DISEASE X: THE PRACTICAL CHALLENGES OF VACCINATING AGAINST THE UNKNOWN

R&D Challenges

A re-analysis in light of the 2020 COVID-19 pandemic

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"Disease X, we said back then, would likely result from a virus originating in animals and would emerge somewhere on the planet where economic development drives people and wildlife together. Disease X would probably be confused with other diseases early in the outbreak and would spread quickly and silently; exploiting networks of human travel and trade, it would reach multiple countries and thwart containment. Disease X would have a mortality rate higher than a seasonal flu but would spread as easily as the flu. It would shake financial markets even before it achieved pandemic status. **In a nutshell, COVID-19 is Disease X.**"

- Dr Peter Daszak, WHO R&D Blueprint

In 2018, a group of a students from Polygeia, a student-run global health think-tank, produced a policy report outlining recommendations for governing global health organisations which could be implemented to improve preparedness for the emergence of 'Disease X'.[1] The third section of this report, **'R&D Challenges'**, presented a review of the challenges facing the rapid research and development of a vaccine in response to a novel pathogen, and the current policies in place to address those challenges. We identified a number of areas for investment and improvement, which we suggested should be overseen by a central governing body.

Here, we present an updated version of this section of the report, discuss each of the challenges we identified in relation to the **COVID-19 pandemic**, and make a number of further recommendations to develop a sustainable and expedited vaccine R&D response moving forward.

Executive Summary

1.1.1 Problem statement

At the time of writing, around 5,404,512 cases of COVID-19 have been confirmed globally, with 343,514 recorded deaths. In order to suppress the pandemic, estimates based on the basic reproduction number (R_0) state that at least 60% of the population must be immune. The only safe way to achieve herd immunity is through vaccination. However, attempts to develop a vaccine against previous epidemic coronaviruses, SARS-CoV and MERS-CoV, have not as of yet come to fruition.

There are three main factors that contribute to the lengthy periods of time required for vaccine R&D:

1. **The lack of adaptable vaccine platforms**, without which the R&D process needs to start from scratch, with each new vaccine requiring its own safety and efficacy trials and regulatory procedures.
2. **The complex guidelines for regulatory approval and licensing**, requiring comprehensive but time-consuming clinical trials.
3. **Lack of funding and incentivisation** due to lack of public demand, lack of incentive, or lack of understanding of the risk posed by a pathogen.

1.1.2 Recommendations

This report reiterates the need for a central organisation to oversee the end-to-end **vaccine R&D** response to **emerging viral pathogens**, named 'Organisation X' below. This organisation should:

a. Improve **collaboration, coordination and conversation** between relevant stakeholders, primarily the WHO Strategic and Technical Advisory Group for Infectious Hazards and R&D Blueprint, CEPI, Gavi, academic institutions, industry representatives and any new council focussed on the emerging infectious disease response.
b. Focus on the **technical, scientific and policy-based challenges** facing end-to-end vaccine development, from basic scientific research to licensure. Although not covered in this report, this should also cover vaccine manufacture and access.

As the Coalition for Epidemic Preparedness (CEPI) evolves from focussing on acceleration of simply phase II clinical development, to the end-to-end response, we believe they may become well-placed to take on this role.

After discussing the challenges facing the acceleration of vaccine R&D with respect to the COVID-19 pandemic, we make a number of secondary recommendations for Organisation X and other current stakeholders.

	Recommendations	Directed at
1	Support and fund research investigating **families of viruses** with epidemic potential	The WHO, CEPI, research funders, local governments, Organisation X
2	Coordinate the development of **animal models** for all priority diseases	The WHO, CEPI, research funders, local governments, Organisation X
3	Facilitate the **sharing of data** and information	The WHO, CEPI, Organisation X, journals
4	Develop **sustainable research infrastructure** in LMICs	The WHO, CEPI, Organisation X
5	Facilitate **international collaboration**	The WHO, CEPI, Organisation X
6	Develop accessible and comprehensive **ethical guidelines** for conducting vaccine clinical trials during pandemics with regards to: • Clinical trials in LMICs • Conducting clinical trials prior to/alongside tests in animal models • Clinical trials in at-risk populations • Clinical trial designs with placebo groups • Human challenge studies	The WHO (Working Group on Ethics & COVID-19)
7	Build relationships between international and local **ethics boards**	The WHO (Working Group on Ethics & COVID-19)
8	Tackle **misinformation** by ensuring internet users are directed to reliable sources of information	The WHO (Vaccine Safety Net and R&D Blueprint), CEPI, Organisation X
9	Work to **increase trust** between the public, researchers and regulatory authorities	All
10	Conduct quantifiable research into **vaccine hesitancy** among populations	The WHO, local governments
11	Prioritise research to understand the **immunopathology** of COVID-19	The WHO, CEPI, research funders, local governments
12	Ensure **regulatory preparedness** by developing Master Protocols for priority diseases and frameworks for emerging pathogens	The WHO, CEPI, Organisation X, local regulators
13	Enhance coordination of clinical trials through **multi-trial platforms**	The WHO, CEPI, Organisation X, vaccine developers
14	Establish a platform for the sharing of reagents and protocols required for **standardised assays**	CEPI, Organisation X

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Note: *All information about SARS-CoV-2 and the COVID-19 pandemic is correct as of the 25th May 2020.*

1 Introduction

Historically, the average time taken for vaccine research and development (R&D) from identification of the pathogenic agent to vaccine licensure is 30 years,[2] making it the rate-limiting step in vaccine production and supply during an epidemic. The 2013-2016 West Africa Ebola virus (EBOV) epidemic demonstrated that is possible to accelerate these responses, even under extremely challenging circumstances. Devastatingly, the response was not fast enough: delays in collecting clinical trial data and acquiring regulatory approval meant that vaccine distribution was not widespread. Out of 28,000 people infected, 11,310 lost their lives. This outbreak prompted an unprecedented reaction from the global health community, with the emergence of several new organisations and funding bodies aimed at conceptualising ways of expediting the R&D response and developing a sustainable model for vaccine development.

Each year the WHO publishes a list of priority diseases, earmarked for accelerated research and development in recognition of their public health risk and current lack of viable medical countermeasures. For the first time, in 2018, this list included "Disease X", which "*represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease*".

On the 31st December 2019 the Wuhan Health Commission, Hubei province, China, reported a cluster of atypical cases of pneumonia with unknown aetiology.[3] By the 9th January 2020, the causative agent had been identified as a novel coronavirus, later named SARS-CoV-2. The following two months saw the confirmation of human-to-human transmission, transmission to 114 countries around the globe, and the implementation of large-scale social distancing and quarantine procedures, leading to the declaration of the outbreak as a global pandemic by the WHO on the 11th March.[4] At the time of writing, around 5,404,512 cases have been confirmed globally, with 343,514 recorded deaths.[5] Dr Peter Daszak, a member of the WHO R&D Blueprint group who coined the term 'Disease X',[6] has stated that COVID-19, the disease caused by SARS-CoV-2, meets the requirements to be the first Disease X. Predictions that Disease X would be caused by a respiratory-borne viral pathogen with an RNA genome,[7] appear to have been realised.

In this report, we present a rapid review of the challenges facing R&D of vaccines for emerging infectious diseases and previously proposed solutions to those challenges. We then discuss each of the challenges with respect to SARS-CoV-2 biology and the 2020 COVID-19 pandemic, and make a number of recommendations for the current and subsequent epidemics. Other important challenges facing the timely and widespread distribution of a vaccine involve manufacturing, distribution and access, which are considered beyond the scope of this report.

1.1 Why do we need a vaccine?

SARS-CoV-2 can be transmitted by infected individuals in the absence of, or before the onset of symptoms.[8] This makes it very difficult to control the spread of the virus through social distancing and quarantine measures. In order to a control an epidemic caused by a pathogen with a basic reproduction number (R_0) of greater than 1 (meaning that spread is sustained), herd immunity needs to be achieved. Herd immunity refers to the indirect protection of a whole population when a proportion of that population is immune to the virus, through either vaccination or natural infection. It is estimated that herd immunity to COVID-19 will be achieved when at least 60% of the population is immune. Vaccination is the **only safe way** to achieve herd immunity without the morbidity and mortality caused by the natural virus infection. Moreover, some studies suggest that natural immunity to SARS and MERS may be relatively short lived, with neutralising antibody titres waning after 2-3 years.[9] In contrast, an optimal vaccine regimen with booster doses could induce life-long immunity. To date, there

is no licensed vaccine for SARS-CoV, MERS-CoV or SARS-CoV-2.[10] The challenge now is to develop and license a vaccine for SARS-CoV-2, much faster than has been achieved for other coronaviruses.

