POLYGEIA

STUDENTS SHAPING GLOBAL HEALTH POLICY

DISEASE X: THE PRACTICAL CHALLENGES OF VACCINATING AGAINST THE UNKNOWN

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SUMMARY OF POLICY RECOMMENDATIONS

THE AUTHORS OF THIS PAPER RECOMMEND THAT A SPECIFIC WORKING GROUP UNDER THE WHO IMMUNISATION, VACCINES AND BIOLOGICALS PROGRAMME IS ESTABLISHED WITH THE OBJECTIVE OF WORKING IN COLLABORATION WITH STAKEHOLDERS TO INCENTIVISE RESEARCH, COLLABORATION, DATA SHARING AND FUNDING TO ESTABLISH A HOLISTIC APPROACH TO THE NOVEL CHALLENGES POSED BY DISEASE X.

Challenge	Description	Specific Recommendations	Addressed by
Research Funding	Underfunding due to an unpredictable market and high likelihood of failure to make profit. Public investment often focuses on the health needs of developed countries	1. Establish an international pooled fund and governing body to effectively raise and distribute funding 2. Encourage collaboration of current stakeholders/organisations	Section 2: Funding and Incentivisation
Time	Pre-emptive research into adaptive technology would enable a more rapid response to unpredictable outbreaks. Process in clinical trials, regulatory approval and licensing needs to be completed in months, not in years, to be effective.	1. Continue developing surveillance and detection projects 2. Develop a streamlined approach for vaccine licensing and regulation in the absence of robust clinical trial data upon emergence of an epidemic 3. Fund development of standardised assays to determine immune correlates of protection and response to vaccine candidates	Section 3: Research and development
Unknown epidemiology	Disease X could have any mode of transmission; "high risk" groups vary. A rapidly transmitting Disease X requires a more rapid response	1. Increase funding of research into clinical outcomes of disease and risk analysis to increase appreciation of risk	Section 3: Research and development
Unknown vaccine type	Different manufacturing plants have different capabilities currently but may need more flexibility to adapt to Disease X	1. Incentivise research into and development of platform technologies 2. Ensure capability to transport different vaccine types	Section 4: Manufacture Section 5: Logistics
Unknown location	Remote locations challenging to distribution effort. Varying transportation lengths due to geographical distributions of suitable manufacturing plants.	1. Cold chain and infrastructure improvements 2. Increasing number and geographical distribution of plants	Section 5: Logistics
Capacity of local health authorities	Outbreak likely in Low-Income Country (LIC) with poor capabilities A focus on outbreak response could disrupt supply of routine vaccines	1. Continue IHR core capacity improvements and monitoring of current state and progress[1] [2] 2. Develop an international stockpile of vaccines prior to outbreak	Section 6: Coverage and demand Section 3: Manufacture

1. INTRODUCTION

> *"One thing that we can be sure of beyond doubt is that the world will face another Ebola, SARS, or even Spanish Influenza. And we aren't ready. Vaccines can be the insurance policy we need to combat that epidemic when it comes." – Richard Hatchett, CEO of CEPI*

The problem of tackling rapidly emerging infectious disease (EID) is becoming increasingly well-recognised in global health policy. Each year the World Health Organisation (WHO) publishes a list of priority diseases, earmarked for accelerated research and development (R&D) in recognition of their public health risk and current lack of viable medical countermeasures. For the first time in 2018, this list (Figure 1) included "Disease X", which "*represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease*".

The list of priority diseases guides a Blueprint of five workstreams:

1. Prioritization of pathogens and operational plan
2. Identification of research priorities
3. Coordination of stakeholders and expansion of capacity
4. Assessment of preparedness and impact of intervention
5. Exploration of funding models for R&D preparedness and response.

Significant progress has been made for many of the diseases on the WHO Blueprint: an Ebola vaccine has been implemented for the first time in the Democratic Republic of Congo, and $130 million has been invested by the Coalition for Epidemic Preparedness Innovations (CEPI) into 12 candidate vaccines for Lassa virus, MERS-CoV and Nipah virus. However, current guidance and policy plans (see Appendix 1) largely overlook the inclusion of Disease X, which is by definition undefined. Without clear knowledge of the threat, progress towards preparedness is more challenging than for the known other priority diseases.

FIGURE 1: WHO LIST OF PRIORITY DISEASES 2018

WHO Priority diseases 2018

Crimean-Congo haemorrhagic fever (CCHF)
Ebola virus disease and Marburg virus disease
Lassa fever
Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS)
Nipah and henipaviral diseases
Rift Valley fever (RVF)
Zika
Disease X

Here we present feasible measures which can be implemented to optimise a response to an unknown pathogen, including

- Educating governments and funding bodies regarding the co-benefits of a proactive and flexible approach to vaccine development, manufacture and delivery
- Directing funding and incentivising the necessary changes
- Facilitating better co-ordination between existing bodies

Due to the inherent variability of Disease X, we recommend that a "toolbox" of pathways and strategies is developed, with the flexibility to choose appropriate pathways based on cultural context and in response to changing scenarios.

1.1. Defining the Disease X strategy

It is difficult to predict the nature of Disease X and the strategies to address it will vary greatly depending on how it manifests. In this report, we focus specifically on how we can ensure a **proactive** response to **vaccine** development upon emergence of an unknown **virus**.

Why a vaccine? Response strategies following identification of an outbreak are multi-faceted:

- Infection Prevention and Control (IPC): reactive and adaptive containment efforts such as quarantine, travel bans, use of personal protective equipment decontamination measures and improved biosecurity of farms.
- Medical interventions: improved diagnostics, therapeutics and vaccination.

A major challenge limiting effective reaction to previous outbreaks has been the availability of a suitable vaccine[3]. Hence, in this report we focus specifically on the challenges of establishing an effective vaccine response (Figure 2).

How will we identify the next Disease X? Several reports reflecting on recent epidemics noted the need for improvements in surveillance and early detection strategies[4,5]. We consider this a significant subject in its own right and beyond the scope of this report. However, we would recommend continued investment in the linked projects listed below and the development of communication links to ensure collected data is shared effectively.

- **Global Virome project (GVP)**: uses genetic sequencing techniques to develop a comprehensive ecologic and genetic database of all naturally-occurring viruses[6]
- **USAID Emerging Pandemic Threats (EPT) PREDICT project**: the first globally coordinated program to conduct viral discovery in wildlife reservoir hosts and characterize ecological and socio-economic factors that drive their risk of zoonotic spill over

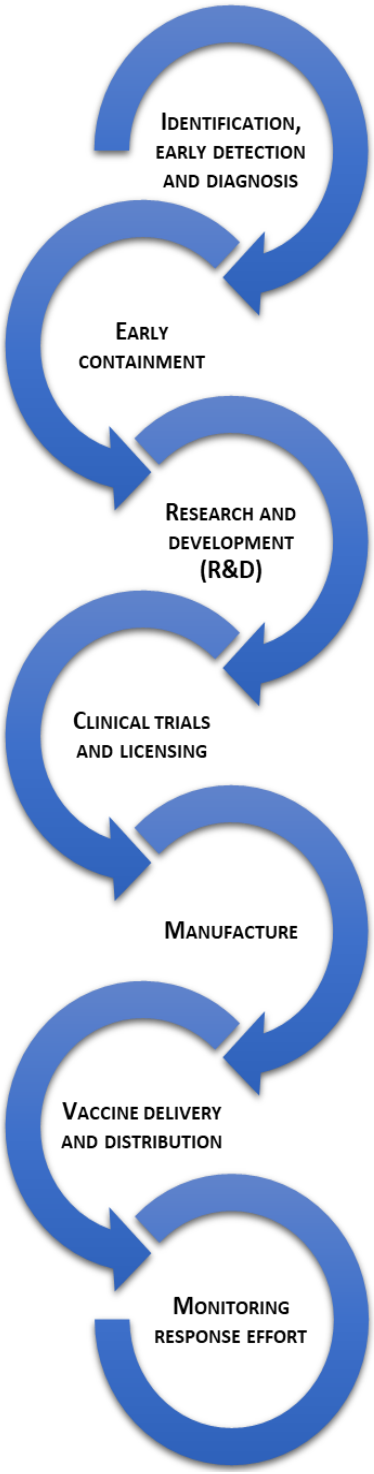


FIGURE 2. THE DISEASE X STRATEGY

What is the timescale? Vaccine development takes time. A proactive approach utilising pre-emptive research is optimal for vaccination to be of significant use in an outbreak. Delaying the initiation of a response until a disease becomes a global threat is too limited in time to prevent a significant outbreak at the time[3]: the peak of the epidemic is often almost over by the time an outbreak is identified such that subsequent interventions are limited in their ability to reduce the overall impact of the disease.

Advances in platform technologies (Section 3.3.) may enable the required acceleration of R&D to start vaccine safety testing within months of a new pathogen being genetically sequenced. Accompanied by streamlining of current testing and licensing procedures (Section 3.2.), this could improve the timescale for the development and use of new vaccines during outbreaks.

What is the cost? It has been estimated that the minimum average cost of progressing one vaccine against one of the WHO Priority Diseases to late stage clinical trials is $2.8 billion[7], not inclusive of the other costs necessary for preparedness including vaccine manufacture, distribution and delivery (Section 4, 5 and 6). However, with an estimated average cost to the global economy of $570 billion per year from the risk of moderately severe to severe pandemics[8], it has been demonstrated that investment into outbreak response capacity is worthwhile

for global health security, and new and innovative models for funding these improvements are urgently required (Section 2).

Why viral? For the purposes of this report we assume that Disease X will be a viral disease, for the following reasons[9,10]:

1. **HIGH PATHOGENICITY POTENTIAL**
    I. All other WHO priority diseases are viral
2. **HIGH REPLICATION RATE**
    I. High potential for rapid transmission
    (e.g. over 1 trillion Hepatitis C virions are produced per day of human infection)
3. **HIGH MUTATION RATE**
    I. Yields host adaptability and increases zoonotic spill-over risk
    II. Increases immune system evasion capacity
    III. Facilitates development of novel characteristics
4. **DIFFICULT MEDICAL RESPONSE**
5. **OTHER MICROBIAL PATHOGENS HAVE LIMITATIONS E.G. BACTERIA**
    I. Lower mutation and transmission rates
    II. Growth restrained by temperature
    III. Antimicrobial drug efficacy

It is worth noting that this report will remain broadly relevant in the case of a bacterial based epidemic, as vaccination responses are also effective against bacterial agents.

