Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Outbreak response as an essential component of vaccine development

Richard Hatchett, Nicole Lurie

The Coalition for Epidemic Preparedness Innovations (CEPI) was created as a result of an emerging global consensus that a coordinated, international, and intergovernmental effort was needed to develop and deploy new vaccines to prevent future epidemics. Although some disease outbreaks can be relatively brief, early outbreak response activities can provide important opportunities to make progress on vaccine development. CEPI has identified six such areas and is prepared to work with other organisations in the global community to combat WHO priority pathogens, including the hypothetical Disease X, by supporting early activities in these areas, even when vaccine candidates are not yet available.

Lancet Infect Dis 2019; 19: e399–403

Published Online June 27, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30305-6

Coalition for Epidemic Preparedness Innovation, Oslo, Norway (R Hatchett MD, Prof N Lurie MD)

Correspondence to: Dr Richard Hatchett, Coalition for Epidemic Preparedness Innovation, London NW1 2BE, UK **richard.hatchett@cepi.net**

Introduction

Over the past two decades, a succession of infectious disease outbreaks and epidemics have challenged the emergency preparedness and response systems of global public health institutions. The 2014–15 Ebola epidemic in parts of west Africa and the 2015–16 Zika virus epidemic in Central America and South America were key events that galvanised global efforts to strengthen global health security.

Examples of the global efforts to prepare for infectious disease outbreaks include the Global Health Security Agenda (GHSA), a partnership of more than 64 countries and international organisations that was established in February, 2014, to strengthen the ability of countries to prevent, detect, and respond to epidemics; the World Bank's Pandemic Emergency Financing Facility (PEF),[1] which was launched in May, 2016, can rapidly make funds available for epidemic response; and the WHO Research and Development (R&D) Blueprint,[2] endorsed in May, 2016, by the World Health Assembly, to increase the speed of medical product development to quell outbreaks. Learning from the lengthy process needed to develop vaccines against epidemic diseases, such as Ebola virus and Zika virus, the Coalition for Epidemic Preparedness Innovations (CEPI), was launched at the Davos Summit in January, 2017, with a mandate to speed the development of vaccines against epidemic diseases.

The global need for CEPI became apparent in the wake of the 2014–15 Ebola epidemic, which exposed deep inadequacies in the responses of the institutions responsible for safeguarding the public against the wide-ranging negative consequences of infectious disease outbreaks.[3] The Ebola epidemic killed more than 11 000 people and cost the economies of Guinea, Liberia, and Sierra Leone, some of the worst affected countries, a cumulative US$53 billion.[4] Despite the public and private sector's successful development and deployment of an experimental vaccine towards the end of the epidemic, the collective response to Ebola virus disease fell short, and a better system to produce effective vaccines against epidemic threats was needed.

CEPI was launched as a response to the emerging consensus that a coordinated, international, and intergovernmental effort was required to develop and deploy new vaccines to prevent future epidemics. As such, CEPI's mission is to stimulate, finance, and coordinate vaccine development against diseases with epidemic potential when market incentives are unsuccessful.

CEPI has prioritised investments in two areas. The first is the development of vaccines against a set of high-priority pathogens, initially the Lassa virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and Nipah virus, and, more recently, Rift Valley fever virus and the chikungunya virus. The second is the development of vaccine platform technologies that will enable rapid vaccine development and manufacturing. CEPI's focus on the high-priority pathogens was informed by WHO's R&D Blueprint for action to prevent epidemics and based on a number of other factors, including the risk of an outbreak occurring, transmissibility of the pathogen, burden of disease, and feasibility of vaccine development.[2] CEPI's investments in vaccine platform technologies aim to expedite vaccine development to improve global capacity to respond to the emergence of an unknown pathogen with epidemic potential (referred to as Disease X in the WHO R&D Blueprint).

For more on **GHSA** see https://www.ghsagenda.org/

CEPI set an initial funding goal of $1 billion, on the basis of an analysis of what it would cost to fund the development of four to six candidate vaccines for two to three diseases on the WHO Blueprint list through to phase 2, and to develop an investigational stockpile of those vaccines.[5] To date, CEPI has secured commitments and aligned investments of more than $750 million toward that goal, which includes investments from Norway, Germany, Japan, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the European Commission, in addition to investments from Australia, Belgium, Canada, and the UK.