1.2 Vaccine platform technologies

One of the main solutions to the lengthy amount of time required for vaccine R&D is the use of **vaccine platform technologies**, which will be discussed frequently in this report. Vaccine platform technologies are based on a highly adaptable module, usually **nucleic acid** or a **viral vector**, which is used to deliver a viral protein into the body.[11] This protein, or 'antigen', mimics the virus and induces immunity **(Figure 1)**. Once developed and licensed for one disease, development of future vaccines simply requires substitution of the genetic code encoding the desired antigen, enabling faster development, production and regulatory approval, as well as reducing costs.[11–13] The use of platform technologies in the past has meant that the time from viral sequence selection to initiation of phase I clinical trials was shortened to around 3 months.[14]

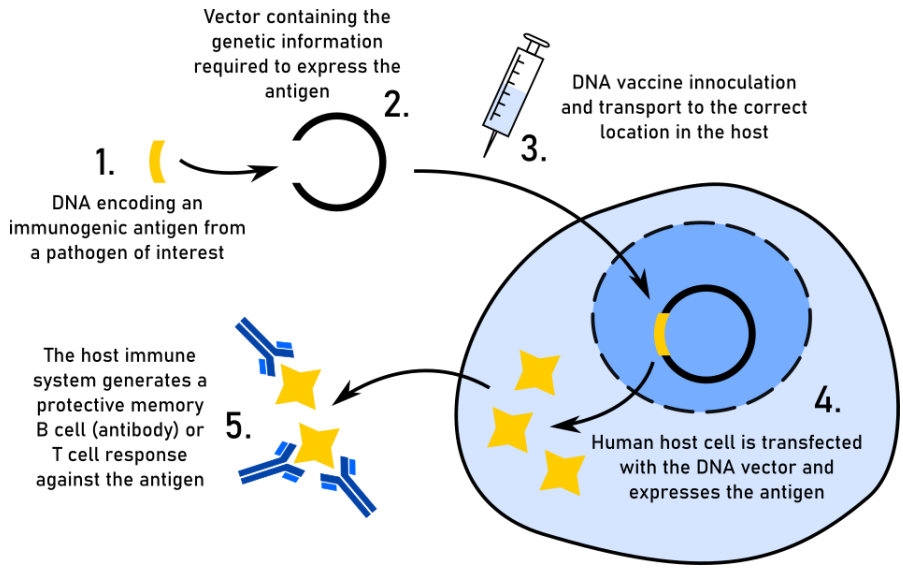

Figure 1: *Mechanism of action of a vaccine based on a DNA platform*

1.3 Stakeholder analysis prior to COVID-19

The end of the 2013-2016 Ebola crisis saw the emergence of several institutions aiming to promote global epidemic preparedness.

The **Coalition for Epidemic Preparedness Innovations (CEPI)** was launched in 2017 and is governed by the governments of Norway, Japan, Germany and India, the Wellcome Trust, Bill and Melinda Gates foundation and the World Economic Forum.[15] Their mission is 'to stimulate, finance and co-ordinate vaccine development against diseases with epidemic potential in cases where market incentives fail' by a) bringing priority vaccine candidates through the end of phase II clinical trials and b) investing in vaccine platform technology that can be rapidly deployed against known and unknown pathogens. As of March 2019, CEPI had awarded a potential sum of $300 million to a number of international academic institutions and pharmaceutical companies for the development of Nipah, Lassa and MERS virus vaccines,[16] and had started inviting submissions to develop vaccines against Chikungunya and Rift Valley Fever. CEPI had also begun to invest in its second aim of developing vaccine platforms for unknown pathogens; $10.6m was allocated to the University of Queensland to develop a molecular clamp platform, $8.4m to Imperial College London for development of a self-amplifying RNA (saRNA) platform, and $34m to CureVac to develop an mRNA vaccine platform. CEPI is currently only resourced to fund development up until phase II trials, but has the goal of eventually aiding end-to-end

development.[17] More recently, CEPI has been focussing on enabling a set of research activities required to accelerate vaccine development, including the development of biological standards and assays, animal models, epidemiological studies, diagnostics, clinical trial capacity and sustainable manufacturing.[18] A limitation of the CEPI funding model is the absence of a policy negotiating public interest conditions prior to funding. The organisation originally had an access policy, committing the recipients of their funding to affordable pricing and equitable access for any vaccine developed, but this was reversed in December 2018.[19]

The **Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)**, is an international initiative with the aim of facilitating communication and collaboration between its 27 member funding bodies.[20] The initiative has four main aims: a) to create links between clinical trial networks, b) to build a framework to facilitate data sharing during epidemics, c) to identify scientific gaps and address research challenges and d) to improve rapid delivery of funds to research projects upon emergence of a new epidemic.

The **World Health Organisation (WHO)** has several **committees and initiatives** aimed at improving vaccine R&D responses. One example is the **Initiative for Vaccine Research**, which facilitates vaccine R&D against pathogens with significant disease and economic burden.[21] In addition, the WHO co-hosts The **Global Vaccine and Immunization Research Forum (GVIRF)**, with the aim of discussing challenges, opportunities and actions in the vaccine R&D field.[22]

Of particular importance is the WHO **R&D Blueprint**, a strategy and preparedness plan to expedite R&D activities during epidemics.[6] It is run by a central **Scientific Advisory Group** and works with partners such as CEPI and GloPID-R. The Blueprint works on the basis of a list of priority pathogens. In February 2018, this list was updated to include Disease X, on the basis that an epidemic could be caused by a pathogen currently unknown to cause human disease.[23] For each priority disease, **R&D Roadmaps and Target Product Profiles** (TPPs) are generated and the appropriate regulatory and ethical pathways identified and developed. TPPs define a set of product characteristics to provide technical guidance to vaccine manufacturers,[24] including the target population, dosing regimen, duration of protection, route of administration, and safety and efficacy requirements. The 2015-2016 Zika epidemic provided an opportunity to use the Blueprint in a real-life scenario and evaluate its effectiveness. It took 5 months from the declaration of the outbreak as a Public Health Emergency of International Concern to generate TPPs for Zika virus diagnostic tests and vaccines. The R&D Blueprint have also established a '**Global Coordination Mechanism**' (GCM), to facilitate a regular dialogue between the stakeholders for R&D preparedness and the response to emerging diseases.[25]

Another important initiative developed by the WHO is the **Emergency Use Listing** (EUL) procedure for vaccines, which can be used to expedite the availability of vaccines needed in a public health emergency, without going through rigorous licensing procedures.[26,27] In terms of the wider outbreak response, within which R&D is one element, **the Strategic and Technical Advisory Group for Infectious Hazards** (STAG-IH) was set up following recommendations from the Review Committee on the Role of the International Health Regulations in the Ebola Outbreak and Response.[28] Despite identifying Disease X as a priority pathogen, there is no section of the WHO or the R&D Blueprint specifically focussed on expediting vaccine development in response to *emerging* pathogens.