1.2. LEADERSHIP AND CO-ORDINATION OF THE RESPONSE

Too many initiatives lead to an uncoordinated response lacking coherence, clarity and accountability. There are currently many different groups working on similar problems to achieve similar goals (See Figure 3 and Appendix 1). The authors of this report agree with the UN High-level Panel on the Global Response to Health Crises [11] that the WHO should lead such a response.

A WHO central Disease X vaccination committee would raise awareness of existing initiatives and organisations for 2 purposes:

1. To ensure that independent organisations are aware of each other and can work together, coordinate and synergise their efforts
2. To attract sources of additional funding for these organisations so that their work on improving worldwide epidemic preparedness will be sustained into the future.

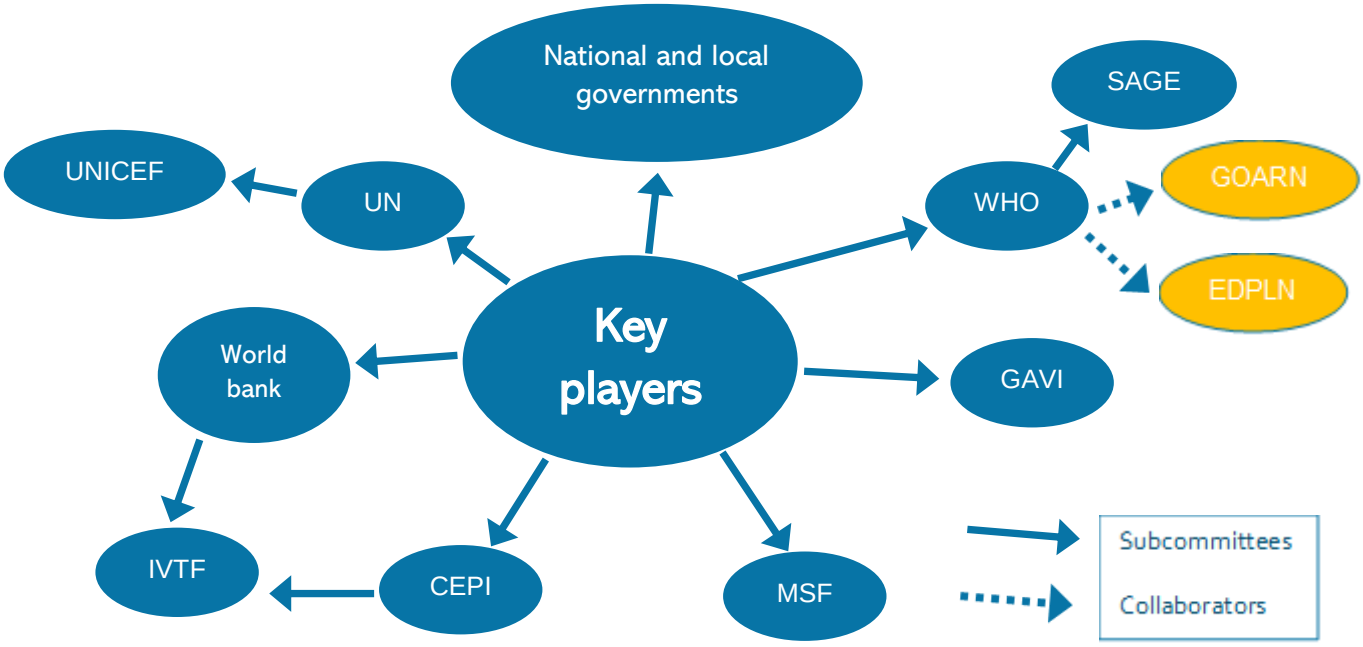


FIGURE 3. KEY PLAYERS IN THE DISEASE X RESPONSE

Abbreviations:
CEPI Coalition for Epidemic Preparedness Initiative
EDPLN Emerging and Dangerous Pathogens Laboratory Network
GAVI Global Alliance for Vaccines and Immunization
GOARN Global Outbreak Alert and Response Network
IPTVF International Vaccine research taskforce
MSF Medecins Sans Frontieres
SAGE Strategic Advisory Group of Experts on Immunisation

Currently, there is no international organisation or working group focussed solely on supporting the vaccine response to an unknown pathogen. We recommend that a specific working group under the immunisation, vaccines and biologicals programme is established with the primary aim of ensuring a quicker response upon emergence of a *novel* viral epidemic, by educating governments and funding bodies regarding the co-benefits of a proactive and flexible approach to vaccine development.

2. FUNDING AND INCENTIVISATION

2.1. CASE FOR INVESTMENT

Despite the large upfront investment generally required for development of new vaccines and the uncertain outcomes of research efforts, the significant social and economic costs of a global epidemic demonstrate that funding R&D into preparedness is a sound investment from the perspective of the global economy. Economic optimisation analysis suggests that mitigation policies, such as vaccination, need to be only minimally effective in reducing disease risk to be worth implementing[2].

In addition, investing in flexible and adaptable technologies for Disease X preparedness can be justified as socially responsible when considering the range of possible co-benefits across the field of public health. However, there is currently a lack of incentive for private and public funding investment into EID vaccine development.

New and innovative funding models are needed to more sustainably fund R&D for emergency response and preparedness. The global nature of the threat necessitates more cross-border collaborative schemes aimed at improving preparedness with international pooled funds guiding strategic investments. The end price of vaccines must also be considered: in a public health emergency it is crucial to decouple the cost of the final product from R&D costs so that cost for those in need is not a prohibitive factor to an effective response effort.

How much is needed?

The Commission on a Global Health Risk Framework for the Future estimates an additional US$1bn. This figure does not include expenses related to other necessary infrastructure improvements and maintenance (*21*).

2.2. FINANCING OPTIONS: HARNESSING PUBLIC AND PRIVATE SECTORS

Multiple initiatives already exist to help fund progress into different areas and various recommendations for financing preparedness efforts have been made by different bodies[1 10], summarised below:

Establishment of a pooled global vaccine development fund recommended by the High-level Panel on the Global Response to Health Crises; the Harvard Independent Panel; and the Commission on a Global Health Risk Framework for the Future. Governments, foundations and the private sector would directly fund this centrally managed entity on a voluntary or mandatory basis, which could then disburse the funds according to identified research priorities. This is an efficient way to organise funding efforts and allow sharing of the risks, costs, and benefits of the process across partners. This is especially useful for smaller funders/countries that lack the capacity to set up independent programmes.

Market shaping via advance market commitments and advance purchase commitments Creation of sustainable markets providing sufficient incentive to trigger investment into specific product development by the pharmaceutical industry (Case study 1). Purchase commitments may only be made provided the company can demonstrate appropriate manufacturing capacity to meet demand in an outbreak.

Case Study 1: Market shaping

In 2016, GAVI committed an initial $5 million toward the procurement of MSD's Ebola vaccine once it was commercially available in a public-private partnership. As part of the deal, MSD agreed to ensure that a stockpile of 300,000 doses of the investigational vaccine was continuously available in case there was an outbreak before the product was licensed. This included 100,000 doses that could be shipped within five calendar days. The vaccine is now in use in the DRC, although it is not yet fully licensed.

Coordination of individual funders on product and/or pathogen level involving distinct funding entities for each pathogen, group of pathogens or product and incentivise co-ordination of research efforts and "work-sharing" agreements. This allows the engagement of funders who cannot—due to formal or other constraints—engage in pooled funding.

Product development partnerships Not-for-profit entities usually funded by public-private partnerships (PPPs) to accelerate R&D of pharmaceutical products for the developing world, often through links between developing country academic programmes, biotechnology companies, and vaccine manufacturers (Case study 2). Current examples include the Drugs for Neglected Diseases Initiative (DNDi 2003), PATH Malaria Vaccine Initiative (MVI 1999) and International AIDS Vaccine Initiative (IAVI 1996)

Case Study 2: PPPs
CEPI aims to incentivise collaboration of partners by promoting sharing of any commercial benefit from product development, despite the primary aim being non-profit development for use in low-to-middle income countries.

Clause 15.2 of their terms for awarding funding states the commitment to "*ensure that the risks, costs and benefits of product development and commercialization are accounted for fairly, proportionately and reasonably when calculating an appropriate share of any commercial benefits.*"

Milestone incentivisation prizes Financial awards made to specific vaccine candidates that pass Phase I clinical trials.

International Finance Facility for Immunisation (IFFIm) This fund, established in 2006, uses long-term legally binding commitments by donors of up to 20 years by selling "vaccine bonds" on the international capital markets. The sale of these bonds provides cash that can be used by the GAVI Alliance to allow funding of breakthrough vaccines rapidly and securely. The long-term commitment provides the predictability that developing countries need to make long-term budget and planning decisions regarding immunisation programmes. A US$2.6 billion has been disbursed to support vaccine purchase and delivery to 71 developing countries.

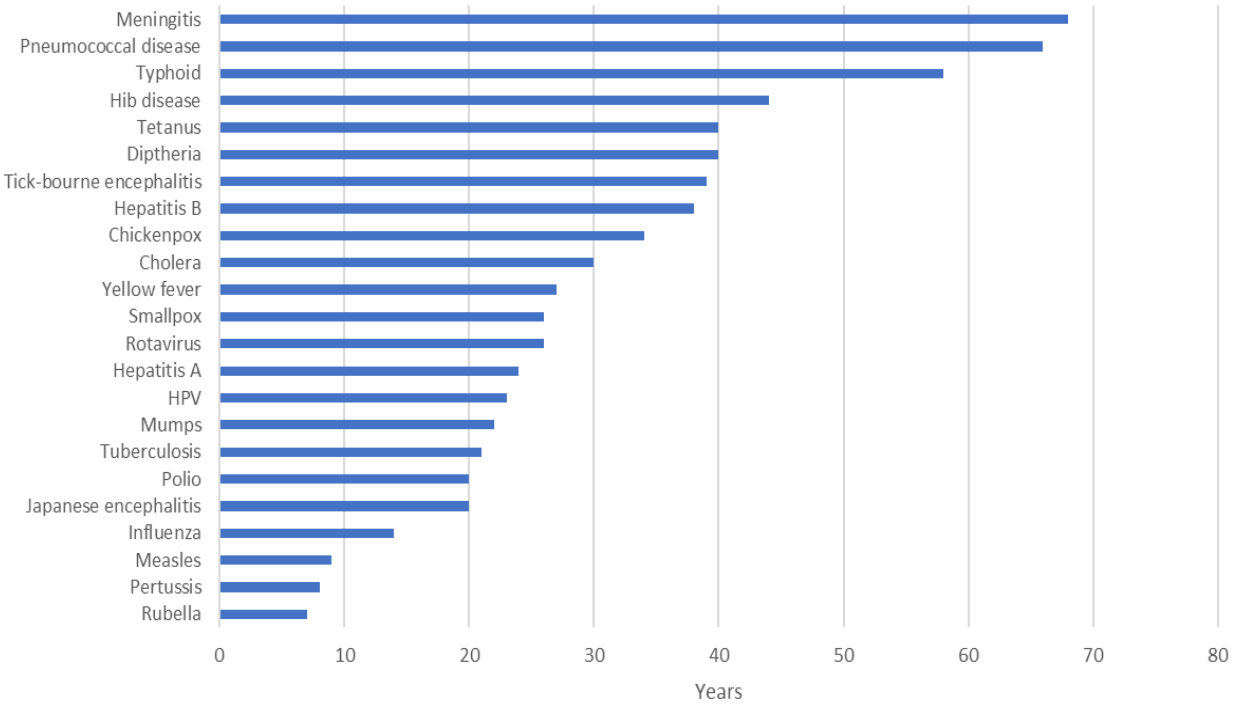
New sources of private finance from outside the health care sector: In the case of an outbreak there is a heavy negative financial impact on sectors including insurance, travel, tourism and the meat and poultry industry. Awareness initiatives promoting the co-benefits of socially responsible investments (e.g. IFFIm) may provide a strong incentive for the private sector to invest in prevention. In addition, where private sector companies contribute directly or indirectly to the risks of disease outbreak and spread by the nature of their business, national governments should introduce regulations requiring such companies to invest in risk mitigation and preparedness, as suggested by the World Bank International Working Group on Financing Preparedness (IWG).

