clinical trials in areas where it is necessary to cope with difficult experimental situations”³².

In 2018, during the Ebola outbreak in North Kivu, it became important to move from compassionate use of therapeutics to a clinical trial to collect evidence in a robust way. The Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) which was being used to administer investigation therapeutics was not developed to collect evidence. MEURI recognises it can be ethical to utilise unproven treatments in settings with a high case fatality rate and it is not immediately possible to conduct a trial due to medical research infrastructure limitations. Given the limited number of patients and complex environment, a more innovative trial design was needed to develop evidence on the effectiveness of the interventions. The resulting trial, led by INRB in DRC, is the first multi-drug, multi-site, multi-country Ebola therapeutics trial and has shown how alternative approaches can be used to collect the necessary data and evidence across outbreaks, countries and time³³. Flexibility built into the trial has allowed the addition of a fourth therapeutic, REGN-EB3, and allows trials to be extended to other sites when needed.

Chapter 2: Gaps, challenges and solutions

2.1. R&D funding, coordination and governance

Collaboration between actors for outbreak response

In many cases, properly evaluating the efficacy and safety of new products and design and test non-biomedical interventions can be done only during an outbreak. Increasing national and regional capacity for R&D and investing before an outbreak occurs puts countries in a better position to undertake rapid research and, alongside manufacturing capacity, make the required products.

Research is now generally seen as a key element of response and has been more integrated over recent years. For example, in the DRC an investigational vaccine was used under a research protocol within a week of the declaration of the Ebola outbreak. This is progress, but working in epidemic settings brings new challenges for R&D. Collaboration between a wide variety of actors becomes even more important. Some of these actors – from, among others, humanitarian, defence, public health and research backgrounds – would not typically work closely together and have very different missions, so aligning them in support of a common goal is not always easy. There are examples of military and private sector collaboration, such as the US military working with Glaxo-Smith-Kline to develop and test the RTS,S malaria vaccines since the 1990s³⁴. In 2019, the vaccine was rolled out in Ghana, Kenya, and Malawi through routine immunisation programmes³⁵. Differing remits and the number of initiatives recently established to support, coordinate or carry out R&D related to epidemics add complexity and can impede swift, decisive action.

Collaboration is also needed between global, national and local actors. UN agencies such as WHO and international humanitarian organisations must work with national governments and at-risk communities in the countries affected. Depending on circumstances, the roles of these actors will vary, including that of the national government – in the Ebola outbreak in North Kivu, DRC, the involvement of local government has been more important than usual due to local political issues. Having national plans in place in advance of outbreaks that have been developed with important community stakeholders would improve preparedness.

Recognising the tensions between many different actors working to prepare and respond to health emergencies, clear norms for R&D should be developed with engagement of all interests, including national governments, humanitarian organisations, international agencies, the military, researchers and the communities affected or at risk. These norms should not be disease-specific and cover standards of behaviour in the research community to work under rigorous scientific and ethical principles, recognise country interests and share data and results rapidly and in the public interest. The development process should bring in and build on the work of existing networks and collaborations for R&D.

Global coordination and leadership

Successful collaboration on R&D for epidemics requires clear governance and leadership. While global systems are in place for health emergencies, numerous initiatives and actors in R&D have emerged in recent years, with overlapping interests and remits. This, compounded by complexities at country level to align to national strategies, can lead to duplication and inefficient use of R&D money.

These initiatives and groups include the R&D Blueprint and its Scientific Advisory Group and Global Coordination Mechanism, the Scientific and Technical Advisory Group for Infectious Hazards (STAG IH), Global Outbreak Response Network (GOARN) and consortia such as PREPARE and GloPID-R. The membership and advisory groups of these groups and initiatives should be representative of countries that experience epidemics. There are many opportunities for synergistic actions across a number of product development partnerships (e.g. Drug for Neglected Diseases initiative, Foundation for Innovative New Diagnostics, Global TB Drug Alliance, Medicines for Malaria Venture), funding initiatives (e.g. UNITAID, the European and Developing Countries Clinical Trials Partnership), and partnerships advancing R&D and capacities (e.g. Special Programme for Research and Training in Tropical Diseases, The Alliance for Health Policy and Systems Research) to create a more effective R&D ecosystem to research and produce new therapeutics, diagnostics, vaccines and non-biomedical interventions.

Rationalising the system would create more focused global leadership with respect to epidemics R&D, reducing fragmentation, recognising overlaps and accelerating innovation. In addition to identifying research needs, this could help to build on progress linking research to response efforts and include more clarity on the command structure in the event of an outbreak. This could also facilitate the streamlining of roles and responsibilities for information sharing, coordination and decision making on R&D, enabling global actors to move more decisively with communities when responding to outbreaks. Present research cultures are competitive, so any mechanism to coordinate R&D for epidemics should emphasise collaboration over competition.