Local governments can also play a role, with a large amount of funding for vaccine R&D coming from public sources. The **UK Vaccine Network** brings together experts from industry and academia to advise the UK government on the most promising investment opportunities to help combat infectious diseases with the potential to cause an epidemic.[29] Under this advice, the **UK government** committed to invest £120 million in vaccine development projects between 2016 and 2021. As of March 2019, £70 million was being used to fund 60 projects throughout the UK, and £10 of funding pledged to CEPI.[30,31]

In summary, the stakeholders involved in the response to emerging infectious diseases include a variety of formal and informal, public and private organisations, with different aims, resources and accountability. Whether this format is optimal to tackle a problem that requires impartiality and multi-disciplinary global collaboration is disputed.[32]

1.4 Stakeholder response to COVID-19

In response to the COVID-19 outbreak, **CEPI** has distributed funding to several pharmaceutical companies and academic institutes to aid the development of COVID-19 vaccine candidates, including Inovio, Moderna Inc., the University of Queensland, CureVac, GSK, Novavax Inc., the University of Oxford, the University of Hong Kong, and the Institut Pasteur.[31]

> "We face one of the greatest challenges humankind kind has faced in the last century: a disease that has spread globally, that is most dangerous to the most vulnerable members of our society, and that threatens our economic order and very way of life"
>
> **– Dr Richard Hatchett, CEO of CEPI**

In addition to their role in coordinating the global response to COVID-19 and advising member states, the **WHO** is also a key player in the R&D response. The **R&D Blueprint** was activated in early January 2020 to accelerate diagnostics, vaccines and therapeutics, and allowing transparent and coordinated information sharing. The Blueprint team established several ad hoc expert working groups, including those focussed on developing a vaccine target product profile, animal models, assay development, Master Protocol writing, clinical trial design, disease modelling, and vaccine prioritisation. These all report to the Scientific Advisory Group (SAG), which provides the WHO with strategic and scientific advice on research priorities.[33] The R&D Blueprint SAG, together with **GloPID-R**, have produced a '**Global Research Roadmap**' to identify immediate, mid- and long-term priorities in order to build a robust global research response, and to ensure the development of sustainable global research platforms that are prepared for the next Disease X epidemic.[33] The Blueprint **Global Coordination Mechanism** (GCM) has the role of facilitating collaboration and data sharing, working with GLOPID-R to coordinate and fast-track contributions from funders.[33]

In April 2020, the **UK government** launched a new **Vaccine Taskforce** to coordinate vaccine R&D efforts.[34] This included a £14 million investment to be shared among 21 research projects working on vaccine development and testing, following an allocation of £10.5 million to 6 UK-based research projects working on various aspects of coronavirus biology. These projects include the phase I/II trial of ChAdOx1, a replication-defective chimpanzee adenovirus vaccine vector (Professor Sarah Gilbert, University of Oxford), and the development of large-scale manufacturing processes for adenovirus vaccines like ChAdOx1 (Dr Sandy Douglas, University of Oxford). The UK government has also given a total of £250 million to **CEPI**.[35]

Gavi, The Vaccine Alliance, brings together key stakeholders in global immunisation from a technical and financial background, such as the WHO, UNICEF, the World Bank and the Bill & Melinda Gates Foundation. Gavi has worked together with the WHO to come up with innovative funding mechanisms to raise money on the markets for ensuring the supply of vaccines to LMICs, and will likely be a key player in ensuring that when a vaccine does eventually become available, it is available to everyone.

2 Challenges, solutions and COVID-19

2.1 Research and pre-clinical development

The development of vaccines follows a number of stages. Pre-clinical development involves research using in vitro lab-based techniques and in vivo studies on animal models. It involves:

a. Identification of the antigens capable of eliciting an immune response
b. Deciding on the method of delivery/vector
c. Evaluation of vaccine efficacy in lab-based assays and animals
d. Evaluation of safety of the candidate vaccine and identification of a safe starting dose
e. Manufacture of the vaccine to Good Manufacturing Practice standards
f. Application to the country's drug administration

At the time of writing, there are 115 candidate vaccines for COVID-19 in preclinical evaluation.[36] An updated rapid review of the challenges facing research and pre-clinical development of vaccines to emerging pathogens, examples and the current solutions being put in place to address these challenges is shown in **Table 1** of the Appendix. In the following sections we discuss each of these challenges with respect to the COVID-19 pandemic.

2.1.1 Challenge 1: Lack of existing literature and research into novel viruses

SARS-CoV-2 shares around 79.5% of its genetic code with the coronavirus SARS-CoV.[37] This has meant that previous research into SARS-CoV has allowed predictions of the relevant immunogenic epitopes and the immune correlates of protection related to SARS-CoV-2, and has greatly expedited this first step of vaccine R&D.[38] Although the genetic code differs too much for SARS-CoV vaccines to be protective against SARS-CoV-2, the previous development and testing of SARS-CoV vaccines will greatly aid SARS-CoV-2 vaccine development. Although there were only a small number of SARS-CoV vaccines in phase I clinical trials at the start of the SARS-CoV-2 outbreak, preliminary results from these trials were encouraging, as the vaccines were safe and induced a protective antibody response.[39]

A number of research groups and companies developing vaccines for SARS and MERS (e.g. Novavax) were able to adapt their platforms to SARS-CoV-2 in just a couple of weeks. Many vaccines in development utilise the SARS-CoV-2 spike protein (S) as the vaccine antigen – the corresponding protein in SARS and MERS has been shown to elicit strong neutralising antibody responses and long-lasting T cell responses.[40] Despite the genetic similarity, the immune response generated to different coronaviruses can vary in length significantly, with evidence of re-infection with some human coronaviruses.[9] Understanding the immune response to SARS-CoV-2, including identifying which aspects of the immune response are most protective, and how long these immune responses last, will be crucial for vaccine development and for directing the public health response.

Recommendation 1: Support and fund research investigating families of viruses with epidemic potential

Without prior knowledge of MERS and SARS coronaviruses, the initial research phase of COVID-19 vaccine development would have been greatly restricted. In the future there should be increased funding of research investigating *families* of viruses that have not been known to cause epidemics, but have epidemic potential.

2.1.2 Challenge 2: Lack of good animal models

Commonly used small laboratory animals such as mice are not naturally susceptible to SARS-CoV and MERS-CoV disease, meaning animal models are lacking.[41] As different coronaviruses use different cellular receptors for entry, the range of hosts they can infect also differs.[42] However, SARS-CoV-2 has been shown to use the same entry receptor as SARS-CoV (ACE2), meaning animal models developed for SARS-CoV, including Syrian hamsters, ferrets and macaques, may be of use.[43–45] More information about coronavirus animal models can be found in an extensive review by Yuan *et al*.[46]

The use of transgenic mouse models and/or organoid/3D tissue systems may permit the study of coronaviruses without traditional animal models.[47,48] Transgenic mice expressing the human ACE2 receptor, which were originally developed to study SARS-CoV, have been shown to be susceptible to SARS-CoV-2, although only show mild disease.[49] Although potentially useful, there are currently not enough of these mice for large-scale testing of vaccines that are being developed across the world.[50]

In the Global Research Roadmap, the WHO identified a priority 'to develop and standardise animal models to evaluate the potential for vaccine and therapeutics effectiveness and to understand the potential for enhanced disease after vaccination'.[33]

Recommendation 2: Coordinate the development of animal models for all priority diseases

There is need for a central organisation to coordinate the development of animal models for all pathogens on the WHO R&D Blueprint list of priority diseases, as well as general research into the properties and use of animal models, including transgenic mouse models. There should be an aim to characterise the immune responses and clinical outcomes in animal models for all virus families with epidemic potential. Such an organisation should work together with CEPI, who are already funding research in this area.

2.1.3 Challenge 3: Lack of data sharing

The WHO Global Research Roadmap defines the timely sharing of all data as an immediate priority.[33] Many international academic journals have stated their commitment to the rapid review and dissemination of articles about COVID-19. Several data sharing forums have been created, including the Lancet COVID-19 resource centre, the NEJM coronavirus page and the Cell Press Coronavirus Resource Hub.[51] A statement on data sharing during the COVID-19 outbreak made by the Wellcome Trust has been signed by more than 120 organisations, journals and publishers.[52]

Recommendation 3: Facilitate the sharing of data and information

Although there has been a great effort to ensure the timely sharing of data during the COVID-19 pandemic, there is need for a global central body to coordinate the data sharing response. This group would need to lead pre-negotiations between R&D stakeholders, pharmaceutical companies, national governments, journals, humanitarian organisations and academics to facilitate timely sharing of data and materials.[113,114] Moving forward, there is need to coordinate data on all virus families of pandemic potential, and to facilitate the sharing of pathogens, virus sequences, reference reagents and protocols, not only during public health emergencies **(Section 2.3.1)**.