3. R&D Challenges

3.1. 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 (Figure 4)[13], 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 expediating the R&D response and developing a sustainable model for vaccine development. In order to respond to threats posed by Disease X, further reductions in vaccine R&D timelines are required. In this section, we present a review of the challenges involved in vaccine R&D and the current policies in place to address these challenges. Based on this review, we identify a number of areas for further investment and improvement that should be overseen by a central governing body.

FIGURE 4. TIME BETWEEN IDENTIFICATION OF A LINK BETWEEN THE PATHOGENIC AGENT AND DISEASE, AND DATE OF VACCINE LICENSURE.



3.1.1. PROBLEM STATEMENT

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

A. **The lack of adaptable vaccine platforms-** for every new virus, the R&D process needs to start from scratch, with each new vaccine requiring its own safety and efficacy trials and regulatory procedures.

B. The strict guidelines for regulatory approval and licensing- requiring comprehensive but time-consuming clinical trials

C. Lack of funding and incentivisation

3.1.2. POLICY ANALYSIS

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[14]. 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 has 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[15]. They are now inviting submissions to develop vaccines against Chikungunya and Rift Valley Fever. During the course of writing this report, CEPI has 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 an self-amplifying RNA (saRNA) platform, and $34m to CureVac to develop an mRNA vaccine platform.

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[16]. 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) improve rapid delivery of funds to research projects upon emergence of a new epidemic.

The **World Health Organisation (WHO)** has several **sub-committees and initiatives** aimed at improving vaccine R&D responses: The Initiative for Vaccine Research facilitates vaccine R&D against pathogens with significant disease and economic burden[17]. The Global Vaccine and Immunization Research Forum (GVIRF) is co-hosted by the WHO, the National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation every second year, with the aim of discussing challenges, opportunities and actions in the vaccine R&D field[18]. The WHO R&D Blueprint is a strategy and preparedness plan to expediate R&D activities during epidemics[19]. 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[20]. 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[21], 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. As of yet, the WHO have not addressed how they will support R&D processes against Disease X. Another important initiative developed by the WHO is the Emergency Use Assessment and Listing (EUAL) procedure for vaccines, which can be used to expediate the availability of vaccines needed in a public health emergency, without going through rigorous licensing procedures[22].

The **UK Vaccine Network** brings together experts from industry and academia to advise the government on the most promising investment opportunities to help combat infectious diseases with the potential to cause an epidemic[23]. Under this advice, the UK government has committed to invest £120 million between 2016 and 2021. Currently, £70 million is being used to fund 60 projects throughout the UK, outlined here[24]. In January, the UK government pledged £10m in funding to CEPI[25].

3.2. REVIEW OF THE CHALLENGES FACING R&D OF VACCINES AGAINST EIDS AND POTENTIAL SOLUTIONS

Appendix 2 displays results of a review of the challenges facing pre-clinical and clinical development of vaccines against an unknown viral pathogens; potential solutions; and areas for improvement.

3.2.1. 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

3.2.2. CLINICAL DEVELOPMENT

Clinical development involves the testing of candidate vaccines in humans. It involves four phases that usually take place over several years:

a. **Phase I:** Small-scale trials (involving 20-80 subjects) to assess safety in humans and the immune response elicited. For diseases affecting developing countries, these trials are usually first performed in European volunteers (phase Ia), and then in populations in the target area (phase Ib).
b. **Phase II:** Assessment of efficacy against artificial or natural infection.
c. **Phase III:** Large-scale trials involving hundreds to thousands of participants across several sites to evaluate efficacy under natural disease conditions. Tests are randomised, blind, and involve the vaccine being tested against a placebo. Phase III trials test the vaccine's safety (rare side effects may only become apparent when larger-scale trials are performed), efficacy, proposed doses and method of delivery.
d. **Phase IV:** Optional studies conducted after licensure. Aims to detect rare side effects and assess long-term efficacy.

3.3. ACCELERATING THE RESPONSE: ADAPTABLE VACCINE STRATEGIES

In order to react to emerging pathogens, vaccine R&D processes must be more adaptable. This allows for a pro-active approach where the majority of pre-clinical testing has been performed and clinical trials are planned and approved. The main requirement of this approach is that the vaccines themselves are adaptable.

3.3.1. VACCINE PLATFORM TECHNOLOGIES

Vaccine platform technologies use a module (platform), usually nucleic acid or a viral vector, which is used to deliver a synthetic immunity-inducing protein (antigen) into the body[26] (Figure 5). Once developed and licensed for one vaccine, development of future vaccine simply requires substitution of the desired antigen, enabling faster development, production and regulatory approval, as well as

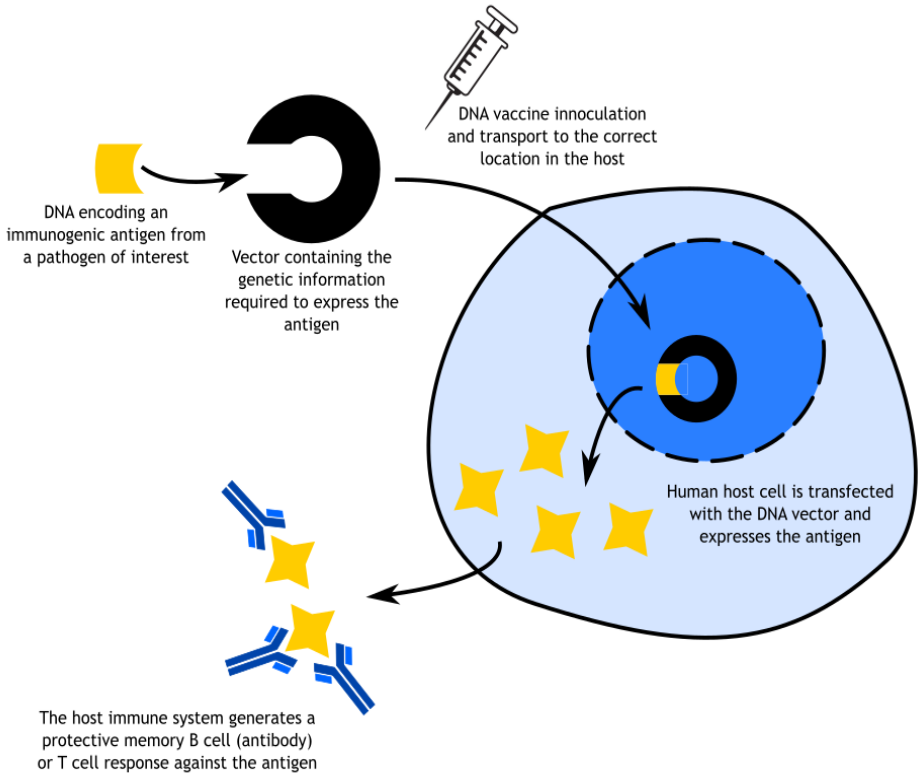


FIGURE 5: THE SIMPLIFIED MECHANISM OF PLATFORM TECHNOLOGY BASED VACCINES. THIS SHOWS A DNA-BASED PLATFORM (OTHER PLATFORMS ARE AVAILABLE).

reducing costs[26–28]. The U.S. National Institute of Allergy and Infectious Diseases Vaccine Research Centre has developed DNA-based vaccines for several viral threats including SARS coronavirus, H5N1 avian influenza, H1N1 pandemic influenza and Zika virus[29]. The use of platform technology meant that the time from viral sequence selection to initiation of phase I clinical trials was shortened to around 3 months[30].

3.3.2. MULTIVALENT VACCINE STRATEGIES

Vaccines can be designed to protect against multiple strains or species of virus, through display of multiple antigens on a single platform or by combining multiple platform products[28]. This is only feasible where two or more viruses are endemic in the same region, and exhibit a similar epidemiology, but has the potential to speed up vaccine development (particularly clinical testing) and reduce costs. A new vaccine protecting against both Zika and chikungunya viruses uses a single vector to express structural proteins from both viruses[31].

3.4. CONCLUSIONS

Both the WHO and CEPI have identified vaccine platform technologies as a tool to speed up vaccine R&D in response to novel pathogens, and have stated plans to invest in development of these technologies[19,32]. There is a vital need for an organisation that focusses solely on improving vaccine production and distribution in response to *novel* pathogens. Given the dependence of faster vaccine R&D on vaccine platform technology, one of the primary aims of this organisation should be to invest in and promote the development of these technologies. Based on our review of the other challenges to expediting vaccine R&D (Appendix 2), we recommend that this new organisation should also:

a. Invest in and coordinate
    - Research into clinical outcomes of disease and risk analysis of emerging pathogens to increase appreciation of risk, hence incentivising governments and vaccine manufacturers
    - Increasing clinical trial infrastructure in developing countries
b. Facilitate pre-negotiations between R&D stakeholders, vaccine manufacturers, national government authorities, humanitarian organisations and academics to enable sharing of data and materials upon the onset of an epidemic
c. Build relationships between international and local ethics boards, national regulatory authorities and vaccine manufacturers to define requirements for product review and enable quick decision making on clinical trial protocols during epidemics
d. Develop a streamlined approach for vaccine licensing and regulation upon emergence of an epidemic in the absence of robust clinical trial data.