WHO has a central role in convening and coordinating the different actors and should continue to build foundations for direction and collaboration, such as the R&D Blueprint and its Global Coordination Mechanism. Ensuring that WHO's leaderships is recognised and that groups such as these have clear mandates and continue to have the right representation will aid their effectiveness. This should include strong links to advisory groups providing normative guidance for WHO (e.g. STAG-IH, Strategic Advisory Group of Experts on Immunization, Pandemic Influenza Preparedness Framework Advisory Group, and others).

Despite increased investment, there are persistent gaps in how R&D for preparedness is done, such as the ability to do R&D at the country level or for diseases on the R&D Blueprint priority list. National research agendas are often developed during an outbreak as part of the R&D Blueprint strategy (Box 3). Having these agendas developed in advance would be a significant step forward. For example, few international programmes are doing research before and across outbreaks involving the wide range of actors across research, response, humanitarian communities and national governments in countries at risk. Progress in research capacity building for epidemics related research, such as ALERRT, PANDORA-ID-NET, the South East Asian Infectious Disease Clinical Research Network, the Nipah network in South Asia and Middle East Respiratory Syndrome (MERS) network in the Middle East

and North Africa. However, efforts outside of Africa have been largely disease-specific and capacity for epidemics related R&D in other regions should receive more focus. Improved leadership and coordination are not just top-down issues: the flow of information, top-down and bottom-up, needs to improve to optimise operational response efforts. A clear command structure helps to facilitate this during an outbreak.

Funding in-country capacity

As demonstrated in the financing and country preparedness papers, there is a big gap in funding core infrastructure and capabilities for preparedness and response in countries most at risk. To be sustainable, international efforts to strengthen research capacities at country level need to be driven by regional and national priorities, and be relevant to addressing day-to-day issues, such as endemic disease programmes, and not focused on building capabilities that are relevant in the event of an epidemic. For example, the Nigeria CDC has led the development of a national research agenda for Lassa fever which is integrated into the country's disease surveillance and monitoring efforts (Box 3).

An example of capacities that are relevant on a day-to-day basis and in outbreaks is integrating genetic sequencing technology into public health and preparedness activities. This would support the use of these technological advances to facilitate disease surveillance, monitoring, the identification of cases and support contact tracing. The lack of local capacity to carry out genetic sequencing can lead to a lack of rapid data sharing to inform the response and equity issues. To address this, supporting the development of genetic sequencing and sample collection/processing capabilities for clinical immunologic analyses that are integrated in the public health and wider health system should be priorities.

Although not epidemics R&D specific, there are a number of research capacity building programmes in Africa and Asia that could serve as useful models for aligning international and national funding. For example, the Wellcome Trust/DBT India Alliance funds biomedical science in India, with the Government of India Department of Biotechnology now contributing twice as much funding as Wellcome. An example of regional efforts addressing everyday challenges that should be built on by any epidemics R&D capacity building efforts is the African Medicine Regulatory Harmonisation (AMRH) programme, which is working to provide an enabling regulatory environment for pharmaceutical sector development in Africa.

Aligning funding with need

Funding is not always well-aligned with the needs of those actors involved in the response and of the countries and communities affected. This is an issue across R&D and innovation, not only in the area of epidemics (Box 6). Even when national research for health agendas exist, differing priorities from government ministries, national research institutions and international funders commonly risk making research less strategic and undermine long-term health outcomes.

Alignment problems can lead to standstills when issues get bogged down, and lives are lost as a result. R&D for epidemics has typically been subject to panic and neglect cycles of interest and investment. Historically, R&D activities of some of the large funders have not been well aligned to each other or responsive to the needs of response actors and affected countries, creating inefficiency. As long-term plans such as R&D Blueprint roadmaps, country-led

research agendas for epidemic risk diseases and National Action Plans for Health Security (NAPHS) are developed, international and national research funders should align their spending on R&D for epidemics.

Box 6:

R&D, innovation and access accelerator

The world is not on course to meet most of the targets in Sustainable Development Goal 3 (SDG3) for health by 2030. In 2018, 12 major global health organisations agreed to develop a Global Action Plan, focused through seven ‘Accelerators’, to accelerate progress in global health. Accelerator 5 examined R&D, Innovation, and Access, and was co-led by the World Health Organization and Wellcome. It identified several problems and actions to tackle them. While broader than epidemics, there are clearly synergies.