2.2 Clinical development

Clinical development involves the testing of candidate vaccines in humans. It involves four phases that usually take place over several years **(Figure 2)**. **Table 2** (Appendix) highlights the challenges facing clinical development, examples and the current solutions being implemented to address these challenges. At the time of writing, there are 10 candidate vaccines in clinical evaluation, the most promising of which are described in a review by Calina *et al.*[53]

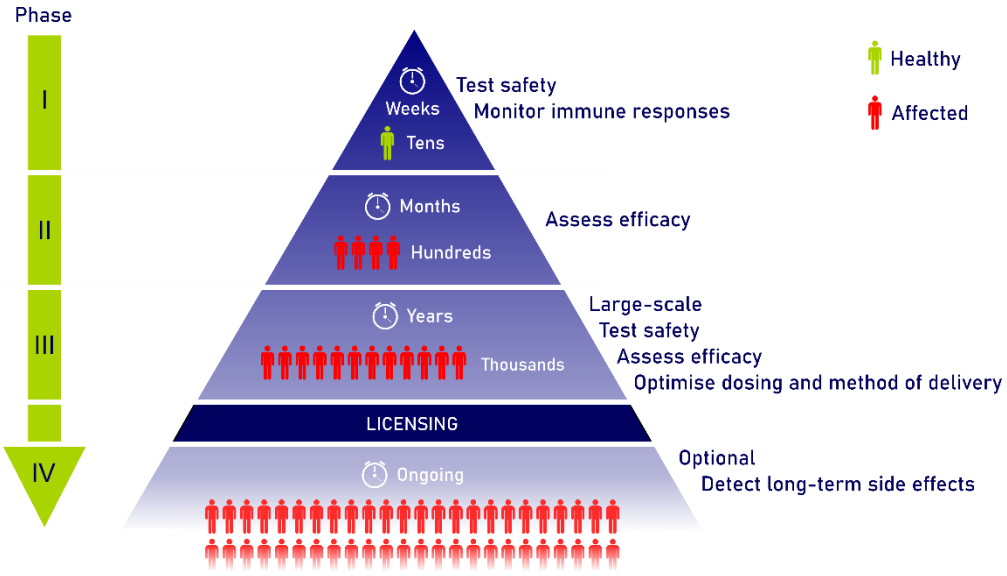

Figure 2: *The phases of clinical vaccine development*

2.2.1 Challenge 4: Changing epidemiology/unpredictable nature of epidemics

Although COVID-19 is currently widespread in many countries, it is likely that many of these outbreaks will be brought under control by quarantine and social distancing measures before any vaccine candidates are ready for phase III studies. Solutions include epidemiological model for identifying suitable trial locations, as well as strategized clinical trial design targeting at-risk populations such as essential workers. Countries at earlier stages in their epidemic curves, or countries where the epidemic curves are likely to progress much slower, may provide feasible scenarios for phase III trials, but this comes with a number of ethical and logistical challenges (see **Section 2.2.3**). It has been proposed that human challenge studies on young, healthy adults could replace phase III trials in order to expedite licensing.[54] A number of scientists have argued against this, describing not only ethical issues but questioning how quickly a proper human challenge study could be conducted.[55]

2.2.2 Challenge 5: Lack of infrastructure required to conduct clinical trials

LMICs across the globe account for a large amount of genetic diversity.[56] If this diversity is not accounted for in clinical trials, it is not possible to generalise clinical trial results to the global population.[57] In resource-poor settings, clinical trials not only test the efficacy of the vaccine but also assess whether the intervention is affordable and adaptable to the specific health-care system and their populations.[58] The WHO SOLIDARITY trial aims test potential treatments and vaccines across all continents, but will face challenges in LMICs where infrastructure required to conduct clinical trials is not readily available.[59]

There are a number of stakeholders working to increase clinical trial infrastructure, particularly in Africa. The African Academy of Sciences are spearheading an effort to develop an open-access Clinical Trial Community (CTC) platform to unify key players in the clinical trial field and identify groups

capable to evaluate potential vaccines.[60] Secondly, the COVID-19 Clinical Research Coalition aims to accelerate COVID-19 research in resource-limited settings, and has recognised a need to identify and support existing clinical trial sites.[58] Finally, the European and Developing Countries Clinical Trials Partnership has called for interest to strengthen research capacities in sub-Saharan Africa, and has donated €18 million to support multi-country clinical trials.[61]

Although this is primarily a problem for LMICs, the lack of adaptable infrastructure in higher income countries has limited their public health responses and testing capabilities, and will also influence their ability to perform clinical trials.

Recommendation 4: Develop sustainable research infrastructure in LMICs

In regards to LMICs there must be a focus on the development of sustainable research infrastructure that will not only facilitate clinical trials, but has the co-benefit of supporting clinical research into COVID-19 and other diseases. There should also be a focus on increasing support to existing research facilities, ensuring they are equipped for clinical trial research and testing.

Recommendation 5: Facilitate international collaboration

International collaboration will enable countries to share not only physical infrastructure, but also expertise in clinical trial assessment, ethical assessment and the social sciences. This will also aid the development of streamlined guidelines for clinical trials and regulatory assessments, facilitating rapid licensing (see **Section 0**). Such collaboration can promoted through support for existing platforms such as the African Academy of Sciences.

2.2.3 Challenge 6: Ethicality of clinical trials in the outbreak setting

The WHO has set up an expert working group on COVID-19 and ethics, to address the ethical issues surrounding the outbreak. This group produced a report summarising the key universal ethical standards to be adhered to during R&D,[62] although there was no specific reference to vaccines or clinical trials.

The issue of ethics and clinical trials in the COVID-19 outbreak has been reported heavily in the media, after two French doctors indicated plans to run a clinical trial in Africa.[63] Although these comments have been condemned by the WHO, the ethics working group must establish protocols for conducting ethical clinical trials in LMICs in Africa, the Middle East and South America. As discussed above, it is important that vaccines are tested in diverse populations, including in LMICs, if they are to be distributed world-wide. Secondly, these countries are likely to reach outbreak peaks much later than other countries and may represent more feasible settings for clinical trials than countries with stabilised levels of infection. Finally, the COVID-19 outbreak poses an opportunity for relatively new research facilities that have sprung up in the post-Ebola era to develop their capacities and train their workforce to perform the clinical tests required for clinical trials. This would ultimately help in developing sustainable infrastructure ready for future epidemics (see Challenge 5). It must be an absolute priority to ensure these countries are not exploited, and that they have equitable access to any vaccines licensed after such trials. It is also important not to burden countries with multiple clinical trials, as was seen in the 2013-2016 Ebola virus outbreak.[64]

Another source of ethical uncertainty is in the use of human challenge studies **(Section 2.2.1)**. During the writing of this report, the WHO COVID-19 and ethics working group released a document outlining the key criteria for the ethical acceptability of COVID-19 human challenge studies.[65] In addition, an independent international multi-disciplinary working group has provided a framework to support controlled human infection trials.[66]

Recommendation 6: Develop accessible and comprehensive ethical guidelines for conducting vaccine clinical trials during pandemics

The WHO COVID-19 and Ethics Working Group must immediately establish ethical guidelines for conducting COVID-19 vaccine clinical trials. This must include specific reference to:

a. Clinical trials in LMICs
b. Conducting clinical trials prior to/alongside tests in animal models
c. Clinical trials in at-risk populations
d. Clinical trial designs with placebo groups
e. Human challenge studies (released during the writing of this report, but will require continual renewal)

In the future, ethical guidelines with respect to these five issues that can be applied to future epidemics caused by emerging pathogens should be made available.

Recommendation 7: Build relationships between international and local ethics boards

Moving forward, the WHO should continue to build relationships between international and local ethics boards, and facilitate pre-epidemic discussion that define who will provide what services and how decisions will be made.[114] This is particularly important in LMICs which may not have the infrastructure in place to perform ethics reviews of clinical trials (see **Sections 2.2.2** and **0**).