Although immunogenicity and efficacy assays will require specific reagents, there should be a move towards standardised protocols and procedures for families of viruses. Funding for these activities should come primarily from national governments, supported by funds from traditional funding agencies (see Section 2 for further details).

4. Optimising Manufacture

4.1. Introduction

Vaccine manufacture is a challenging process which, due to biological, economic, and technological limitations, currently struggles to produce sufficient vaccines for all the known diseases in the world. The rapid production of a vaccine against any new disease is difficult; vaccinating specifically against Disease X presents further challenges requiring inventive solutions (Table 1).

TABLE 1. CHALLENGES AND SOLUTIONS IN VACCINE MANUFACTURE

Challenge	Solution
Uncertain vaccine type	Investment in platform technology-based manufacturing facilities (see Section 3)
Disruption of usual vaccine production	Stockpiling of routine vaccines where possible
Unequal global distribution of manufacturing facilities	Investment in platform technology-based production plants in low and middle-income countries

4.2 Challenges and Solutions in Vaccine Manufacture

4.2.1 Flexibility

The vaccine production facilities currently in use do not have the flexibility to switch between producing different vaccine types; however, this flexibility would be a valuable asset in the manufacture of a rapid response vaccine to Disease X and the use of relatively new and flexible platform technologies may provide a solution (see Section 3).

Thus, we recommend incentivising building of platform technology production facilities by making clear the co-benefits associated with these technologies (Table 2). These facilities could then relatively easily be used to produce a rapid-response vaccine against Disease X early in the outbreak.

TABLE 2. PROBLEMS AND CO-BENEFITS OF INVESTMENT IN PLATFORM TECHNOLOGIES

Problems

Vector	Limitation
Adenoviruses, poxviruses	Anti-vector immunity due to previous infection or immunisation reduced efficacy[59].
Viruses, DNA	Risk of insertional mutagenesis (alterations to the genome of the host cell)[60]
DNA	Inefficient delivery into human cells limits potency[59].

These could largely be avoided by choosing the most suitable vector and vaccines based on mRNA have demonstrated proof of concept in humans and have very bright prospects[59].

Co-benefits

Vaccine platforms can overcome many of the issues faced by traditional vaccine manufacturing. Advantages include:

- They can rapidly generate safe vaccines at a low cost[61].
- They are more appropriate for targeting pathogens with a high rate of genetic change[61].
- Faster production of new vaccines[62].
- Reduced investment in building manufacturing facilities[62].
- Streamlined regulatory processes[62].

4.2.2. ROUTINE SUPPLY

The re-allocation of vaccine production facilities would disrupt the supply of vaccines for routine immunisation programmes. Thus it would be prudent to strategically stockpile vaccines where possible to provide protection against the possibility of a temporary, brief interruption in the production of a vaccine[33]. Stockpiles are usually established at the national level[34], but individual countries will differ in their ability to do this. Negotiation of pooling such resources to mitigate the effects of Disease X on routine vaccine supply of affected countries would be a possible solution. However, the decision to establish and maintain a vaccine stockpile is complex and considerations include[34]:

- Disease and vaccine characteristics
- Stockpile management
- Funding and ethical issues regarding access to vaccines
- Stockpile location and relationship to distribution

4.2.3. FACILITY LOCATION

Despite the innate unpredictability of Disease X emergence, modelling shows that the risk of an emerging infectious disease event is highest in the tropical regions, where many low- and middle-income countries are located[35] and which typically have fewer, simpler vaccine manufacturing facilities as well as poor epidemic preparedness (Figure 6).

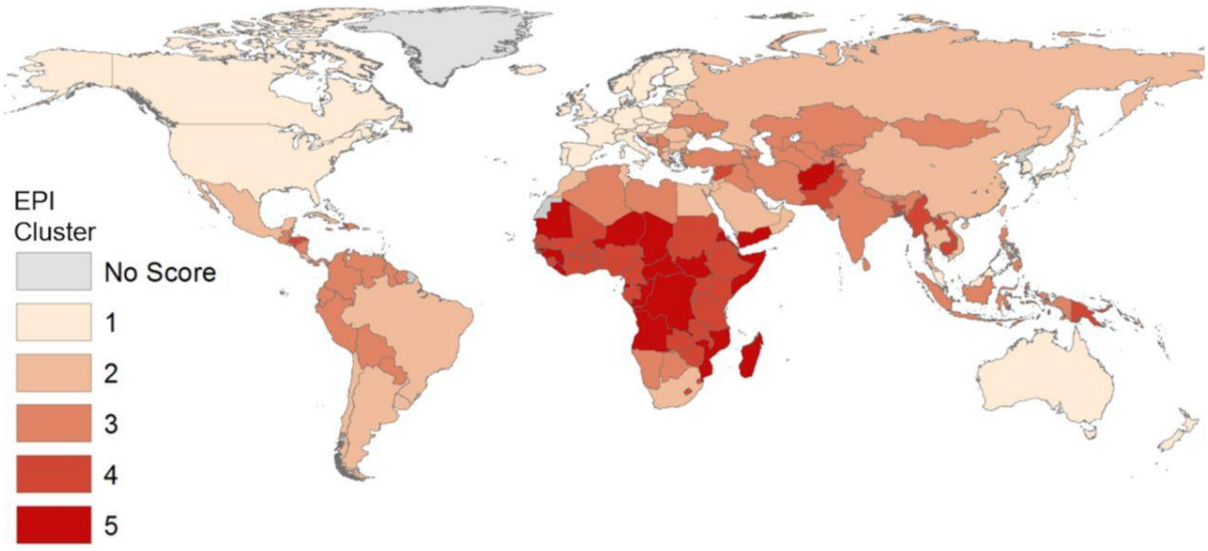


FIGURE 6. GLOBAL DISTRIBUTION OF EPIDEMIC PREPAREDNESS INDEX (EPI) SCORES (1=MOST PREPARED, 5=LEAST PREPARED). FROM METABIOTA [75]

Local manufacturers in low- and middle-income countries (LIMCs) have supplied traditional EPI (The WHO Expanded Programme on Immunisation) vaccines to countries for many years, using relatively simple technology and have been able to do so without significant research and capital investment[36]. However, these manufacturers are likely unable to adapt their processes to produce a vaccine against Disease X, and there are a number of factors which would make it difficult to build the new production facilities which would be required to produce this vaccine. These are outlined in Table 3 alongside the associated co-benefits.

TABLE 3. THE CHALLENGES AND BENEFITS ASSOCIATED WITH ESTABLISHING VACCINE PRODUCTION FACILITIES IN LIMCS (37)

Benefits	Challenges
Supply security	High failure rate of preceding efforts
Production scheduling and sustainability control	High cost and time to establish complex processes
Control of costs	Capability for production of a broad vaccine portfolio
Socio-economic development	Fragmented or inconsistent demand
Rapid response to local epidemics including EIDs	Diverse regulatory requirements
	Limited local competence and experience
	Equipment, staff and consumables require initial importing, limiting benefits to the local economy

Current policy is improving the geographical distribution of vaccine manufacturers (see Case Study 3 for two initiatives). UNICEF has increasingly procured vaccine stock from developing country manufacturers, representing ~20% of UNICEF's $218M procurement portfolio in 2001 to 41% of their $1,725M portfolio in 2015[38]. However, UNICEF only procures vaccines that have met stringent WHO prequalification standards[38].

Case Study 3: Gavi and DCVMN initiatives

Gavi are expanding their manufacturing base to include more numerous and geographically dispersed manufacturers, reducing the costs of the vaccines they procure. In 2001, Gavi procured prequalified vaccines from 5 manufacturers, one of which was based in Africa. By 2016, Gavi's manufacturing base had expanded to include 16 manufacturers, 9 of which were based in Africa, Asia and Latin America [63]. The **Developing Countries Vaccine Manufacturers Network** (DCVMN) includes nearly 50 vaccine manufacturers in 17 developing countries in Latin America, Africa, the Middle East and Asia[64]. It is a public and private alliance with the goal of manufacturing and supplying high-quality vaccines at affordable prices[65]. The DCVMN members' pipeline is especially focused on regional diseases and network members have the collective technologies, capability and capacity to produce more than 40 vaccine types[65].

The ability of platforms to target multiple pathogens securely justifies the investment required to build and maintain manufacturing plants that specialise in one platform, mitigating some of the difficulties outlined above and promoting trade. In order to expand vaccine production in developing countries, manufacturers should work with the WHO and the DCVMN to sustainably meet WHO prequalification standards.

4.3. CONCLUSIONS

In the case of a Disease X outbreak, vaccine production facilities would ideally be ready to manufacture doses soon after a vaccine has been approved. The best way to achieve this would be by basing this vaccine on platform technologies such that current manufacturing facilities simply swap the antigen on which the vaccine is based and produce it using their current equipment and operators. This relies on the capabilities of existing facilities which are not possible at present. Rapid switching would unfortunately interrupt routine vaccine production and whilst stockpiles could be created to prepare for this, this may not be feasible for all vaccines or in all countries. Central management of stockpile distribution can supplement vaccine supply in disrupted countries.

There is still a significant disparity between manufacturing capacities in developed and emerging economies and the establishment of even basic manufacturing capacities in low-income countries would strengthen epidemiological capabilities, utilise knowledge regarding locally prevalent disease and ensure a greater domestic supply of vaccines in case of an outbreak[11]. Therefore, we recommend that a co-ordinating group lead efforts to assist developing countries in building manufacturing capacities for vaccines, for example by accelerating technical and financial support to initiatives such as the DCVMN[11].

5. Optimising Vaccine distribution

5.1. Introduction

There are a number of uncertainties in vaccine distribution (see Figure 7) which can be managed using both new strategies and those in current use. Plant location is discussed above in Section 4; vaccine destination variability and human factors are discussed in Section 6; and transportation and infrastructure are addressed here.