Major problems identified:

- Poor coordination and alignment of research priorities
- A sub-optimal innovation system
- National voices are not always heard
- Access is not built into the R&D pathway

Actions proposed:

- Develop Global Good Access Practices for Innovation in Health
- Establish and maintain a new annual global forum to coordinate and accelerate the late stage pipeline of critical medical and health products
- Country-led forums to accelerate the scaling of innovations
- Governments and international funders should explore opportunities for co-funding to help drive decision making to countries and regions
- WHO to curate an evidence-based list of existing innovations that could be scaled

These actions would help to address some of the challenges in R&D for epidemics. In the short-term, more coordination of R&D through forums with the right stakeholders in the room, and developing and encouraging the use of good access practices guidelines so products (including those relevant for epidemics) reach the people who need them. In the longer-term, encouraging a shift in decision-making to countries will drive more demand in-country for R&D priorities, including to prepare and respond to epidemics. The Global Action Plan will be launched at the UN General Assembly in 2019.

2.2 Gaps and priorities for R&D

Putting communities at the centre of R&D and response

As epidemics increasingly emerge in the context of conflict, insecurity, and vulnerable and displaced people, placing communities at the centre of the response is critical.

Understanding people's behaviours, their cultural norms and values, and their political and economic realities is essential for an effective response^{36 37}. Tools like vaccines and diagnostics are of little use if their implementation has not been adapted to the community - otherwise mistrust builds and these tools will not be widely accepted. The effective generation and use of contextual information, including engaging with and listening to the communities, is essential for adaptive planning, agile decision-making, and ensuring that interventions are appropriate for the community they serve.

Non-biomedical interventions, such as behaviour change, play a crucial role in preparedness, and can work alongside biomedical interventions. One example, is research on non-biomedical interventions to reduce the number of cases of Nipah. Drinking raw date palm sap is a risk factor for people to contract Nipah virus as fruit bats, the natural reservoir of Nipah virus, can contaminate raw sap with their saliva³⁸. A number of interventions have shown to be effective, including behaviour change to stop people from drinking raw date sap³⁹ and interventions to reduce bat-sap contact⁴⁰.

The West Africa Ebola epidemic demonstrated how neglecting social and cultural contexts hindered work with affected communities and undermined the response. Anthropology played a critical role in addressing major routes of transmission of Ebola, including funeral rites^{41 42} that can include complex washing and handling of the body by friends, family and the community. Advice from social scientists enabled funeral rites to be adapted, maintaining the essence and symbolism of these traditions while ensuring that they limited risk for transmission^{43 44}.

In the response to the 2018-2019 Ebola epidemic in DRC, social sciences have shaped community engagement practices⁴⁵. For example, the University of Kinshasa is working with Wilfrid Laurier University, Bluesquare and the University of British Columbia to look at integrating routine health information into the response to Ebola⁴⁶. Social Science in Humanitarian Action is providing advice on contextual considerations including burial, funeral and mourning practices, changing behaviour and care-seeking practices, and the political, economic and security context of the region – this advice has informed strategic and operational decisions⁴⁷. However, the complex context of increasing violence, acute humanitarian need and community mistrust has severely limited efforts to manage the outbreak. Vaccination programmes have been interrupted and treatment centres temporarily closed⁴⁸. Despite improving practices to be more relevant to local contexts, it is an uphill battle as long as social and behavioural sciences are not systematically used across all elements of the response.

Many social scientists lack the exposure to outbreak response training and biomedical concepts, including the basic principles of epidemiology, emergency response and policy frameworks and the financing, ethics and exigencies of humanitarian systems. At the same time, those working in public health and humanitarian fields may have limited understanding of social science. This creates a significant gap in the ability to use social sciences to

generate insights from time-sensitive studies that accept uncertainty and that can be operationalised⁴⁹. This must be addressed through greater training of social scientists and response agencies, and longer-term opportunities to work together outside of outbreak responses.

WHO and implementing agencies such as UNICEF need to build on existing efforts and further integrate social sciences into their programmes so that evidence shapes practice.

Reducing the gap- diagnostics and therapeutics

Therapeutics, diagnostics and vaccines share significant barriers to development, such as the lack of commercial market and complexity of the regulatory pathways to assess and approve products (see section 3.3). Diagnostics serve a number of purposes related to epidemics, including identifying outbreaks, detecting diseases in animals, surveillance of communities with a history of infection, and detecting the presence of an immune response. They also enable targeting of vaccines to effectively manage an outbreak, so a lack of suitable diagnostics undermines progress in vaccine development. Rapid and effective diagnostics have implications for guiding interventions, even in the absence of medical products. Diagnostics for the R&D Blueprint priority diseases range from limited to non-existent despite efforts to build capacity to detect and monitor outbreaks of priority diseases. While there are laboratory-developed tests for many priority diseases, they vary in effectiveness, may be difficult to access⁵⁰ and typically require moderate to high levels of training and equipment, meaning they are not usually appropriate for a rapid response and limited resource settings^{51 52}.