For more on **CEPI** see http://www.cepi.net

Initiatives like CEPI, GHSA, PEF, and WHO R&D Blueprint are mutually reinforcing; for example, the PEF has released funds to support the response to the 2018–2019 outbreak of Ebola virus disease in the Democratic Republic of the Congo.[6] Under the rubric of the WHO R&D Blueprint, WHO will publish disease-specific roadmaps, describing key knowledge gaps relevant to the prevention, diagnosis, and treatment of

outbreaks of priority pathogens, including those related to CEPI's development efforts.[7] These roadmaps highlight core product-development needs, including animal models for testing vaccines and biological standards and assays required for assessment of vaccine candidates, which must be addressed to successfully develop and test vaccines. These needs, in turn, are included in CEPI's initial vaccine development projects and other crosscutting initiatives that aim to advance vaccine candidates for these diseases.

The importance and limitations of disease-specific roadmaps

The roadmaps are an important articulation of the knowledge gaps and critical needs that exist for the development of vaccines, diagnostics, and therapeutics for priority pathogens. The development of these roadmaps and the information within them, which have not previously been consolidated into one place, required a major effort led by WHO and its partners, including the members of disease-specific task forces and the Center for Infectious Disease Research and Policy at the University of Minnesota (Minneapolis, MN, USA) among others.

Although the roadmaps are an important starting point for epidemic preparedness, they alone cannot drive progress. Translation of these roadmaps into action is essential. WHO, with its unparalleled ability to convene multisector stakeholders and capacity for global advocacy, will be pivotal to the translation process. However, WHO does not directly support research and will have to work through its partners to make progress. In fact, no single organisation, coordinating authority, or national government is accountable for ensuring that the knowledge gaps outlined in the roadmaps are specifically addressed in a timely manner, especially during outbreak situations, which provide rare opportunities to study the priority pathogens. Clear identification in advance of research activities that can be undertaken during or immediately after an outbreak of the epidemic is also an essential part of preparedness.

The global community will need to come together to fill the gaps identified by the disease-specific roadmaps in an efficient, organised, and coordinated way. In view of its mandate to develop vaccines against diseases that pose an epidemic threat, CEPI is both willing and well positioned to help fill outbreak-related gaps identified by the WHO roadmaps as they relate to vaccine development.

Outbreaks as an opportunity for vital research

CEPI initially envisioned it would support research in an acute outbreak only once the candidate vaccines it is supporting were ready for phase 3 clinical trials. However, it is clear that, while they might often be brief, outbreaks present important opportunities to collect essential data that have the potential to accelerate vaccine and other medical countermeasure development.[8] To take full advantage of these opportunities, closing the gap between the onset of an outbreak and the execution of research is critical.

Outbreaks involving the pathogens highlighted in the WHO R&D Blueprint are sporadic, but they can be deadly. In 2018 alone, there were outbreaks of six of the ten priority pathogens.[9] Therefore, acting with urgency to expedite and optimise the vaccine development work that can be achieved between outbreaks and preparing for the work that can only be done during outbreaks is crucial.

CEPI has identified a set of research activities it believes are needed to accelerate vaccine development, which can be undertaken during outbreaks and before the availability of vaccine candidates that are ready for testing in humans. These activities will hasten vaccine development and result in earlier vaccine deployment in future outbreaks and thus should be prioritised in current plans.

We have identified five areas of vaccine-related research that can be advanced during outbreaks, speeding vaccine development (table). These proposed areas of research build on the WHO R&D Blueprint and disease-specific roadmaps as well as the key components of a research response to public health emergencies identified by Lurie and colleagues[8] and Modjarrad and co-workers.[10]

Although this list of research areas is not exhaustive, it represents a focused set of research and data collection priorities from a vaccine development perspective. Where invited to do so by competent authorities in the affected countries, CEPI stands ready to support these activities as they relate to WHO priority pathogens and Disease X.

The table describes key activities related to vaccine development that can be advanced through research done during outbreaks, along with relevant preparatory actions that should be completed in advance. Tailoring the activities to the needs and capabilities of the countries and investigators involved will be essential. We believe that these efforts, although challenging, can be undertaken alongside and in coordination with WHO and others involved in outbreak-control and outbreak-response efforts and that with careful planning there can be important synergies with these activities. CEPI's long-term goal is the development of vaccines that could affect outbreak control in the future.