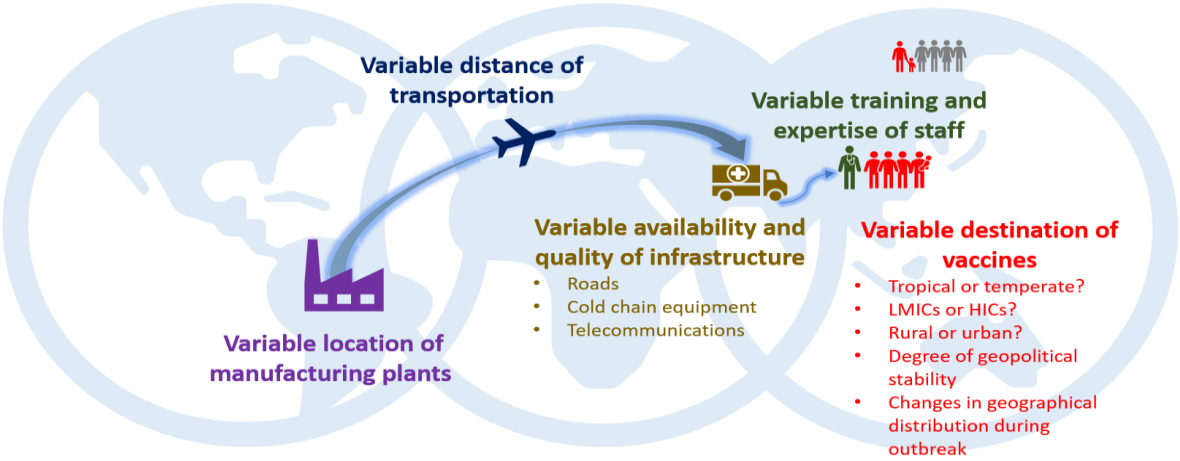


FIGURE 7. UNCERTAINTIES IN THE DISTRIBUTION OF A DISEASE X VACCINE

5.1.1 Policy Analysis

Initiatives committed to improving supply chain infrastructure worldwide include the comprehensive Effective Vaccine Management (EVM) framework developed by the WHO/UNICEF Immunization Supply Chain and Logistics Hub, Gavi's Cold Chain Equipment Optimization platform, Project Optimize collaboration between the WHO and PATH, the 2017 Addis Declaration on Immunization, organisations such as VillageReach, and commercial partnerships such as Global Good (see Appendix 1)

5.1.2. Recommendations

A central WHO committee would work to ensure that the multitude of independent organisations are aware of each other and can work together to coordinate and synergise efforts. Proactive infrastructure development options include:

- Safely and sustainably expanding the global vaccine manufacturing base
- Improving the management and efficiency of vaccine distribution vehicle fleets
- Improving maintenance and management of poorly performing supply chains using a combination of remote temperature monitoring (RTM), roaming cold chain equipment (CCE) technicians, and a centralised stockpile of replacement parts
- Establishing reliable national grid connectivity and backup power supplies
- Development and commercialisation of specific phase change materials (PCMs) for atypical cold chain temperature ranges

5.2. VARIABLE DISTANCE OF TRANSPORTATION

Variability in the geographical distance over which Disease X vaccine may need to be transported encompasses both uncertainty in Disease X outbreak location and uncertainty in manufacturing plant location (see Section 4). However, a number of initiatives can affect transportation directly. For example, management of vehicle fleets can be successful in achieving low operational cost per kilometre (case study 4). Vehicles are also needed for disease surveillance and sample transportation[39], improving the ease with which samples can be delivered to research laboratories for vaccine R&D.

Case study 4: Transport on the ground

In Ethiopia in 2003, the operational cost of the WHO EPI vehicle fleet was USD 0.13/km. The 35-vehicle EPI fleet primarily facilitated acute flaccid paralysis surveillance for poliomyelitis cases as part of the Global Polio Eradication Initiative, but also supported supplementary immunisation activities and integrated disease surveillance and reporting. The low operational cost per kilometre was achieved by efficient management at all levels, including drivers who were committed to maintaining and economically refuelling vehicles. Monthly, quarterly and annual transport reports that were shared with WHO Regional Office for Africa (AFRO) via the WHO Country Representative. In addition, all vehicles had functional radios for communication with other vehicles, the Ethiopian WHO/EPI office, and the UN (WHO, 2015).

The variable distance of distribution becomes less problematic if the ease with which we can transport vaccine stock per unit distance is improved, which itself relies on the availability and quality of infrastructure. By improving both the geographical distribution of manufacturing plants and the infrastructure of recipient locations, problems with transportation can be minimised.

5.3. VARIABLE AVAILABILITY AND QUALITY OF INFRASTRUCTURE

Overcoming these issues is achieved by two methods:

a) Changing the **external environment** in which the vaccine is stored and transported. This encompasses vehicles, roads, telecommunications and cold chain equipment (CCE)
b) Changing the **properties of the vaccine itself** to withstand more extreme external environments

These factors can be optimised in a number of inventive ways and are not necessarily mutually exclusive.

5.3.1. THE EXTERNAL ENVIRONMENT

Case Study 5: Reliable Power supply

The rVSVΔG-ZEBOV-GP candidate Ebola vaccine was trialled during the 2014 – 2015 Ebola outbreak in Sierra Leone. Due to limited stability data, the vaccine was distributed using a cold chain operating at -60°C or colder. Cold chain equipment used included -80°C ultracold freezers, which were installed at one central and two rural satellite study sites, and passive vaccine storage containers

- Due to unreliable grid power for the freezers, voltage regulators were installed to protect CCE from power surges, and multiple backup power sources (batteries and fuel-powered generators, and solar lighting[42].) were installed to prevent vaccine spoilage during grid outages
- Effective storage containers maintained temperatures of -74°C to -70°C for approximately 5 days, outlasting the longest power outage experienced (5 hours and 50 minutes) and proved useful in replacing the function of one failed ultracold freezer; containers were rotated with the remaining functional ultracold freezers to store vaccine vials indefinitely[42]

Distribution can be optimised by ensuring quality vaccine storage through maintenance of the cold chain and power supply. The practice of storing and transporting vaccines within recommended temperature ranges utilises a 'cold chain' involving refrigerators, transport vehicles, personnel, and information communication and management systems. Maintenance of this cold chain with as few interruptions as possible maintains vaccine integrity. The temperatures to which vaccines are exposed affect the rate at which vaccines lose potency[40] and different vaccines have different recommended ranges[41]. The temperature range within which most vaccines remain stable and maintain potency lies between +2°C and +8°C (Figure 8). These limits should be sufficient to ensure the thermostability of any novel Disease X vaccine, provided that the novel vaccine is not entirely different from existing types of vaccine. However, it is possible that data on vaccine stability at different temperatures will be limited during early Disease X vaccine trials, necessitating cold chains which operate at temperatures outside these limits[42].

Should Disease X vaccine distribution require a cold chain operating outside the usual +2°C to +8°C, storage containers can be developed to match these atypical cold chain specifications and help to overcome many of the problems of unreliable power (Case study 5). This would also facilitate other supply chains, including those for frozen biological samples[43] for the purposes of vaccine R&D.

FIGURE 8. STABLE TEMPERATURE RANGES FOR DIFFERENT VACCINES (FROM WHO, 2005). OPV – ORAL POLIO VACCINE, BCG – BACILLE-CALMETTE-GUERIN (TUBERCULOUS VACCINE), HIB – HAEMOPHILUS INFLUENZAE TYPE B, MR – MEASLES-RUBELLA, MMR – MUMPS-MEASLES-RUBELLA, HEPB – HEPATITIS B, DT – DIPTHERIA-TETANUS, DTP – DIPTHERIA-TETANUS-PERTUSSIS, IPV – INACTIVATED POLIO VACCINE, TT – TETANUS TOXOID, TD – TETANUS TOXOID AND DIPTHERIA (REDUCED COMPONENT)

Case study 6: Cold chain integrity

Simple non-technical solutions, such as education on checking thermostat settings and keeping solar panels clean, should not be underestimated. At study sites in Mozambique, correction of thermostat settings increased the number of correctly functioning refrigerators by 30%. The number of temperature excursions above 8°C decreased by 78%, and excursions below 2°C decreased by 60%[44].

The cold chain can be reliably improved by basic education and record keeping to reduce human error[44] (Case study 6). Technical solutions to reduce machine error include:

- Wireless remote temperature monitoring (RTM) of refrigerators
- A centralised replacement parts stockpile managed by roaming technicians dispatched in response to RTM (a lack of technicians able to diagnose and repair solar devices in remote regions has been identified as a barrier to the successful maintenance of solar-powered refrigerators[45]).
- Record keeping of faults and repairs to aid preventative maintenance on site and identify which parts to maintain in the central stockpile[44].

5.3.2. Vaccine Properties

Case study 7: Thermostability and storage

In June 2017, the government of South Sudan announced the death of 15 children due to contaminated measles vaccines. Inadequate storage, including lack of refrigeration, and poor administration practices, such as reusing syringes, were cited as some of the reasons for this incident[66].

Disease X vaccines will likely need to be distributed to remote regions with poor accessibility and infrastructure; hence, vaccine shipments should ideally be able to withstand breaks in the cold chain. Both better insulating packaging and thermostable vaccines are potential solutions for maintaining vaccine potency during cold chain breaks (Case study 7). High performance vaccine cold boxes and carriers are already used, particularly for outreach immunisation activities[46]. However, in 2015 there were no commercially viable thermostable vaccines despite investment in their development[47]. However, safe distribution of vaccines can be facilitated by:

- **Replacing existing vaccines with thermostable vaccines**[45,48,49]
- **Designing new vaccines so that they are thermostable**[47]
- **Exploiting the thermostable ranges of existing vaccines**[40,47]

If thermostable vaccines were to become commercially available, computational modelling studies have shown that **replacing current vaccines with thermostable vaccines** should free up cold chain capacity[49]. The initial costs of the more expensive thermostable vaccines would be reimbursed in medical cost and productivity savings[45]. Levin *et al.* (2007) suggest that, "Freeing up cold chain space through the introduction of thermostable vaccines could greatly facilitate the introduction of new vaccines." Thus, the cold chain capacity freed by thermostable routine vaccines could be used to transport and store non-thermostable Disease X vaccine. A problem with this idea is that once some cold chain capacity is no longer needed, there is no incentive to maintain excess cold chain equipment. This excess equipment and the spare capacity it represents could be defunct or missing by the time Disease X vaccines need to be distributed. However, an industry trend towards merging vaccine and medication supply chains could provide the incentive for maintaining cold chain equipment in between vaccination campaigns[46].

With regards to **designing a thermostable Disease X vaccine** in the first instance, Karp *et al.* (2015) note that investments in improving vaccine thermostability "have failed to result in the development and deployment of any commercial vaccine product with improved thermostability." Given the difficulties of producing an unknown novel vaccine, it will be even more difficult to design and produce a thermostable formulation of Disease X vaccine initially. In the long term, researchers remain hopeful that emerging technologies could one day remove the need for cold chains for routine vaccinations[46,47,50]. For now, Karp *et al.* (2015) conclude that "Improving cold chain infrastructure and supply chain system design is likely to have the largest impact on total system costs and coverage [in Low-Middle Income Countries] in the short term".