2.2.4 Challenge 7: Societal mistrust of foreign entities conducting clinical trials

Several global health experts and news outlets have expressed thoughts that the severity of the COVID-19 pandemic will help to reverse the increasing societal mistrust of vaccines.[67] This appears to be backed up by data from the UK that showed that while 7% of people would have rejected a coronavirus vaccine in mid-March, this dropped to 5% in April.[68] However, it must be noted that a failed vaccine, particularly one which is associated with toxicity, will greatly augment the problem, and may have devastating consequences for future COVID-19 clinical trials and childhood vaccination efforts. A recent study investigating the anti-vaccination social media landscape showed that although anti-vaccination pages have fewer followers, they are more numerous that pro-vaccination ones, and have more exposure to undecided groups.[69] In addition, another study by the same group has shown that COVID-19 misinformation and other malicious content spreads quickly between social media platforms (pre-print).[70]

The Vaccine Safety Net is a WHO initiative aiming to help internet users find reliable information on vaccine safety.[71] As of May 2020 they have not released any information to explain how they are aiming to tackle vaccine misinformation during the COVID-19 pandemic.

Recommendation 8: Tackle misinformation by ensuring internet users are directed to reliable sources of information

The WHO Vaccine Safety Net should work specifically with the R&D Blueprint to target misinformation about COVID-19 vaccines and ensure that internet users are directed to reliable sources of information. As well as providing reliable information, there is also a need to effectively communicate the challenges involved in vaccine development in order to manage public expectation. This will help protect vaccine developers from reputational harm should a vaccine candidate fail, which would also reduce incentivisation **(Section 2.3.3)**.

Recommendation 9: Work to increase trust between the public, researchers and regulatory authorities

All stakeholders, including national governments and regulatory authorities, pharmaceutical companies and academic organisations, and other organisations involved in science communication should work together to educate the public about vaccination and clinical trials, and foster an environment of trust between the public, researchers and regulatory authorities.

Recommendation 10: Conduct quantifiable research into vaccine hesitancy among populations

Recommendation 9 is not COVID-19 specific, and should form part of long-term plans to tackle vaccine hesitancy and increase public trust of scientific evidence more generally. These actions should be facilitated by and overseen by the WHO, who should also monitor the progress of member states by conducting quantifiable research into vaccine hesitancy among populations. This will enable local governments to set goals and monitor progress.

2.2.5 Challenge 8: Lack of efficacy and safety data due to expedited clinical trials

A major concern with COVID-19 is whether vaccine trials and licensing will be able to be expedited without compromising on safety requirements.[72] The immunopathology of COVID-19 (disease caused by the immune response to the pathogen rather than the pathogen itself) plays a big role in the disease manifestation, and it will be vital to ensure that SARS-CoV-2 vaccines do not elicit the same detrimental immune responses. Based on the analysis of responses to SARS-CoV vaccines in animal models, it has been suggested that a vaccine to SARS-CoV-2 could lead to the upregulation of life-threatening immunopathology by T_H2 or T_H17 T-cells, types of white blood cell.[73,74] One of the most vital scientific questions about SARS-CoV-2 is how the immune system interacts with not only the pathogen but also any vaccine mimicking the pathogen.

In addition, vaccines against other coronaviruses have previously been shown to increase virus infection by a process called antibody-dependent enhancement (ADE) of virus entry in animal models.[45,75,76] Encouragingly, most descriptions of enhanced immunopathology or ADE have occurred in animal model settings without strong clinical evidence, casting doubt on the idea that these situations could occur in humans.[73]

The WHO has stated that 'evaluating the potential for enhanced disease in humans is critical before the vaccine can be assessed through large-scale studies'.[33] In addition, CEPI has partnered with the Brighton Collaboration, a program belonging to the Task Force for Global Health, to support streamlined safety assessments of vaccine candidates.[77]

Recommendation 11: Prioritise research to understand the immunopathology of COVID-19

Funding for research into the immunopathology of COVID-19 in humans should have an equal priority to funding for vaccine R&D. There is a need for enhanced collaboration between academics and industry to expedite scientific understanding of this topic.

2.2.6 Challenge 9: Lack of regulatory preparedness

One of the immediate research actions of the WHO Global Research Roadmap was to 'accelerate the evaluation of investigational therapeutics and vaccines by using multi-country 'Master Protocols'' for phase IIb/III trials. This will provide a collaborative research framework under which key research questions will be defined by multiple stakeholders, facilitating a coordinated and efficient evaluation of vaccine suitability.[33] The COVID-19 Clinical Research Coalition is also aiming to facilitate rapid and joint protocol reviews by ethics committees and national regulatory agencies.

Recommendation 12: Ensure regulatory preparedness by developing Master Protocols for priority diseases and frameworks for emerging pathogens

The WHO should continue to facilitate connections between local regulators, vaccine manufacturers, and experts in the field of clinical trial design,[114] and should work with CEPI to develop 'Master Protocols' for all priority diseases. More general protocols and frameworks should be developed to improve preparedness for unknown pathogens.

2.2.7 Challenge 10: Regulation disparity between countries

The licensing phase of vaccine development is hindered by the fact that every country has its own processes for reviewing and approving vaccine candidates, imposing different clinical trial and data requirements on the vaccine manufacturer. The development of 'Master Protocols' should in part help to streamline clinical trials, ethics reviews and the evaluation of investigational vaccines, allowing expedited licensing across all countries. Additionally, the WHO SOLIDARITY project will permit a multi-site, adaptive trial of multiple vaccine candidates, facilitating streamlined regulatory submissions as well as expediting the trial process and permitting comparison between candidates.[59]

Several regional groups have been established to enhance dialogue between vaccine developers, regulators and ethics committees and coordinate the review process. One of the goals of the European Medicines Agency (EMA) COVID-19 pandemic Task Force (COVID-ETF) is to enable vaccine developers to gain regulatory input on their R&D plans and clinical trial protocols.[78] Another example is the WHO African Vaccines Regulatory Forum (AVAREF), which aims to improve the regulatory oversight of clinical trials conducted in Africa. AVAREF recently facilitated an agreement between national regulatory authorities and ethics committees from across Africa to combine their expertise to expedite clinical trial review.[79] In light of the quarantine measures implemented during the COVID-19 outbreak, AVAREF have developed an online platform for joint reviews of clinical trial applications and are coordinating virtual meetings for participating countries. Finally, in order to facilitate coordination of regulators worldwide, the International Coalition of Medicines Regulatory Authorities (ICMRA) have held workshops to help share expertise and streamline requirements.[80]

Recommendation 13: Enhance coordination of clinical trials through multi-trial platforms

Academic organisations and industry partners involved in vaccine development should seek opportunities to be involved in platform trials, as well as establishing contact with local and global regulators and organisations such as COVID-ETF and AVAREF early in their research.

2.3 Challenges that face both pre-clinical and clinical development

Table 3 of the Appendix shows the challenges facing **all stages** of vaccine development, examples and the current solutions being implemented to address these challenges.

2.3.1 Challenge 11: Lack of standardised assays to measure immunological responses to vaccine candidates

In the Global Research Roadmap, the WHO identified a priority 'to develop and standardize assays to support vaccine development, particularly to support the evaluation of immune responses and to support clinical case definition. Basic reagents should be shared to accelerate the development of international standards and reference panels that will help support the development of ELISAs, pseudovirion neutralization and PCR assays'.[33] Sharing of such reagents and protocols will facilitate assessments of vaccine efficacy during the pre-clinical and clinical stages, as well as allowing comparison between vaccine candidates.

Recommendation 14: Establish a platform for the sharing of reagents and protocols for standardised assays

There is a vital need for an organisation that develops, or at the least facilitates the timely sharing of standardised reference reagents and protocols for a range of viral threats, and develops platforms for the sharing of new reagents and protocols upon emergence of a novel pathogen.