In Angola, during the largest yellow fever outbreak in the last 30 years, vaccines prevented over 360 deaths and 5000 cases in the city of Luanda alone⁵³. This was possible due to vaccination programmes and confirmation of yellow fever in the regional reference laboratory, although there were delays in acquiring the necessary reagents as these are not available commercially. While there are laboratory diagnostics for yellow fever, there are still major time lags and gaps in capacity; as a result, Gavi is supporting diagnostic capacity development for yellow fever, including market pull incentives for test kits.⁵⁴

Rapid diagnostics tests and point of care diagnostics remain a big gap⁵⁵ (Table 2). For example, there are no diagnostics that can be used in health care settings for Lassa fever, Nipah virus or MERS CoV, each of which is clinically similar to other diseases. Tests that distinguish between endemic diseases are vital and another reason why a public health approach is needed, rather than a disease specific product approach. Therefore point-of-care diagnostics remain a priority for R&D because they are essential to identify infected individuals and ensure they receive the best possible care.

Table 2:
R&D Blueprint priority diseases and diagnostic gaps

R&D Blueprint priority disease	Diagnostic need (red: critical, yellow: important; green: available but may need improvement)*	Situation overview⁵⁶
Crimean-Congo haemorrhagic fever	Critical	No established reference test. Very limited availability of commercial assays, with very low usage and limited performance data.
Filoviruses (Ebola and Marburg)	Important	Recent high-profile outbreaks resulted in international focus and funding, which has enabled the development and introduction of critical diagnostics. Additional work is needed to improve current diagnostics, develop point of care (POC) tests and ensure reliable availability.
	Available but may need improvement	
Lassa fever	Critical	Limited commercially available tests, none of which are easily deployable in the settings needed.
MERS-CoV	Important	Limited availability of validated assays, restricted to highly complex tests. Lack of POC diagnostics.
SARS	Important	High-profile outbreaks resulted in international focus and funding, which has enabled the development and introduction of critical diagnostics. Additional work is needed to improve current diagnostics, develop POC tests and ensure reliable availability.
	Available but may need improvement	
Nipah and henipaviral diseases	Critical	Limited commercially available tests, none of which are easily deployable in the settings needed.
Rift Valley fever	Critical	Limited commercially available tests, none of which are easily deployable in the settings needed.
Zika virus disease	Important	Recent high-profile outbreaks resulted in international focus and funding, which has enabled the development and introduction of critical diagnostics. Often co-circulating with dengue, YF and chikungunya, so need for diagnostics to distinguish between them.
	Available but may need improvement	

		Additional work is needed to improve current diagnostics, develop POC tests and ensure reliable availability.
Disease X	Critical	Need for diagnostic platforms that can rapidly adapt and support diagnostics for unknown pathogens.

* Red/critical: diagnostics needed but not currently available or validated; yellow/important: diagnostics currently under development; green diagnostics available but may need improvement. Table adapted from Kelly-Cirino CD, Nkengasong J, Kettler H, et al. (2019) Importance of diagnostics in epidemic and pandemic preparedness. *BMJ Global Health*;4:e001179.

Similar to diagnostics, therapeutics for epidemic risk diseases are scarce. Immunotherapies such as monoclonal antibodies may offer broad protection against a virus or family of viruses. Therapeutic candidates in development typically have limited safety and efficacy data so a common priority across the R&D Blueprint disease roadmaps is to develop protocols for conducting safety and efficacy trials despite gaps in the underpinning biological understanding of these diseases (more discovery science is also needed). The therapeutic pipeline for various epidemic diseases is heavily weighted at the earlier pre-clinical stages (Table 3). A lesson from drug development is that the vast majority of products don't make it through to phase 3 trials, and for epidemic risk disease the barriers are even greater, such as the small markets for products and challenges of testing products on diseases with sporadic outbreaks. It is also a concern that there is a lack of progress in therapeutics development for epidemic risk diseases, aside from Ebola. For example, there are currently no therapeutics in phase 3 for Marburg, Lassa, Nipah or Zika.