Exploiting the thermostable ranges of existing vaccines involves recognising that exposure to temperatures outside recommended ranges does not automatically result in loss of vaccine potency or safety[40]. This may be used to exploit the thermostable range of a Disease X vaccine for brief periods during cold chain breaks, or the routine EPI vaccine stock to temporarily free up cold chain capacity for the Disease X vaccine. However, this 'off-label' use of vaccines stored outside their recommended temperature ranges carries serious risk. Such practices are likely to erode recipient trust and acceptability and are therefore not recommended in this report.

It therefore appears that changing the external environment (section 5.3.2.) is more likely than changing vaccine shipment properties (section 5.3.3.) to yield immediate results in improving ease of Disease X vaccine distribution.

5.4. CONCLUSIONS

Enabling Disease X vaccine distribution means equitably improving supply chain infrastructure worldwide. Improving supply chain infrastructure in the poorest, most remote regions must be a priority because, although the outbreak location for Disease X remains uncertain, the greatest challenges to successful Disease X vaccine distribution will arise in regions without supply chain (or other basic) infrastructure.

Sections 5.2. and 5.3. discussed different approaches to developing supply chain infrastructure in advance of a Disease X outbreak. Actionable approaches are recommended in section 5.1.2. In addition to facilitating Disease X vaccine distribution, taking action to develop supply chains where needed brings wider co-benefits: facilitating routine immunisation activities, access to healthcare, and disease surveillance.

These co-benefits represent incentives for stakeholders to invest in proactive supply chain development. Organised collaboration among many stakeholders (governments, NGOs, public and private initiatives as outlined in section 5.1.1.) is needed to ensure that global supply chains are fit for purpose when Disease X emerges. To this end, we recommend a central committee is established to promote collaboration between stakeholders and ensure a concerted effort towards Disease X pandemic preparedness.

6. VACCINE COVERAGE AND DEMAND

6.1. INTRODUCTION

Once the vaccine is available at the outbreak location, how can we ensure that it is used most effectively? Ring vaccination is likely to be implemented with the aim of breaking transmission chains, but requires identification of contact networks, an understanding of local behaviours and willingness of target individuals to receive the vaccination. However, vaccine hesitancy and refusal are a problem worldwide and a lack of co-operation may result from fear and uncertainty surrounding Disease X.

This section explores how these social factors could potentially limit the impact of an otherwise effective vaccine and stresses the importance of community engagement in facilitating a tailored approach to local contexts.

WHO Global Vaccine Action Plan– Strategic Objective 2:

"...individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility."

6.2. VACCINATION STRATEGY AND TARGETS

Due to the time lag between the emergence of a new disease and the development and distribution of a vaccine, vaccine supply is commonly short at the beginning of an outbreak[51]. Making efficient use of the limited resources necessitates the initial identification of transmission networks as well as individuals at high risk of mortality or severe morbidity.

Ring vaccination requires identification of contact patterns

A commonly used initial strategy to target at-risk individuals is ring vaccination, whereby contacts and contacts-of-contacts of infected persons are vaccinated (Figure 9). This aims to reduce and ultimately eliminate transmission of the virus in order to minimise the number of infected persons. In all outbreaks, vaccination of healthcare workers and other frontline staff is key due to their frequent contact with infection and to prevent understaffing at healthcare facilities. Other high-risk groups depend on local transmission networks and the pathogen transmission route (See Case Study 8). While the latter will be unknown prior to the outbreak, it is most likely to be via the respiratory system[52].

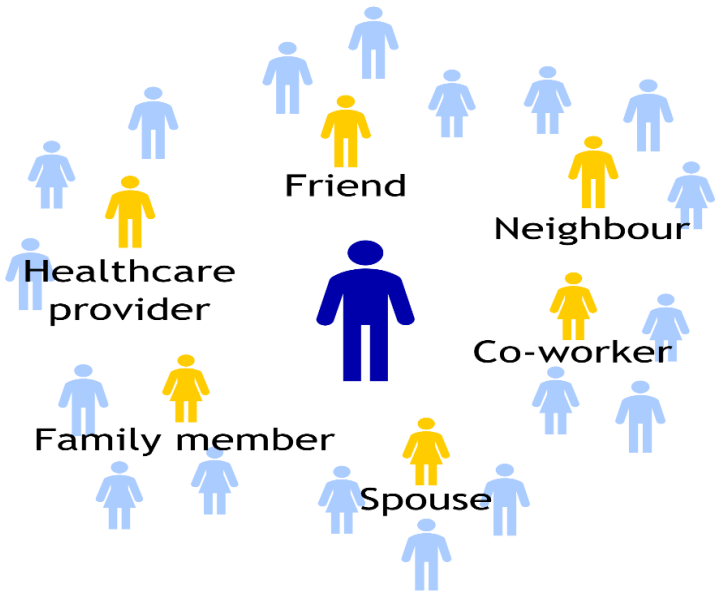


FIGURE 9. RING VACCINATION

Case study 8: May 2018 Ebola DRC

Motorcycle taxis are a key mode of transportation in the health zones of Bikoro and Iboko. Taxi drivers in the areas called for the rVSVDG-ZEBOV-GP Ebola vaccine due to high rates of exposure and infection. They also likely contributed to transmission across the communities due to the large distances travelled each day. The vaccine was already being administered to healthcare providers and known contacts of infected persons. Taxi drivers in the areas were subsequently offered the vaccine.

Certain groups are at high risk of severe morbidity and mortality from Disease X

Demographic groups most at risk of severe morbidity and mortality from an outbreak are often the very young, very old, expectant mothers and the immunosuppressed. However, other at-risk groups are often identified in the early stages of the outbreak and targeted by the time the vaccine has been manufactured and distributed. Again, an understanding of local contact patterns and demographics allows the context-specific identification of high-risk groups.

6.3. Data collection and recording

When using a new vaccine, assessment of coverage and efficacy is an important part of development of the vaccine and may be better monitored by utilising new digital technologies (Figure 10). Tracking coverage can highlight geographical areas which require more attention, while collecting data on seroconversion and side effects is useful for research purposes (see section 3) and predicting optimal dosing schedules.

The potential of digital systems to reduce human error and improve efficiency has been recognised by global stakeholders[53], and the evidence to support their use is becoming increasingly available. Gavi is currently exploring this via its annual Innovation for Uptake, Scale and Equity in Immunisation (INFUSE) program, which in 2018 called for 'proven digital technology innovations that provide more effective methods of identity registration and authentication to accelerate and improve immunisation coverage and delivery.'

Figure 10. Use of digital technology during the vaccine response

Biometrics used to identify individuals, link them with existing health records or, if none exists, one is created

Records can be accessed via mobile app. Healthcare provider enters details of vaccine given and supplementary information such as symptoms, diagnostic test results, and seroconversion data

Analytics used to monitor vaccine coverage and efficacy. Following the acute outbreak, individuals who received partial schedules can be contacted for a booster dose

6.4. Improving vaccine Uptake

> *"Historic experiences, personal narratives and community memories are not forgotten, particularly when they have triggered past anxiety and concern. In the context of acute uncertainty and risk, trust becomes key. Reflecting on where episodes of vaccine reluctance and refusal have exposed underlying distrust, political tensions and underlying hostilities can help anticipate where trust building is needed most. We cannot wait until pandemics strike, we must prepare for the next "big one", when trust and cooperation will be key to containing the spread of disease and mitigating its health and societal impacts."*
>
> *– Larson et al, 2018*[67]

6.4.1. Perceptions of vaccines

An available vaccine, adequate supplies and effective distribution network are of no use if the target population refuses the vaccine. Attitudes towards vaccines can be thought of as existing along a spectrum (Figure 11) where, ideally, members of the public would be actively seeking the vaccine during an outbreak. Reasons for vaccine hesitancy and refusal are diverse, context–specific, and variable within a country or region. They include:

- Religious belief
- Fear of side effects
- Preference of traditional medicine[54]
- Distrust of healthcare providers
- The spread of misinformation and belief[55]

Figure 11. A continuum of attitudes and behaviours towards vaccines

Adapted from SAGE Working Group on Vaccine Hesitancy, Final Report. October 2014.

Vaccine uptake correlates with perceptions of vaccines in general as a method of preventing disease (see Case Study 9). Demand greatly facilitates effective campaigns and relies on positive perceptions of vaccination, which should be regularly and pre-emptively promoted to both improve uptake of new vaccines and of routine vaccinations. The WHO estimates that 1.5 million children die year from vaccine-preventable diseases (VPDs) and that 30% of deaths of children under 5 globally are due to VPDs.

Case Study 9: Uptake correlates to vaccine perceptions

A study of reasons for uptake of the Human Papilloma Virus (HPV) vaccine in Uganda, Vietnam, Peru and India were often given in general terms, such as "vaccines are good for health" or "vaccines prevent disease", rather than relating to the specifics of HPV[68].

Another study in the Netherlands found that 88% of parents would be willing to vaccinate their children against HPV, despite the fact that less than a third had ever heard of the virus[69]. Conversely, following legitimate concerns in the Philippines about new dengue vaccines, immunisation rates for established vaccines such as tetanus, polio, and tetanus also plummeted between 2015 and 2018.[70]

Vaccination must, however, be considered in the context of the whole health system. Too great a focus on vaccination at the expense of other basic services can be counter-productive (Case study 10). If communities currently lack trust in healthcare providers, improving the provision of basic health services would:

- Increase satisfaction with the government's healthcare efforts, thus increasing trust in the services they provide, including vaccination
- Allow cases of a potential future outbreak to be identified sooner through contact with healthcare workers, reducing the delay of the response

Case study 10: Polio vaccine refusals in Kumbotso LGA, Kano, Nigeria[71]

This mismatch between weak health services and intense polio campaigns in Kumbotso, Nigeria has fostered distrust in the vaccination campaign. Government provision of basic services is lacking and the routine vaccination coverage is 9%. In contrast, door-to-door polio campaigns are carried out every other month and are well-organised and well-funded by the Global Polio Eradication Initiative (GPEI).

One ground-level worker explained that "If boreholes [providing clean water] and other essential amenities should be provided to these communities, the polio vaccine would be more acceptable."

6.4.2 TRAINING AND DEPLOYMENT OF HEALTHCARE PROVIDERS

In the case of an outbreak, it is important to have sufficient healthcare workers who are adequately trained and trusted by target communities. Staff are needed to provide locals with information regarding the vaccine to allow informed consent as well as to physically administer the vaccine.

Where possible, it is preferable to make use of local healthcare providers who understand the needs of and are trusted by the local community. This is not always possible, and mobile vaccination teams may be required to reach rural or remote areas where the vaccine would otherwise not be accessible. Initiatives such as Village Reach are already improving access to healthcare at this 'last mile'.