2.3.2 Challenge 12: Time required for research and development

The time required is an issue for both pre-clinical and clinical development of vaccines. One way to speed up the whole response is to use **vaccine platform technologies (Figure 1, Table 3)**, of which many of the SARS-CoV-2 vaccines in development are examples.[36] A significant issue that could arise with these types of vaccines is that they are relatively new technologies. In particular, mRNA vaccines have not been approved for use in humans before, meaning longer trials to ensure safety may be required as well as the development of novel manufacturing techniques.[45]

Developing a SARS-CoV-2 vaccine will require deviation from the standard lengthy vaccine development process that consists of a linear sequence of steps. It has been suggested that phase I clinical trials may be able to proceed in parallel with animal testing (a stage which usually takes 3-6 months), and that large-scale manufacture should begin before substantial safety and immunogenicity data is available.[64] Moderna, Inc have taken this strategy, working on non-clinical research in parallel to testing in humans. However, this method is controversial, especially as the vaccine being developed by Moderna is based on mRNA, and so far no mRNA vaccines have been licensed for use in humans.[50] Similarly, the Oxford University ChAdOx1 vaccine underwent animal trials during the recruitment phase of the human study. This was more easily justified as the same vector, encoding antigens of more than 10 different diseases, has previously been used in thousands of recipients.[81]

A method to make vaccines accessible during an epidemic prior to licensing is through the WHO Emergency Use Listing procedure, which aims to 'assist interested UN procurement agencies and Member States on the acceptability for use of specific products in the context of a public health emergency, based on an essential set of available quality, safety, and efficacy/immunogenicity/ performance data'.[27] However, despite two vaccine developers applying for EUL status during the 2013-2016 Ebola virus outbreak, no vaccines have ever been accepted, and submissions for COVID-19 vaccines are currently not open. There are concerns about what would happen if a vaccine was listed by the WHO under the EUL procedure - if this occurred before large-scale manufacture of the vaccine, this could lead to vaccines only being distributed to the countries that can pay the most.

Similarly to the WHO EUL procedure, the COVID-19 European Medicines Agency pandemic Task Force has been established to coordinate fast regulatory action on the development, authorisation and safety assessment of vaccines.[82] Mechanisms in use include rolling review, accelerated assessment and recommendation on compassionate use. The EMA has also developed the voluntary PRIME scheme for developers to receive advice on clinical trial design and regulatory requirements.[83]

In general, the lack of coordination between vaccine developers and regulators, and between different vaccine developers, is a major time constraint. Vaccine developers each have to optimise their own protocols for assessing efficacy and for performing clinical trials. An encouraging development has been the WHO SOLIDARITY multi-vaccine trial which will permit coordination from initiation of the clinical trial to analysis of data and regulatory submission.[59] In the US, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership between the National Institutes of Health (NIH), FDA, CDC, BARDA, the EMA, and a number of industry and academic representatives was established to facilitate data sharing and coordination between vaccine efficacy studies.[84] There is need for a similar framework to be established worldwide, under the organisation of a central independent body (Section 3).

2.3.3 Challenge 13: Funding

Reasons for the lack of an approved and available vaccine for either SARS-CoV or MERS-CoV include the lack of public demand and the lack of financial incentive for pharmaceutical companies, as the outbreaks of these viruses are small and unpredictable.[73] Given the high transmissibility, high death rate, and widespread incidence of COVID-19 across the world, many countries are diverting record levels of public money into SARS-CoV-2 vaccine development. However, the chances of a vaccine being ready before the current outbreak has subsided is slim. The challenge for funding will come after the primary stages of vaccine development and the first wave of the pandemic, when either i) outbreaks of COVID-19 are sporadic and short-term, controlled by periods of social distancing measures or ii) when SARS-CoV-2 becomes endemic across the globe, causing seasonal outbreaks similar to influenza. Under these circumstances, the demand and incentive for development of a vaccine may be reduced, especially if an efficacious vaccine proves difficult to develop.

Many scientists believe that if we had a licensed vaccine against SARS or MERS, we would have been able to have produced a SARS-CoV-2 vaccine in a much shorter time-frame, and would have had better understanding of the immunopathological and safety concerns. It is important that lessons are learnt – increased funding should be directed towards vaccine development against different families of viruses with epidemic potential **(Section 2.1.1)**. As long as any emerging virus is sufficiently closely related, sequences encoding the immunogenic antigens could quickly be switched, facilitating a move straight to later stage clinical development.

The WHO has identified funding as an immediate priority, stating that they aim to 'maintain a high degree of communication and interaction among funders so that critical research is implemented[33]'. It is essential that the WHO works with GLOPID-R to identify long-term and sustainable sources of funding for SARS-CoV-2 vaccine development that are guaranteed to be available if/when the first global outbreak subsides. In the longer-term, there is a vital need for a global financing system that supports not only R&D, but also the large-scale manufacturing required for phase III trials and vaccine use, ensures fair allocation and increases incentivisation by providing protection for private-sector partners **(Table 3)**.

Finally, given the severity of the COVID-19 pandemic and the level of public and media scrutiny, there is an essential need to effectively communicate the challenges involved in vaccine development in order manage public expectation.[17] Failures in vaccine development could not only result in significant reputational harm for any company or academic institution involved, but also discourage funders and manufacturers in future epidemics.

3 Conclusions and Primary Recommendation

As we identified in our Disease X report, there is no single entity solely focussed on coordinating end-to-end R&D efforts against emerging infectious diseases. Even prior to the COVID-19 pandemic, there have been calls for a multidisciplinary council to address the health, social and economic risks associated with emerging infectious diseases.[32] With the breadth and magnitude of challenges highlighted in this report facing just vaccine R&D, we believe the establishment of an organisation focussed solely on this topic would be appropriate. Resulting competition between this organisation and the WHO in this field will likely have a positive effect, as shown for other fields of global health.[32,85]

The Coalition for Epidemic Preparedness (CEPI), appear to be making moves to fill this space. Although with an original goal of simply accelerating vaccines through phase II trials, they are now focussing on several wider issues related to vaccine development, including the development of biological standards and assays, animal models, epidemiological studies, diagnostics, clinical trial capacity and sustainable manufacturing. If CEPI continues to grow, we believe they would be well placed to deliver many of the recommendations in this report.

Primary recommendation:

We recommend the formation of an independent organisation to pre-emptively and pro-actively facilitate an expedited **vaccine R&D** response to **emerging viral pathogens**. This organisation should:

a. Improve collaboration, coordination and conversation between relevant stakeholders, primarily the WHO Strategic and Technical Advisory Group for Infectious Hazards and R&D Blueprint, CEPI, Gavi, academics, industry and any new council focussed on the emerging infectious disease response.
b. Focus on the technical, scientific and policy-based challenges facing end-to-end vaccine development, from basic scientific research to licensure. Although not covered in this report, this should also cover vaccine manufacture and access.
c. In particular, they should aim to fill in the gaps identified in this report, by:
    - supporting research into families of viruses with epidemic potential
    - coordinating the development of animal models
    - facilitating the sharing of data, information, reference reagents, pathogens and protocols
    - developing sustainable research infrastructure, particularly in LMICs
    - promoting international collaboration
    - developing Master Protocols for clinical trials and regulatory reviews
    - facilitating interactions between vaccine developers, local and global regulators, and ethics committees, to expedite and coordinate review procedures
    - coordinating regulators to streamline regulatory demands
    - establishing multi-trial platforms

If CEPI develops to focus on end-to-end vaccine development, they would be ideally placed to deliver these recommendations.

4 Appendix

Table 1 *displays results of a rapid review of the challenges facing pre-clinical development of vaccines against an unknown viral pathogen, potential and existing solutions and recommendations.*