Table 3:

Therapeutics pipeline for some epidemic risk diseases

Disease	Pre-clinical	Phase of clinical development		
		Phase 1	Phase 2	Phase 3
Marburg	13	2	0	0
Plague	4	0	3	1
MERS	9	2	0	1
Lassa	11	0	1	0
Nipah	2	1	0	0
Zika	26	1	0	0
Ebola	35	4	5	5

Data for table taken from R&D Blueprint Mapping Tool

The accelerated development of rapid diagnostics and of therapeutics beyond disease-specific approaches and towards platforms for development, to complement advances in vaccine development such as CEPI, should be a priority for R&D. The R&D Blueprint roadmaps for five out of eight of the priority diseases have identified priorities for product development and research more widely, but there is a lack of actors and organisations who can advance diagnostic and therapeutic needs in a concerted and coordinated way. Advancing diagnostics and therapeutics R&D should include basic biological understanding of diseases and the factors that affect emergence and transmission, as well as clinical research. CEPI could serve as a model for pooling the resources into a mechanism that considers the regulatory and delivery issues early in R&D.

Developing international biological reference materials and clinical care standards for priority diseases were both identified as key gaps in the R&D Blueprint roadmaps for Lassa fever, Nipah virus, CCHF, and Ebola/Marburg. Biological reference materials, such as antigens and antibodies, are essential for the development of diagnostics, therapeutics and vaccines⁵⁷. Reference preparations enable consistency and comparison, for example assuring quality and optimal standard for use in laboratories around the world carrying out diagnoses of diseases. Before the West Africa Ebola epidemic, there were no international biological reference materials for Ebola, or any of the WHO R&D Blueprint priority diseases. It took over two years from initial development to the endorsement of the first international Ebola antibody reference standard in October 2017⁵⁸. Frameworks for accelerating the development of these standards need to consider aspects such as consent, ethical considerations and equitable benefit sharing⁵⁹.

The absence of an evidence-base for supportive care hinders the evaluation of experimental medical countermeasures and undermines ongoing R&D efforts. Very little has been published on how variations in supportive care affect evaluation of medical measures, but the R&D Blueprint roadmaps for Lassa, Nipah, Ebola and CCHF identified optimal case management and clinical care as a strategic R&D goal, recognising the need for minimum standards of care in at-risk locations. Agreed minimum standards of care will facilitate the accurate interpretation of research findings and their successful application in a clinical context.

Accelerate R&D for Disease X

The next epidemic could be caused by a pathogen not yet known to infect humans, just as SARS emerged to infect over 8,000 people in 29 countries in the early 2000s. On average, there have been two new human viral pathogens identified per year since 1901.⁶⁰ The WHO has recognised the importance of this risk, making “Disease X” one of the eight priority diseases of the R&D Blueprint and started work on a roadmap for product development. The average development time for conventional vaccines is more than 10 years, so approaches that allow fast development and that could be adapted for a previously unseen disease are a priority. The benefit of using techniques previously successful for other viruses is clear when comparing SARS in 2002-2003 with the Zika epidemic in 2015-2016. The time between sequencing of the disease and phase I trials of candidate vaccines decreased from 20 months to close to three months⁶¹, as using an established process sped up development of the Zika candidate vaccine⁶².

A key concept in R&D efforts to prepare for Disease X is the development of platform technologies, which can be used to advance development of multiple vaccine candidates at the same time. The technique to develop the rVSV ZEBOV vaccine for Ebola is one model, as it uses a fragment of Ebola Zaire virus attached to the surface of the VSV vector. These fragments, encoded in a gene, can be replaced by genes from other viruses, as with the Lassa fever vaccine candidate, rVSVΔG, now in preclinical development funded by CEPI. The implication is that some stages of clinical development could be expedited if a platform technology already has clinical data, such as safety data. This could potentially extend to manufacturing, allowing progress in setting up production facilities before the targets of the vaccines to be produced are decided. Platform technology approaches include DNA and mRNA vaccines, adjuvants, monoclonal antibodies, host directed therapies and broad-spectrum antivirals.

In addition to platform technologies, a number of other technological developments should be harnessed to expand Disease X R&D. The wealth of sociodemographic, geographic and environmental data and the advances in computational and mathematical tools, combined with epidemiological and genetic data, can provide insights that were not possible until recently. More affordable technology for real time genetic sequencing can generate data to track and map the spread of a disease, and provide insight into the factors and mechanisms driving the spread of a Disease X when traditional epidemiology based on case data may be less reliable⁶³.

2.3. Improving ability to do and use R&D: regulation & innovative and adaptive approaches to R&D

Clearer regulatory pathways for products

Fast tracking product development is one thing, but without systems in place to identify effective interventions and access treatments, progress in R&D will not help anyone. Limited infrastructure for clinical research in the countries where epidemics are likely to happen is a challenge⁶⁴. This includes national and regional regulatory frameworks, capacity to provide appropriate oversight for research, and expertise to assess risks and make swift decisions.