Education of healthcare providers is key to facilitating an effective response to novel disease. For example, in addition to providing in-person training during the outbreak, healthcare leaders can pre-emptively ensure that their staff have access to and are familiar with using OpenWHO, an online learning platform developed by the WHO to provide free courses on the biology, transmission, prevention and treatment of specific diseases, enabling healthcare workers to keep up to date with the latest WHO-recommended practice for current diseases. Conversely, following an outbreak, the WHO should ensure an OpenWHO course concerning Disease X is made available as soon as possible.

6.4.3. Culturally appropriate communication

> *"Because they are poor and ill conceived, the communication strategies used have not succeeded in triggering wide acceptance of immunization let alone community demand for it, and the planning and delivery of immunization services often are not based on community inputs or needs related to convenience, reliability and quality of services."*
>
> *– African Regional Strategic Plan for Immunization 2014–2020*

Establishing trust between individuals and healthcare providers is especially important in the case of Disease X, as the uncertainties surrounding the disease could lead to increased fear and subsequent lack of cooperation. However, the WHO has noted that communication strategies to date, both for increasing routine immunisation coverage and during public health emergencies, have been largely ineffective as local contexts have been ignored and community engagement not prioritised. Increasingly, NGOs and governments are recognising the importance of engaging key community leaders to help design context-appropriate strategies (Case study 11) as well as a guideline for emergency risk communication (ERC) policy and practice developed by the WHO[56], which provides evidence-based recommendations which could apply to any disease outbreak.

Case study 11: Vaccination during the 2018 DRC Ebola outbreaks

During the May 2018 Eastern DRC Ebola outbreak, there was a high vaccine uptake rate: an estimated 98% of those eligible were vaccinated. Health workers spoke directly to patients, their families and the wider community to dispel rumours, build trust and avoid panic. They explained to community leaders the urgency of the situation, ensuring the local people knew that this was not merely another mass vaccination campaign[72]. Oly Ilunga Kalenga, minister of health in DRC, got himself vaccinated during the outbreak, to "show the vaccine's safety and break the stigma around it"[73].

However, in September and October, the vaccine response to another outbreak within the North Kivu and Ituri provinces was complicated by the active conflict occurring in the regions. Vaccine refusals and reluctance to be taken to Ebola treatment centres were reported[74]. On October 17th, a WHO Emergency Committee concluded that the situation did not constitute a Public Health Emergency of International Concern (PHEIC) but noted that 'A critical determining factor is the safety and security of the population, which, in turn, affects the community's perception of the response', and recommended that community engagement receive attention.

6.5 Conclusions

To ensure a successful ring vaccination campaign, social mobilisation and community engagement should be prioritised to increase vaccine demand and facilitate the identification of contacts. Furthermore, it is important to accurately collect coverage and efficacy data for the novel vaccine to inform decision-making during the initial outbreak, and for future outbreaks. Local governments and community leaders must play a central role in preparing for the outbreak and in leading the response. Prior to an outbreak, efforts should continue to be made to improve positive perceptions of vaccines, but vaccines should not predominate at the expense of other basic healthcare services. Improved communication and co-operation between international organisations and local leaders will help ensure all aspects of the preparation and response strategies are context-appropriate and hence more effective.

7. Report Conclusions

Disease X "*represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease".* In this report we outlined the challenges to establishing an effective vaccine response to such an epidemic and steps which can be taken to overcome these challenges. Many of these steps are currently under development by different organisations, yielding successful outcomes in many cases. To optimise this effort, co-ordination and collaboration of the various organisations is necessary.

The authors of this paper recommend that a specific working group under the WHO Immunisation, Vaccines and Biologicals programme is established, working in collaboration with stakeholders to incentivise research, collaboration, data sharing and funding and establish a holistic approach to the novel challenges posed by Disease X

This group should play a key role in determining the global strategy following the initial containment response to a novel outbreak. The peak of the epidemic is often almost over by the time an outbreak is identified, such that subsequent interventions are limited in their ability to reduce the overall impact of the disease. However, our report focuses on the measures that should be taken if the decision is made to escalate the vaccine response effort, analysing the current capabilities for response and identifying key areas for improvement of our preparedness. Improving preparedness carries a number of co-benefits relevant not only to the emergence of a novel outbreak:

1. **Improvements to health system infrastructure will improve routine vaccination programmes and public health systems,** which helps progress towards the Millennium Development Goals. The GVAP *Strategic Objectives* highlight other key benefits which can be achieved through developing health systems for vaccine delivery, such as providing a platform for other priority health interventions to be successfully administered, stronger supply-chains and improvements in information systems providing high-quality data that can be used to further improve performance
2. **Vaccines not only prevent disease, but also poverty**. A 2016 study by John Hopkins University[57] found that for every US$1 spent on immunisation in Low- and Middle-Income Countries, US$16 is saved in healthcare costs, lost wages and lost productivity due to illness. Accounting for the broader benefits of individuals living longer, healthier lives, the return on investment rises to US$44 per US$1 spent
3. **Developing funding strategies** such as IIFIm (see Section 2) can be extended and developed to source financing for other social schemes, such as the IFFEd for Education. These education schemes can have knock-on effects in improving health, limiting spread of disease and increasing awareness and acceptance of vaccines
4. **Developing detection and early warning systems** (e.g. The Global Virome Project) will help to prevent future epidemics and generate more data which can be used by scientists in novel research
5. **Progress towards improving the IHR national core capacities** [58] will improve the ability of health systems to respond to any major health disaster in the future, not limited to a novel epidemic of "Disease X"

Disease X is hypothetical, but the threat to global health that it represents is not. The WHO Blueprint identifies diseases for which there are currently insufficient countermeasures and the inclusion of Disease X on the list poses significant scientific, manufacturing, logistical and social challenges. However, by preparing for a Disease X eventuality we can be better equipped to respond to any outbreak, known or unknown.

7.2. LIMITATIONS

- A mitigative response is most cost-effective: prevent initial emergence of epidemic by controlling factors leading to spread of disease rather than dealing with the effects once it has occurred. However, in this report we focus on the scenario occurring once an outbreak has started
- *Surveillance* is usually the rate-limiting factor for being able to identify an outbreak soon enough to be able to make a difference to course of the outbreak, as by the time an outbreak is identified, it is almost always already beginning to subside naturally (the peak of the epidemic is over). Any interventions then put in place are unlikely to reduce the number of further cases or deaths. Our report is useful at the point of the decision-making process when an outbreak has been identified, and it is decided that scaling up Disease X vaccine production is needed as a method of disease control
- Despite our focus on viral outbreaks, evidence from one paper suggests that 54% of EID events were actually caused by bacterial or rickettsial agents[10]. In terms of epidemic potential, we still consider viral causes to be the most likely and vaccination is also effective against bacterial infection
- Antibiotic resistance could be the cause of a Disease X outbreak. Vaccination of humans and animals is an effective way to limit the spread of antibacterial resistance by reducing the need for antibiotic use, therefore a focus on developing vaccines which will have the greatest impact on antibiotic use reduction is also an important part of a global mitigative strategy. Whilst not covered in depth in this report, similar principles apply
- Only considering the vaccination response, other potential response efforts could be based on monoclonal antibodies (antibodies are faster to develop and license than vaccines so they could represent a natural first line of protection, can be multipotent and stockpiled and even isolated from infected individuals to rapidly accelerate development process in a reactive response etc.) Vaccination may make limited difference to the first Disease X outbreak, both because of the delay in recognising an outbreak, and because of the delay in producing a vaccine. It could however be very powerful in preventing subsequent outbreaks
- All response efforts need to be balanced and co-ordinated for the optimum strategy when faced with an epidemic: response should also include immediate containment efforts such as a quarantines, travel bans, protective masks/gear and improved biosecurity of farms. (reactive and adaptive responses)
- We are not specifically considering a global influenza epidemic, as although this could be caused by a novel viral strain could have a very high socioeconomic cost, the global vaccine production facilities are better set up for manufacture of influenza vaccines and the research is already more advanced. There are other difficulties such as egg availability, appropriate prioritisation over seasonal vaccine production etc. which we have not discussed in detail in the report.

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Appendix 1: Current organisations facilitating vaccination worldwide

Organisation	Divisions and Sub-committees	Role (of Division or Sub-committee)	Example of Initiatives and Projects	Aim of Initiative or Project
World Health Organisation (WHO)	**Department of Immunization, Vaccines and Biologicals (IVB)** subcommittees: • Initiative for Vaccine Research • Access to Technologies • Quality Assurance and Safety of Biologicals • Vaccine Assessment and Monitoring • Expanded Programme on Immunization (EPI)	**Initiative for Vaccine Research** coordinates research and development on both existing and new vaccines and immunisation-related technologies. **Access to Technologies** aims to reduce financial and technical barriers to the introduction of these vaccines and related technologies. **Quality Assurance and Safety of Biologicals** produces standardised global guidelines for vaccine and biologicals quality and safety. **Vaccine Assessment and Monitoring** identify diseases with the greatest public health impact and identify how best to implement effective immunisation programmes for these target diseases **EPI** collaboratively produced the WHO-UNICEF Guidelines for Comprehensive Multi-Year Planning for Immunization (cMYP). cMYPs are used by Gavi in their assessment of a country's need for Gavi support.	1. WHO/UNICEF Global Immunization Vision and Strategy (GIVS) 2006 – 2015 2. WHO/UNICEF Global Vaccine Action Plan (GVAP) 2011 – 2020 a. Comprehensive effective vaccine management (EVM) framework 2015 – 2020 3. Integrated Disease Surveillance (IDS)/Integrated Disease Surveillance and Response (IDSR) framework	2. GVAP set vaccine coverage and equitable access targets. Developed by the WHO/UNICEF Immunization Supply Chain and Logistics Hub, the EVM framework builds on a 2010 - 2014 EVM initiative which helped countries evaluate the performance of their immunisation supply chains against best-practice standards and develop plans for improvement. The comprehensive EVM framework continues this work and aims to implement evidence-based improvement plans which work alongside existing cMYPs. 3. Co-ordinated by WHO Regional Offices, IDS/IDSR strengthens national multi-disease surveillance in regional members states by providing human resources and laboratory support, clear case definitions, and improving reporting and communications systems. IDS/IDSR approaches all surveillance activities in a country as a common public service and aims to closely integrate surveillance and control functions. While recognising that control of different diseases may require different data and therefore specialised surveillance systems, IDS/IDSR looks for opportunities for synergy in surveillance.
	Performance, Quality and Safety (PQS)	**PQS** set specifications for cold chain equipment and independently validate equipment to ensure that these specifications are met.		