Key vaccine development actions that should occur during an outbreak

Sequence, serotype, and share the outbreak strain

Pathogen sequencing has become a normal part of outbreak response and helps clarify the origin of the outbreak and its transmission patterns. Serotyping is important for identifying whether a vaccine candidate is likely to protect against the circulating strain. Access to circulating viruses is crucial for the development of regulatory tools, such as biological standards, assays, and animal models, which are central to vaccine development, testing, and licensure. In addition, newer techniques,

	Actions before an outbreak	Actions during an outbreak
Sequence, serotype, and share outbreak strain	Identify people and agencies, including local investigators, who will be expected to undertake this activity; ensure that MTAs, safe storage and transport, and fair allocation mechanisms for sharing specimens are in place; ensure mechanisms are in place for rapid release of funds to support the research	Sequence, serotype, and disseminate results; share outbreak strain with vaccine and animal model development teams
Collect acute and convalescent blood samples and other body fluid specimens	Identify and fund investigators, including local investigators collaborating with front-line caregivers, who will collect and process specimens and maintain chain of custody; ensure specimen collection and handling is consistent with expected analytic needs; ensure that protocols, MTAs, and safe storage and transport (if needed) are in place; seek preapproval of protocol from ethics committee; ensure funding, supplies, and personnel are ready to begin when outbreak starts	Collect and transport or safely store specimens; if not done in advance with WHO, convene a scientific advisory committee to prioritise how samples should be interrogated and who they should be allocated to
Accelerate development of diagnostic tests that can serve as endpoints for vaccine trials	Determine which diagnostic tests will likely be needed to support vaccine development, particularly tests that are different from those needed for outbreak detection and response; identify possible researchers and organisations who can develop these tests, and ensure protocols and agreements are in place, and that they have needed access to funds; collaborate with the specimen collection effort to ensure panels for test validation are rapidly assembled, and a process for allocating them is in place	Develop and validate diagnostic tests that will be needed for vaccine development; if relevant, ensure additional specimens are available for post outbreak validation and confirmation
Do epidemiological studies essential for vaccine development	Identify and assess current surveillance systems and address key gaps relevant to vaccine development; ensure investigators who will work alongside outbreak response teams to collect data needed for vaccine development, trial design, and planning are trained and prepared; to the greatest extent possible, develop collection and testing protocols with investigators and public health authorities in advance of outbreak, and seek preapproval from the ethics committees; plan coordination between clinical trial teams and outbreak investigators, if a trial or vaccination effort is anticipated (eg, ring vaccination); ensure personnel, supplies, and rapidly available funding are in place	Collect and analyse epidemiological data (eg, seroprevalence, incidence, transmission dynamics, and geographical distribution) to support vaccine trial planning
Understand cultures and beliefs	Identify behavioral and anthropological science team with relevant linguistic and cultural competencies; develop generic protocols for understanding knowledge, attitudes, beliefs in community, and seek preapproval of ethics committees; develop a just-in-time training package for local community members who will be involved in the work; ensure personnel, supplies, funding, and rapidly available funding are in place	Understand community beliefs regarding the disease, its control, and vaccination; provide community education through locally trained and trusted workforce

MTA=material transfer agreement.

Table: **Key vaccine development activities that should occur before and during a disease outbreak**

such as deep sequencing, could be helpful if considered early in the response.

Collect acute and convalescent specimens

Well curated, acute, and convalescent blood (or other body fluid) specimens are crucial, particularly for poorly understood pathogens. Characterising the human immune response to infection is essential for identifying correlates of protection and for developing suitable animal models for vaccine development; an important component of this work is the collection of blood from survivors. Collection of appropriate volumes of antibody-rich serum from survivors are essential for the international standards and assays that are needed for vaccine (and diagnostic test) development, testing, and release, and for comparing one product (or even vaccine lot) with another. Similarly, specimen processing to obtain and analyse peripheral blood mononuclear cells, although a more labour intensive process, is pivotal for the isolation and identification of light-chain and heavy-chain antibody sequences and the development of recombinant antibodies. Such specimens can also be used for the development of rapid diagnostic tests, vaccine design, therapeutics, and for the identification of correlates of protection, which can be useful as surrogate endpoints in vaccine trials. Validated measures of immune response are required before any regulatory authorisation for vaccine use can be granted. Such measures do not currently exist for Lassa virus, MERS-CoV, or Nipah virus, CEPI's initial priority pathogens, nor will they exist for the hypothetical Disease X. Ideally, the scientific community should agree on priorities for specimen analysis in advance of an outbreak, and the collection and distribution effort should be designed to serve the needs of vaccine, diagnostics, and therapeutics developers. However, if a disease outbreak occurs and consensus on an analysis plan has not been reached, specimens could be safely processed and stored, maintaining a chain of custody in a national or regional biobank until the outbreak has ended and a scientific consensus on their analysis can be achieved.