The African Vaccine Regulatory Forum (AVAREF) supports joint reviews of products and inspections of manufacturers in the region, and its remit has recently been expanded by the African Union to cover all products, not just vaccines. While these and other efforts to fast track product assessment and overcome regulatory capacity challenges during health emergencies have been regarded as progress, pathways for product licensure are still a challenge. Paths are not harmonised, are often cumbersome or not adapted to a true emergency, and the level of regulatory expertise and implementation among investigators and affected countries can vary significantly. Platform technologies for development of multiple candidates may help to speed up approvals, as delays are a significant barrier to investment in R&D, especially in the later clinical stages.

Regulatory assessment and approval processes must keep pace with the speed at which epidemics happen. In many cases, this means using alternative procedures that have been developed by regulatory authorities because of the immediate need to treat people as well

as possible and standard assessments take too long. Those in the European Medicines Agency (EMA) can take more than 200 days. The case for alternative procedures is especially strong for diseases with few or no known treatments, when a clinical trial would be the best way to determine safety and efficacy. A key requirement is that the clinical studies up to phase II do not wait for an outbreak – preclinical studies, such as animal studies, can provide important data about safety and effectiveness to guide decisions on product authorisation for use in a clinical trial.

National regulatory authorities (NRAs) such as the US FDA and EMA have a number of emergency and non-emergency processes for accelerated authorisation for use and licensure of products that address an unmet serious health need (Table 4). These processes require less comprehensive data than standard authorisations, recognising that the products are likely to have more limited data than usually required. If a health emergency happens in a country with an under-resourced NRA, they may rely on the technical support of, or in some cases, decision of a stringent NRA such as the FDA or EMA.

Table 4:
Alternative regulatory pathways

	Non-emergency	Emergency
US FDA ⁶⁵	Fast track Breakthrough therapy Accelerated approval Animal rule Treatment investigational new drug (IND)	Emergency IND Emergency Use Authorization (EUA)
EMA ⁶⁶	Accelerated assessment Approval under exceptional circumstances Priority Medicines (PRIME)	Conditional market authorisation Marketing authorisation under exceptional circumstances (such as orphan conditions) Article 58 (enables the EMA to give a scientific opinion to the WHO and can be used in an emergency)
WHO	Abbreviated assessment (relying on the work of stringent NRAs to inform a WHO Prequalification decision)	Emergency Use Assessment and Listing procedure

NRAs and WHO have also developed specific emergency processes that allow authorisation for time-limited use of products. The West Africa Ebola epidemic demonstrated the need for such emergency processes and in July 2015, the WHO established its Emergency Use Assessment and Listing procedure (EUAL) for assessing product quality, safety and efficacy during an outbreak. Triggering these processes often requires formal processes that set the bar high, such as a declaration of a public health emergency under the International Health Regulations (2005). The WHO is updating the EUAL process to create an Emergency Use

Listing procedure (EUL) and developing a pre-EUL process, both of which have been out for public consultation⁶⁷. The EUL procedure aims to define the steps that WHO will take to establish eligibility of products, the minimum information required and the process for assessment to make a product available under a limited time listing status. Several options exist for diseases that are not eligible for EUL, including accelerated or emergency assessment under the NRA of the country where the outbreak is taking place (often with support from WHO and regional bodies like AVAREF), or assessment by a stringent NRA whose decision can then be recognised by other countries and WHO.

Which emergency or non-emergency procedure should be followed, or which NRA is carrying out the assessments, is decided on a case by case basis, therefore a major challenge for trial investigators and product developers is to map out which procedures they will have to follow for authorisation or licensure. This has implications for R&D as different data may be required for different regulatory processes, all of which makes investment in product development higher risk. The multitude of options for regulatory pathways for products adds complexity when quick decisions are needed. Clarifying the regulatory authorisation for use and licensure pathways is essential so that these considerations inform R&D and delays in effective products reaching people are minimised.

Developing innovative approaches to R&D that fit the context

Existing ways of doing R&D and delivering interventions may not be effective or practical for infectious diseases emerging in new contexts. Innovative tools, methods and approaches to delivery raise important scientific, ethical and logistical questions. For example, in response to a global shortage of yellow fever vaccine caused by outbreaks in Angola and DRC, the WHO developed a research agenda for fractional dose yellow fever vaccination, which allowed a total of over 30 million people to be vaccinated⁶⁸ (Box 7).