Challenge	Examples	Solutions
Lack of existing literature/research into novel viruses For most emerging infectious diseases, there is only a limited understanding of pathogenesis and epidemiology at the outset of an outbreak.[86]	**Ebola virus** (EBOV) was first identified in 1976.[87] By the start of the EBOV outbreak in 2013, understanding of the immune response to the virus was still very limited.[88] The relative importance of humoral and cellular immunity to **Zika virus** is still poorly understood.[89] There are many gaps in the knowledge of innate, cell-mediated and humoral immune responses to **Lassa fever virus** (LASV) and the determinants of infection and disease severity.[90]	**Pre-emptive research** Related viruses are likely to share therapeutic and vaccine targets. Research into *families* of viruses may permit identification of novel immunogenic antigens that can be used to tackle emerging pathogens.[88] In addition, lists of key experts should be assembled and collaboration encouraged. These experts should be representative, with particular inclusion of those from geographic areas most likely to be affected by a particular pathogen. **Assess epidemic threats and define priority pathogens** The **WHO R&D Blueprint** list of priority diseases has identified which *known* diseases pose the biggest public health risks.[23,91] The **Johns Hopkins Center for Health Security**[92] recently identified respiratory-borne RNA viruses as the infectious agent most-likely to cause the next global epidemic.[7] **The Global Virome Project**[93] aims to increase understanding of the diversity and ecology of viral threats, providing data for public health interventions against future pandemics.
Lack of good animal models Animal models are imperative for understanding host tropism, immune	**MERS-CoV** only infects primates, bats and camelids. Non-human primates and camelids exhibit very different pathologies	The **WHO** identified a need for better understanding of animal models in its R&D Blueprint.[6]

responses and modes of transmission, and for the testing of therapeutics and vaccines. Good animal models will be natural hosts for the virus, and share routes and outcomes of infection similar to those in humans.[94] Problems with finding a good animal model include: - Lack of natural hosts due to host species restriction - Ethical considerations - Cost and availability of large animal models Efficacy data based on studies in animal models may be key to achieving approval for use in epidemics by 'the Animal Rule' **(Table 2)**.[95,96]	to humans upon infection, and are expensive and difficult to use.[89] Vaccines for **filoviruses** are usually tested in rodent models, despite the viruses causing limited disease in these species.[97]	The **Filovirus Animal Non-Clinical Group** (FANG) aims to use clinical data from filovirus disease outbreaks in humans to guide animal model development.[98] **One Health approaches**.[99] More effective collaboration between veterinary and human fields will aid animal model development.
Lack of data sharing during epidemics Due to conflict between the academic community (who withhold data due to right to publish) and the members of the public health response (who withhold information due to patient confidentiality).		Solutions should facilitate **data and sample sharing** while maintaining interests of both the academic and public health communities. Sharing of negative results should also be encouraged. A meeting of representatives from major biomedical journals at a WHO consultation in September 2015 led to an agreement on the rapid and open sharing of data and results in public health emergencies, in particular that pre-publication dissemination of results to the WHO or national public health authorities would not prejudice publication.[100] **The WHO R&D Blueprint** identifies a need for platforms that expedite data sharing.[6]

	The GloPID-R Data Sharing Working Group has released a framework for data sharing during outbreaks.[101] **The International Severe Acute Respiratory and Emerging Infection Consortium** (ISARIC) provides a platform for researchers to share protocols and data tools.[102] The **WHO's Pandemic Influenza Preparedness Framework** has developed a system for the sharing of influenza viruses with pathogenic potential.[103] **GlaxoSmithKline**[104], the **Global Alliance for Genomics and Health**[105], and the **Biomarkers consortium**[106] are all pioneering data transparency models.

Table 2 *displays results of a rapid review of the challenges facing clinical development of vaccines against an unknown viral pathogens, potential solutions and areas for improvement*

Challenge	Examples	Solutions
Changing epidemiology/unpredictable nature of epidemics	**MERS-CoV** remains endemic in Saudi Arabia, but cases are rare and scattered throughout the country – makes design of an efficacy trial for a vaccine very challenging.[89] The current unpredictability and lack of future **Zika virus** outbreaks is a major impediment to vaccine development.[107] Several vaccines are now in phase II clinical trials, but it will be very difficult to move to phase III. The epidemiology and sporadic nature of **Nipah and Chikungunya virus** outbreaks makes large scale clinical trials logistically challenging – no clinical trials for NiV of CHIKV vaccine candidates have begun.[108,109]	**Clinical trial design** Clinical trials should be designed with the epidemiology of the specific virus in mind. Population-based vaccination for those at high-risk may be possible where cases are rare – e.g. since nosocomial spread of MERS-CoV has been documented, a study to prevent infection in health care workers may be feasible.[89] **Epidemiological studies that model disease dynamics** Understanding disease dynamics can tell us where the epidemic is likely to spread to and how long the epidemic will last, helping to inform clinical trial design. **Adaptive clinical trial design** promoting introduction of pre-specified modifications in the design or statistical procedures during the study, depending on data acquired during the early stages of study implementation.[110,111] **Human challenge**, only with pathogens that cause mild symptoms e.g. Zika virus.[112]
Lack of infrastructure required to conduct clinical trials[90,113,114] • This mainly refers to LMICs, but will be relevant in many higher income countries too • Challenges in setting up clinical sites with the administrative, research, clinical and laboratory infrastructure and workforce to conduct trials	Current outbreak of **EBOV** in the Équateur province of the Democratic Republic of Congo provided an opportunity to study the effects of the rVSV-ZEBOV vaccine. This region is at the centre of one of the densest forests on the planet, with few roads. Before the 2014 outbreak, EBOV-affected countries had little experience in running clinical trials or for the review of complex clinical trial protocols.[115]	**Strengthen clinical research capacity and sustainable health systems in LMICs**[113] Capacity strengthening efforts should not be limited to services that solely benefit study participants, and should benefit the local population as a whole.[114] Research capacity that can be mobilised quickly and effectively in countries susceptible to epidemics is a requirement for the rapid deployment and testing of candidate vaccines.[116] The **International Vaccines Task Force (IVTF)** was created to produce recommendations to strengthen sustainable clinical research capacity in low- and middle-income countries.[116]

• Lack of information on disease burden estimates to guide the selection of clinical trial sites • Lack of reliable water and electricity sources, impacting clinical care and research facilities • The remote and occasionally politically unstable nature of the endemic area • Lack of functional ethics committees and expertise in social sciences to make decisions about candidate vaccines and clinical trials		The **WHO** facilitated connections between Guinea's national authorities and regulatory and ethics experts in order to facilitate an examination of the EBOV vaccine efficacy trial during the 2013-2016 outbreak.[115] **The African Centres for Disease Control** was established to improve the continent's public health infrastructure. In the DRC, this has involved building an emergency operation centre, deploying an epidemic response team and helping to fund the response.[117] Recommendations for strengthening clinical research capacity are defined in 'Money & Microbes: Strengthening Clinical Research Capacity to Prevent Epidemics', a review by the IVTF[116] and 'Integrating Clinical Research into Epidemic Response: The Ebola Experience'[114], an independent review by the National Academies of Sciences, Engineering and Medicine.
Ethicality Highest strength data is generated by randomised, double-blind, placebo-controlled trials. This is not always ethically acceptable in the epidemic setting where a disease has high mortality.[115]	**EBOV** vaccine trials were challenged by ethical concerns over whether to include a control arm.[86]	**Other randomised controlled designs** can collect clinical data to provide evidence for analysis.[115] The solution reached in the rVSV-ZEBOV ring vaccination trial was to randomise primary cases into immediate versus delayed.[118] Other designs include testing multiple vaccines simultaneously using a shared control group.[64] Adaptive clinical trial design will allow changes to placebo groups based on ethical considerations and results. **Collaboration between international Ethics Panels and national regulatory bodies** In August 2014, the same month that the EBOV outbreak was determined a Public Health Emergency of International Concern, the WHO convened an international ethics panel who defined the conditions of non-licensed vaccine use in terms of safety, ethical standards, clinical care, data collection and data sharing.[115,119,120] Existing regulatory networks can facilitate communication and information exchange: The **WHO African Vaccine Regulatory Forum (AVAREF)** provided a collaboration platform for regulators, ethics committees and sponsors.[121]

		The **WHO** has produced Guidance for Managing Ethical Issues in Infectious Disease Outbreaks.[122]
Societal mistrust of foreign entities conducting clinical trials leading to challenges in patient recruitment Often due to ineffective community awareness, sensitisation and education programmes[90].	Societal mistrust of vaccination occurs around the world. Polio eradication efforts have been hampered by distrust of the vaccine, particularly in Pakistan and Afghanistan. Social resistance has had a big effect on vaccine uptake in the DRC. In higher income countries, anti-vaccination movements against childhood vaccines are gaining momentum, with 33% and 11% of people believing that vaccines are unsafe in France and the US, respectively.[123] The WHO declared vaccine hesitation in its top ten threats to global health in 2019.	**Community engagement in research and response** In LMICs it is crucial to use a sustainable bottom-up approach, educating key community leaders about the disease, research and clinical trials.[113] **Education and consent** Participants should be informed about all aspects of the protocol before consent.[113,124] A programme run by the Kenya Medical Research Institute-Wellcome Trust Research Programme engages members of the local community to create consent forms that are socially and culturally sensitive to local needs.[125] In order to address vaccine hesitancy more widely, the **WHO Vaccine Safety Net** aims to help internet users find reliable information about vaccines.[71]
Lack of efficacy/safety data Largely due to changing epidemiology/unpredictable nature of epidemics (see above).	Clinical trials of vaccines in the **EBOV** outbreak began too late – it became difficult to collect enough efficacy data to satisfy regulators such as the FDA.[126] Partly due to difficulties collecting clinical trial data, rVSV-ZEBOV was not licensed in any African country until 2020, after two major outbreaks.	There are two alternative approval processes for drugs and vaccines designed for 'serious or life-threatening conditions' for which there is no robust efficacy data:[126] **The 'Animal Rule':** Two requirements: a. Proven safe in humans b. Protected vaccinated non-human primates (NHPs) that are challenged with the virus **Accelerated approval** Requirements: a. Determine which immune responses protect vaccinated NHPs b. Show the vaccine elicits a similar response in humans Both should be followed by post-marketing studies during future outbreaks.