Accelerate development of diagnostic tests that can serve as endpoints for vaccine trials

Diagnostic tests can serve multiple functions, including surveillance, diagnosis, and the guidance of clinical decision making. Development of diagnostic tests specifically for vaccine development might not be of the highest priority during an outbreak response. However, these tests are required to guide an outbreak response and are likely to aid the performance of epidemiological studies, the organisation of vaccine clinical trials, and the measurement of the immune response. Diagnostic-test developers can facilitate vaccine development by focusing on tests (eg, highly accurate PCR tests and serological assays) that can simultaneously support rapid case identification and management while serving as clinical endpoints for regulatory vaccine trials. Given the low number of and poor access to health care and laboratory infrastructure in the countries where some of the WHO priority pathogens are endemic, newer techniques that support the development of both point of care testing and antigen detection that can be used in vaccine trials (eg, next-generation sequencing and

targeted genome or pathogen capture methods) should be prioritised.

Implement epidemiological studies essential for vaccine trial design

Epidemiological studies are not only essential for disease prevention and control but also for planning and preparing clinical trials of promising vaccine candidates. Understanding of how to better prevent and control many of these diseases will only be possible through targeted epidemiological studies during outbreaks. Establishing the baseline incidence, seroprevalence, and transmission dynamics of the target disease, determining the role of vectors and potential need for animal vaccines, identifying disease hotspots, elucidating seasonal patterns of exposure, understanding the full clinical spectrum of illness, and having a validated widely shared case definition that can serve as a trial endpoint will facilitate planning for and increase the efficiency of clinical trials done both in the interepidemic period and during an outbreak. Given the sporadic and unpredictable occurrence of outbreaks, the study designs suitable to different prototypes of transmission dynamics, and infrastructure must be in place and tested before an outbreak begins. Even if vaccines are licensed through alternative pathways, such as the US Food and Drug Administration's Animal Efficacy Rule, post-licensure effectiveness data will need to be generated during outbreaks. Doing epidemiological studies in populations at risk before the implementation of clinical trials will also strengthen local research capacity and facilitate community engagement, which in turn might result in better enrolment in vaccine effectiveness studies.

Understanding cultures and beliefs

Social and anthropological factors will affect disease control and, ultimately, serve to guide community mobilisation and facilitate vaccine acceptance. Having a safe and effective vaccine that is unacceptable to a population who could benefit from it would represent a failure of vaccine development and outbreak management. Outbreaks represent a time of both fear and of exceptional focus, presenting important opportunities for behavioral and anthropological science team to enhance understanding of knowledge, attitudes, and beliefs that might shape participation in clinical trials and vaccine acceptance more generally.

CEPI's role in outbreak research

Recent accounts of the challenges facing research during outbreaks are sobering but motivating, highlighting both progress and the importance of good preparation, and operational and diplomatic excellence.[11] The WHO R&D Blueprint, disease-specific roadmaps, and Global Coordination Mechanism are fulfilling essential roles in highlighting research gaps related to outbreaks, coordinating aspects of the research response, research funding during outbreaks, and highlighting the research priorities of affected countries. Our goal in this paper is to highlight the research areas that are central to vaccine development and important subsets of outbreak response activities.

Because planning is central to any disease outbreak research effort, CEPI has begun to identify and support preparedness activities that will enable a rapid research response in areas essential for vaccine development, even before vaccine candidates are ready for human trials.

Using Lassa fever research as proof of concept for preparatory research activities that can be done in advance of clinical trials, CEPI issued calls for proposals aimed at collecting blood specimens from survivors of Lassa fever, to allow better characterisation of the immune response and to accelerate the development of assays and standards in September 2018.[12] Similarly, CEPI will fund collaborative efforts among research groups to analyse epidemiological data needed to design and support vaccine trials.[13] Both efforts require research teams in endemic countries to be preidentified, have protocols that have been reviewed, at least provisionally, by national ethics committees, have good working relationships with their respective ministries of health and frontline caregivers, and be able to engage with communities.