Box 7:

Yellow fever fractional dosing

A 2016 outbreak of yellow fever across central Africa depleted the vaccine stock three times, but large populations remained at risk. Research had shown that using a fifth of a standard dose would still provide protection against the disease for at least 12 months and possibly longer. As a result, fractional dosing was used in Kinshasa, where a total of 7.9 million individuals received a fractional dose⁶⁹. This strategy was also used in Brazil in 2018, when it was implemented in 77 municipalities at the greatest risk of yellow fever⁷⁰.

RCTs such as double-blind placebo controlled studies are traditionally considered the gold standard for evidence. Historically, RCTs are planned at the outset and do not typically allow deviations from the original plans. Using more “traditional” trial designs can be a challenge in research on epidemic risk diseases, where there may not be existing treatments to compare to, or uncertainty on the numbers of people that can be recruited to take part. For example, there are practical challenges with a trial arm treatment that is placebo in an outbreak setting, where the moral imperative is to give people the best possible access to treatment, even if they are investigational. There are examples of when communities are mistrustful of trials where not all patients are receiving the same treatment and care^{71 72}.

Innovative approaches to trials and RCTs, where trial design allows for flexibility for adapting dosages or stopping early for futility can accelerate progress in epidemics R&D. These pre-planned changes can optimise a trial for compassionate access to treatments and efficacy for the greatest number of participants. These new approaches can make carrying out clinical trials in places with disease burden, such as outbreak settings more feasible and produce evidence more quickly by leveraging developments in clinical research and technology. Alternative trial designs include cluster randomised trials and stepped wedge trials. During the West Africa Ebola epidemic, the EMA supported alternative trial designs and concluded “adaptive design would be best utilised as a tool for planning clinical trials in areas where it is necessary to cope with difficult experimental situations”⁷³.

The recent IRNB-NIH Ebola therapeutics trial was designed to collect evidence across outbreaks, countries and time to build a picture of the effectiveness of four drugs (Box 8). Innovative ways of deploying vaccines can be used to ensure that there is sufficient supply and so that issues such as maintaining cold chain don’t become a barrier to effective interventions. Alternative trial designs offer a number of potential advantages, particularly in LMIC settings⁷⁴ and there needs to be more support in how to evaluate, implement and run these complex trials, including ethics and community engagement aspects. The Platform for European Preparedness for Re(emerging) epidemics is looking at adaptive trial design while establishing a common European clinical research infrastructure. Further work to support adaptive clinical trial models that allow flexibility and real-time learning will ensure that people’s health outcomes are improved more quickly in crisis settings.

Box 8:

Multi-drug, multi-site, multi-country Ebola Therapeutics Trial

In the 2018-2019 Ebola outbreak in North Kivu, it became important to move from compassionate use of therapeutics to a clinical trial. Given the limited number of patients and complex environment, a classic trial design wasn’t appropriate, so an alternative design was used. The trial being led by the National Institute for Biomedical Research (INRB) in the DRC, is the first multi-drug, multi-site, and multi-country trial⁷⁵. It aims to compare mortality among patients who receive one of three investigational drugs (Mab114, Remdesivir, REEN-Eb3), with a control group receiving the monoclonal antibody cocktail Zmapp⁷⁶.

Flexibility has been built into the trial design to allow it to be extended to other sites when needed, and the trial protocol allows individual countries to decide what the control arm is. Despite concerns over Zmapp being used as a control because of the resources required to administer it to patients, including a long infusion time and high staffing requirements, DRC did not want standard care to be the control arm. This highlights why quality standards of care are needed to ensure the evidence from these studies are robust, as well as ensuring patients receive consistent, high-quality treatment.

Another example of innovation in trials are human infection studies, which have historically been conducted in high-income countries. Acknowledging that some emerging diseases are not appropriate candidates for human infection studies, these studies have the potential to be more effective and indicate much earlier whether a vaccine or treatment will work than alternative methods. Where appropriate to use, they have the power to rapidly accelerate the development of vaccines and treatments in disease endemics settings, as well as helping to develop them in and for the communities most at risk of these diseases.

Capacity building is needed to ensure that clinical trials, including adaptive trials and human infection studies can take place where they are needed, focusing on technical and clinical skills but also ethics and regulatory capacity so that these studies can be done safely and reliably.

Despite abundant evidence of the efficacy of interventions, practical understanding of how to deliver those interventions effectively in diverse settings and within the wide range of health systems is a challenge⁷⁷. An intervention that has shown effectiveness may not have the same impact in an epidemic setting. Implementation research, which seeks to understand and work within real world conditions rather than trying to control for these conditions or remove their influence as casual effects⁷⁸, can help with the delivery of interventions where they are needed. It is not enough to know if an intervention is effective, it is also necessary to understand why the intervention works, how, for who and in which context. Implementation research should be integrated in the design and review of response activities to epidemics, to ensure continual learning of what works, to inform future preparedness and response activities.