		While a vaccine may be used on a compassionate basis during an ongoing emergency, the main goal should be product approval for future epidemics.[115]
Lack of regulatory preparedness		**National regulatory authorities should have effective preparedness and response plans in place** In December 2016, the WHO held an informal consultation on options to improve regulatory preparedness.[127–129] **Communication** between regulatory agencies to define requirements of product review submissions is key (see 'Regulation disparity between countries' below) – connections should be made *before* the onset of an epidemic and regulatory requirements defined. **Prior preparation of clinical trial strategies** Regulators should work together to identify acceptable clinical trial design options.[115] Countries should identify experts in negotiation of clinical trial and material transfer agreements before the onset of an epidemic.[114]
Regulation disparity between countries Each country has its own processes for reviewing and approving vaccines.	All industrialised countries have an efficient vaccine regulatory system, but only around one quarter of LMICs do.[130] The conventional approach to clinical trial review is for each agency to review applications independently without oversight of each other's inputs. Before **rVSV-ZEBOV** was licensed in four African countries in 2020, Russia and China had already licensed two different EBOV vaccines, both based on limited preclinical and clinical trials and neither of which were prequalified by the WHO.[97] **H1N1 Influenza outbreak**: Each country's national regulatory authority	**The WHO prequalification system** was established to advise national regulatory bodies on the suitability of available vaccines, and to ensure that every country has a properly functioning regulatory authority.[130] Works in collaboration with the European Medicines Agency (EMA) Article 58 procedure.[133] There is need for explicit pathways via which local regulators can implement recommendations from regulatory authorities such as the WHO, FDA and European Medicines Agency (EMA).[17] **Streamlined processes**[113,115] Countries should: a. Align requirements of regulatory submissions for product review from manufacturers, so there is no need to adapt submissions to each country's requirements. b. Divide tasks associated with product review c. Move toward more common data and evidence requirements d. Share outcomes of product reviews **International Coalition of Medicines Regulatory Authorities (ICMRA)** aims to support enhanced communication, information sharing and crisis

	imposed its own requirements for vaccine approval,[131,132] which had an impact on efficacious donation and distribution from manufacturers.[113]	response, address regulatory science issues and identify areas for streamlining [134].

Table 3 *displays the challenges facing all stages of vaccine development, examples and solutions currently being implemented.*

Challenges	Examples	Solutions
Lack of standardised assays to measure immunological responses to vaccine candidates Understanding of the mechanism of protection against both natural virus infection and vaccination are important to a) evaluate the consistency of vaccine production, b) investigate the susceptibilities of individuals and populations after vaccination, and c) expedite approval of vaccines when efficacy trials are not possible or ethical.[135]	The use of different immunological assays in different clinical trials during the **EBOV** outbreak hindered the comparison of immunogenicity induced by different vaccine candidates.[88] The methodology used for assays measuring humoral immunity following vaccination against **Chikungunya virus** varies widely across studies.[109] The absence of diagnostic assays to distinguish between acute illness, prior infection, and the response to vaccination is hindering **Lassa fever virus** (LASV) R&D.[90]	Centralised standardised assays and biological standards for a range of virus families An anti-**EBOV** IgG reference reagent has been established by the WHO Expert Committee on Biological Standardisation (ECBS) to permit comparison of humoral responses.[136] The Filovirus Animal Non-Clinical Group (FANG) have developed a standardised ELISA assay that has approval from the FDA.[98,137] In general, there should be a push towards use of standardised protocols.[113] The **World Organisation for Animal Health (OIE)**, coordinates a programme for the preparation, validation of International Standard Reagents for diagnostic assays for veterinary infectious diseases.[138] A similar programme is required for all families of human viruses.
Time taken for vaccine R&D	The average time from identification of a pathogen to licensing of a vaccine is 30 years. The success rate is less than 10%, even for vaccines that enter clinical trials.[45]	**Platform technologies** Once a vaccine platform has been developed and licensed for one target, development of the following vaccines will only require substitution of the immunogenic antigen. Majority of preclinical studies determining safety, route of administration and doses can be performed before an epidemic begins. Effectiveness trials can then begin swiftly upon identification of an antigen. **Monoclonal antibodies** Because human monoclonal antibodies are faster to develop than vaccines, they may provide an effective protection method early in epidemics before establishment of vaccine manufacture and distribution [12]. May be possible to generate cross-reactive monoclonals against most known viral threats that will be ready to distribute upon emergence of a new outbreak.

		Lessons from the EBOV outbreak Clinical trials during the EBOV outbreak proceeded relatively quickly. Reasons for this included:[86] a. Advancement to phase II/III while phase I studies were being completed b. Large-scale vaccine production before safety and immunogenicity assessments were complete c. Novel clinical trial designs **The WHO Emergency Use Listing Procedure (EUL).**[26] Aims to provide guidance to UN procurement agencies and Member States on the use of vaccines during public health emergencies. Although submissions for two vaccines were received during the 2014-2016 Ebola virus outbreak, none were listed.[27]
Lack of funding Lack of funding often causes a deceleration in the R&D response to pathogens with epidemic potential, and is caused by a lack of incentive, public demand or a lack of understanding of the risk posed by a particular pathogen. Lack of incentive derives from the substantial investment required and the high risk of failure (94%) associated with vaccine development.[139]	Early pre-clinical development of **EBOV** vaccines was slowed by a lack of funding.[86] Funding for **LASV** vaccine R&D has been insufficient as incentives to invest are not clear – disease is endemic in an under-resourced West African region.[90] The lack of known of severe clinical consequences associated with **Zika virus** hampered vaccine R&D.[89] Appreciation of the potential global threat from **MERS-CoV** was delayed for about a year,[89] leading to a lack of funding.	**Platform technologies** As well as decreasing the time required for early vaccine development, platform technologies also help reduce costs required by cutting out some steps of early research and development that can be costly. **Pro-active pre-emptive approach**[12] Public resources should be allocated in advance of any outbreak.[17] **Cover opportunity costs** resulting from the need to cease standard research and manufacturing pipelines.[17] **Maintain interest, funding and incentive after resolution of an epidemic** Main success of the response to the EBOV outbreak – vaccine development continued after the peak of the epidemic, leaving us with a highly effective vaccine (rVSV-ZEBOV, Merck),[140] that has been used in recent outbreaks in Guinea and the Democratic Republic of Congo (DRC)[141,142] and was licensed by the DRC, Burundi, Ghana and Zambia in February 2020.[143]

	Improve supply and demand forecasting[17] This is especially important as manufacturing processes and facilities are a component of licensure – any additional capacity required after licensure must be approved by all countries receiving the vaccines before it can be used. **Fund research** investigating the risk posed by novel viral pathogens, including potential for geographical spread, clinical outcomes and potential to evolve new highly-virulent strains. **Protection for manufacturers against product liability claims and reputational harm**[113,131] Manufacturers making vaccines based on limited safety data may face legal and reputational risks.[17] As part of their R&D Blueprint, the WHO is exploring insurance options to indemnify recipients of vaccines which have not yet been fully clinically evaluated and licensed, and to cover liability for manufacturers of these products.[6] **Involve stakeholders in clinical trial design**[86]

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