CEPI is committed to data sharing and transparency. The coalition is a signatory to the WHO statement of Public Disclosure of Clinical Trial Results[14] and is committed to publish its data in open access journals. CEPI expects the research teams it supports to uphold these commitments. If these Lassa virus-related efforts are successful, CEPI will support related efforts for MERS-CoV and Nipah virus.

CEPI has set aside funds for vaccine development during outbreaks and, pending vaccine availability at the time of an outbreak, the coalition stands ready to support the research response areas described previously for the priority pathogens and for unknown pathogens against which vaccine development is contemplated. The knowledge generated through this research is crucial for vaccine development and planning for clinical trials. The activities outlined in the table should be viewed as necessary to initiate or accelerate vaccine development but they might also be useful in clarifying whether, and how far, vaccine development should proceed. Given the magnitude of investment needed to develop a new vaccine and take it to licensure, CEPI anticipates that its early funding of these types of activities will be essential for rapid decision-making processes involving a wide range of global stakeholders. CEPI will work closely with affected countries and the WHO Emergencies Programme to coordinate and support this potentially catalytic work.

CEPI is both a freestanding organisation and a coalition, and its mandate to speed the development of vaccines means that in the event of an outbreak of a new disease, or if such provisions are not in place when an outbreak begins, CEPI will work with affected countries and global partners through the Global Coordination

Mechanism to support the conduct of such critical work as quickly as feasible. CEPI will continue to work with the international community on plans to implement vaccine trials during an outbreak once its vaccine candidates reach an appropriate stage of development, and to establish investigational vaccine stockpiles. Ultimately, development of a response to outbreak research will be pivotal to the success of CEPI's mission to advance vaccines against epidemic diseases.

Contributors
Both of the authors contributed equally to the conceptualisation and writing of this paper

Declaration of interests
We declare no competing interests

References

1 World Bank. Pandemic emergency finance facility. http://www.worldbank.org/en/topic/pandemics/brief/pandemic-emergency-financing-facility (accessed Oct 2, 2018).
2 WHO. About the R&D Blueprint. 2016. http://www.who.int/blueprint/about/en/ (accessed Oct 2, 2018).
3 Moon S, Sridhar D, Pate MA, et al. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. *Lancet* 2015; **386:** 2204–21.
4 Huber C, Finelli L, Stevens W. The economic and social burden of the 2014 Ebola outbreak in west Africa. *J Infect Dis* 2018; **218:** S698–704.
5 Gouglas D, Thanh Le T, Henderson K, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. *Lancet Glob Health* 2018; **6:** e1386–96.
6 World Bank. World Bank Group's Pandemic Emergency Financing Facility (PEF) makes first $12 million commitment to bridge financing gap for ebola response in DRC. 2018. https://www.worldbank.org/en/news/press-release/2018/05/22/world-bank-groups-pandemic-emergency-financing-facility-pef-makes-first-12-million-commitment-to-bridge-financing-gap-for-ebola-response-in-drc (accessed June 4, 2019).
7 CIDRAP. WHO roadmap development: development of roadmaps for priority pathogens of concern. http://www.cidrap.umn.edu/ongoing-programs/who-roadmap-development (accessed Oct 2, 2018).
8 Lurie N, Manolio T, Patterson A, et al. Research as part of public health response. *N Engl J Med* 2013; **368:** 1251–55.
9 Weber L. More dangerous outbreaks are happening. Why aren't we worried about the next epidemic? 2018. https://www.huffingtonpost.com/entry/outbreaks-epidemic-preparedness_us_5b4f85fbe4b0de86f4892daa (accessed Oct 2, 2018).
10 Modjarrad K, Moorthy V, Embarek P, et al. A roadmap for MERS-CoV research and product development: report from a World Health Organization consultation. *Nat Med* 2016; **22:** 701–04.
11 Haug C. Keeping Your cool—doing Ebola research during an emergency. *N Engl J Med* 2018; **378:** 2353–55.
12 CEPI. Past call for proposals, biological standards and assays. Biological standards to support and accelerate Lassa fever vaccine development. https://cepi.net/get_involved/cfps/ (accessed June 4, 2019)
13 CEPI. Past call for proposals, data collection. Preparing for Lassa vaccine trials with targeted epidemiology studies. https://cepi.net/get_involved/cfps/ (accessed June 4, 2019).
14 WHO. Joint statement on public disclosure of results from clinical trials. https://www.who.int/ictrp/results/jointstatement/en/ (accessed Oct 2, 2018).