Conclusion

Epidemics have devastating consequences for lives and livelihoods around the world, and can erode the progress made in health systems. A range of R&D activities are critical to understand, prevent and stop these infectious disease outbreaks.

There has been some progress in a number of areas related to R&D for epidemics in recent years, including the fact that research is now widely accepted as an essential element of the response to epidemics and preparedness. Our changing world also offers new opportunities to accelerate progress for a world better prepared for epidemics. More connected societies can share information easily, and cheaper, and developments in data analytics and technologies such as genetic sequencing to be faster, more portable and easier to use mean that we can gain new insights into diseases in real time. But there are also new challenges for R&D in terms of speed, coordination and governance, as research is increasingly being done in epidemic settings.

More systematic thinking and approaches are urgently needed, that move beyond the disease specific and link R&D with critical areas research infrastructure, community engagement, ethics, regulatory pathways and innovative approaches to research. This paper lays out what needs to be done now, to ensure that R&D is harnessed to address epidemics.

Based on our assessment of the challenges for R&D identified in this paper, we propose the following potential solutions for the GPMB and others to consider:

1. **Rationalise the system for coordinating R&D activities** to create more focused global leadership with respect to epidemics R&D, reduce fragmentation, recognise overlaps and accelerating innovation. As part of this, WHO's role needs to be further strengthened and resourced to provide leadership across preparedness and response.
2. **Develop norms**, ethics, and standards of behaviour for all actors including national governments, humanitarian organisations, international organisations, militaries, researchers, and communities.
3. **Develop multi-year plans** for R&D that move **beyond disease specific** approaches, to avoid cycles of panic and neglect.
 - a. These plans should reflect a sustained commitment to R&D **beyond immediate emergencies** and complement national research agendas and centres of research excellence, National Action Plans for Health Security and regional activities.
 - b. Efforts to strengthen in-country R&D capacity should be **more epidemic sensitive than epidemic specific**, addressing day-to-day issues and not focused on building capabilities that are only relevant in the event of an epidemic.
 - c. As long-term plans are developed, international and national research funders should **align their spending** on R&D for epidemics to these, such as R&D Blueprint roadmaps, country-led research agendas for epidemic risk diseases and National Action Plans for Health Security (NAPHS).

4. Plans for R&D should address the following gaps:
 - a. **Systematic integration of social science into response programme** activities, and further training and collaboration opportunities for social scientists to work with response actors across the entire preparedness/response continuum. WHO and implementing agencies, such as UNICEF, need to build on existing efforts and further integrate social sciences into their programmes so that evidence shapes practice.
 - b. Accelerate development of **rapid diagnostics and therapeutics**. Building the foundations for this R&D should include biological reference materials and clinical care standards as well as basic biological understanding of diseases and the factors that affect emergence and transmission, as well as clinical research.
 - c. Expand **R&D for “Disease X”**, including investment in platform technologies for R&D on epidemic risk diseases and harnessing the potential of technological developments such as real-time genetic sequencing and geospatial mapping.
5. Improve the ability to do R&D on epidemic risk diseases
 - a. National regulatory authorities should develop and improve **pathways for emergency use** of products that are fit for purpose.
 - b. Work to expand the use of **adaptive clinical trial models** and other innovative approaches to R&D, that generate the most actionable findings and are appropriate for studying epidemic risk diseases, especially in the places where those diseases happen.
 - c. Significant **strengthening of country capacities**, especially those with few resources, including **ethics, regulatory capacity, and technical and clinical skills**, to ensure that innovative R&D approaches such as adaptive trials and human infection studies are ethical, rigorous and can take place when and where they are needed.
 - d. **Implementation research** should be integrated in the design and review of response activities, to ensure continual learning of what works, to inform future preparedness and response activities.

Annex I:

Experts consulted

We are very grateful for the insights of those who participated in our interviews including:

Katy Athersuch, Senior Policy Advisor, Medecins Sans Frontieres

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Annex II:

Issues that require in-depth analysis and are suggested to be out of scope of this paper

- Preventing the rise of epidemics, addressing environmental, biological and social factors
- How to address barriers to data sharing for research for epidemic risk diseases
- The impact of international frameworks related to sample sharing, such as the Convention on Biological Diversity.
- Market incentives for developing products for epidemic risk diseases, including stockpiling of products
- Development and manufacturing of products, including surge capacity to do so in the event of an outbreak
- In depth analysis of capacity building in epidemic risk countries for clinical trials, diagnostic evaluations, infrastructure, equipment, sample repositories etc.

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