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	Strategic Advisory Group of Experts on Immunization (SAGE)	Established by the Director-General of the WHO in 1999, SAGE is the principle advisory group to the WHO for vaccines and immunisation. SAGE advises on WHO overall global policies and strategies. Working groups established for detailed review of specific topics prior to discussion by the full group		
	WHO/UNICEF **Immunization Supply Chain and Logistics Hub**	Established with funding contributions from the Bill and Melinda Gates Foundation and Gavi, the Immunization Supply Chain and Logistics Hub developed the comprehensive EVM framework to help achieve the targets outlined in the WHO/UNICEF Global Vaccine Action Plan (GVAP).		
	Ad hoc Advisory Committee for the Emergency Use of Vaccines (AACEUV)	Review Emergency Use Assessment and Listing Procedure (EUAL) applications and provide advice to WHO about the suitability of vaccine candidates.	Consultation May 2017 (Geneva) on options for regulatory pathways for products for priority pathogens in emergency and non-emergency settings, covering vaccines, diagnostics and therapeutics and review of EUAL procedure	
	WHO R & D Blueprint Scientific Advisory Group (SAG)	Responsible for development of the WHO R&D Blueprint and reviewing the list of priority diseases	R&D Blueprint	Initiative to reduce the time between the declaration of a public health emergency and the availability of effective diagnostic tests, vaccines, and treatments that can save lives and avert a public health crisis.
	WHO Expert Committee on Biological Standardization (ECBS)	Establish detailed recommendations and guidelines for the manufacturing, licensing, and control of blood products, cell regulators, vaccines and related in vitro diagnostic tests.		

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	African Vaccine Regulatory Forum (AVAREF)	AVAREF improves regulatory oversight of interventional vaccine clinical trials conducted in Africa, and facilitates information sharing between countries during public health emergencies. AVAREF was a key player in the fast-track approval of clinical trials of candidate Ebola vaccines during the West Africa Ebola epidemic.		
United Nations Children's Fund (UNICEF)	**UNICEF Supply Division (SD) & Country Offices**	SD procures vaccines which have undergone the WHO prequalification process and equipment validated by WHO PQS. SD ships vaccines and equipment to recipient member countries. Upon receipt of a shipment, a copy of a completed standard WHO vaccine arrival report (VAR) must be forwarded within 3 days to both the SD in Copenhagen, Denmark, and to the UNICEF country office in the recipient country. In addition to handling VARs for the recipient country, the country office is the first point of contact for any problems with vaccines procured through UN agencies.		
Gavi, the Vaccine Alliance (*formerly Global Alliance for Vaccines and Immunisation*)		GAVI brings together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world's poorest countries. They have four strategic goals: 1. The vaccine goal: Accelerate equitable uptake and coverage of vaccines 2. The systems goal: Increase effectiveness and efficiency of immunization delivery as an integrated part of strengthened health systems	Cold Chain Equipment Optimization platform	Cold Chain Equipment Optimization platform helps countries modernise cold chains with high-performing equipment.

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		3. The sustainability goal: Improve sustainability of national immunization programs 4. The market shaping goal: Shape markets for vaccines and other immunization products		
International Coordinating Group (ICG) on Vaccine Provision	Composed of 4 member organisations: • **International Federation of the Red Cross and Red Crescent Societies (IFRC)** • **Medicins sans Frontieres (MSF)** • **WHO** • **UNICEF**	ICG maintains stockpiles of vaccine against cholera, meningitis and yellow fever. Any country may apply to the ICG secretariat for vaccine stocks in the event of an outbreak of any of these 3 diseases. Release of stock is dependent on an assessment by the ICG of the country's need. Vaccines released by the ICG are funded by Gavi (see above) for Gavi-eligible countries, and by a revolving fund supported by various donors and international agencies for non-Gavi eligible countries.	-	The ICG aims to: • rapidly deliver vaccines to respond to disease outbreaks • provide equitable vaccine allocation through careful risk assessment, based on epidemiological and operational criteria • coordinate the use of limited amounts of vaccines and essential medicines • reduce wastage of vaccines and supplies; advocate for readily available, low-cost vaccines and medicines • work with manufacturers through UNICEF and WHO to guarantee the availability of vaccine emergency stock supplies at the global levels • follow standard operating procedures and establish financial mechanisms to purchase emergency vaccine supplies and ensure their sustainability
PATH (Program for Appropriate Technology in Health)	**Epidemic Preparedness Group**	Help countries build strong health systems, complete with the laboratories, information systems, clinics, and well-trained staff they need to prevent, detect, and stop disease outbreaks before they can become epidemics or pandemics.		
Developing Countries Vaccine		A public health driven, international alliance of manufacturers, working to strengthen vaccine manufacturers through the provision		

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Manufacturers Network (DCVMN)		of information and professional training programs, technology improvements, innovative vaccine research and development, encouraging technology transfer initiatives, and educating the public about the availability of safe, effective and affordable vaccines for all people Mission: To increase the quality and availability of vaccines affordable to all.		
Coalition for Epidemic Preparedness Innovations (CEPI)	**International Vaccines Task Force (IVTF)**	CEPI works with public, private, philanthropic and civil organisations to promote and finance the development of vaccines against infections of epidemic potential. It aims to accelerate early stage clinical trials to demonstrate vaccine safety and efficacy, to allow full trials or emergency deployment during outbreaks. CEPI also works to ensure the smooth licensing of vaccines and to accelerate manufacturing capacity in preparation for epidemics, helping countries at risk of epidemic threats make sustainable improvements to epidemic preparedness. IVTF works to increase research capacity in low income countries.		
VillageReach	**Supply Chain and Logistics** **Information and Communication Technology** **Human Resources for Health** **Private Sector Engagement**	A non-profit organisation which develops, tests, implements and scales new systems, technologies and programmes to improve healthcare accessibility and quality in low-resource settings worldwide. VillageReach primarily focuses on overcoming barriers presented by human resource constraints, poor information availability and lack of infrastructure.		

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	Advocacy and Change Management			
African Coalition for Epidemic Research, Response and Training (ALERRT)	Composed of **21 partner organisations** from **9 African countries** and **4 European countries**	Funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), ALERRT aims to build a sustainable clinical and laboratory research preparedness and response network in Sub-Saharan Africa.		
Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)	**Clinical Trial Networks (CTN) Working Group** **Data Sharing Working Group**	Chaired by the European Commission together with Brazil, Canada, France, South Africa, and South Korea and composed of 27 member organisations across the globe, GloPID-R does not fund projects but shares and coordinates information among funding organisations.	Network of Social Sciences Research Expertise Long-Term Research Agenda	The international Network of Social Sciences Research Expertise aims to better address governance and other challenges in prevention and response to infectious threats. Long-Term Research Agenda aims to identify and address long-term generic research challenges using information provided by its Scientific Advisory board (SAB), which consists of global experts.
International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)	• Working Group 1: "Inter-pandemic clinical trials" • Working Group 2: "Global data collection and collation" • Working Group 3: "Genomics, Pathogenesis and Pharmacology" • Working Group 4: "Changing Clinical Research paradigms for rapidly emerging public health threats"	A global initiative aiming to ensure that clinical researchers have the open access protocols and data-sharing processes needed to facilitate a rapid response to emerging diseases that may turn into epidemics or pandemics.		
Platform for European		EU funded network for harmonized large-scale clinical research studies on infectious		

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Preparedness Against (Re-)Emerging Epidemics (PREPARE)		diseases (IDs), prepared to rapidly respond to any severe ID outbreak, providing real-time evidence for clinical management of patients and for informing public health responses.		
World Bank Group (WBG)		A quick-disbursing financing mechanism offering coverage to all low-income countries eligible for financing under IDA (International Development Association)	Pandemic simulations Pandemic emergency financing committee (**PEF**)	Raise awareness of threat, incentivise investment and test current systems (aimed at policymakers and governments) More involved in response than preparedness. Rapid deployment of a trained health workforce, medical equipment, logistics and food supplies etc. In the event of an outbreak.
United Nations (UN)	**High-level Panel on the Global Response to Health Crises** **Global Health Crises Task Force**	To propose recommendations that would strengthen national and international systems to prevent and respond effectively to future health crises, considering lessons learned from the Ebola response To support and monitor the implementation of the recommendations of the High-level Panel on the Global Response to Health Crises	Report 2016: Protecting Humanity from Future Health Crises	
John Hopkins Center for Health security		Involved in monitoring US government action in preparedness and response. Most projects are supported by the Open Philanthropy Project.	Clade X project	Clade X is a day-long pandemic tabletop exercise that simulated a series of National Security Council–convened meetings of 10 US government leaders, played by individuals prominent in the fields of national security or epidemic response. Drawing from actual events, Clade X identified important policy issues and preparedness challenges that could be solved with sufficient political will and attention. These issues were designed in a narrative to engage and educate the participants and the audience.

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			ELBI Fellowship: Emerging leaders in Biosecurity	A fellowship to inspire and connect the next generation of leaders and innovators in the biosecurity community.
Modality Solutions		A private cold chain management consultancy involved in the transport of rVSVΔG-ZEBOV-GP Ebola vaccine trialled during the 2013 - 2014 West African Ebola outbreak.		
Global Good		Funded by the Bill & Melinda Gates Foundation, Global Good is the pro bono portfolio of private intellectual property venture capitalist company, Intellectual Ventures. Global Good introduces technologies to improve global health and development, and oversees the technology pipeline from invention, development, field trials and commercialisation. Of relevance is Global Good's involvement in bringing high performance cold chain equipment to market.		

Appendix 2: results of a review of the challenges facing the development of vaccines against an unknown viral pathogens, potential and existing solutions and areas for improvement

Table 1: Challenges of pre-clinical development

STAGE	CHALLENGE	EXAMPLES	SOLUTIONS	RECOMMENDATIONS
Identification of relevant antigens	**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[1].	**Ebola virus** (EBOV) was first identified in 1976[2]. By the start of the EBOV outbreak in 2013, understanding of the immune response to the virus was still very limited[3]. The relative importance of humoral and cellular immunity to **Zika virus** is still poorly understood[4] Many gaps in knowledge of innate, cell-mediated and humoral immune responses to **Lassa fever virus** (LASV) and the determinants of infection and disease severity[5].	**Pre-emptive research** Related viruses are likely to share therapeutic and vaccine targets. Research into *families* of viruses using cryo-electron microscopy, B cell cloning, and antibody repertoire sequencing may permit identification of novel immunogenic antigens that can be used to tackle emerging pathogens[3]. Lists of key experts in the molecular biology and immunology of different virus families should be assembled. **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[6,7]. The Johns Hopkins Center for Health Security[8] recently identified respiratory-borne RNA viruses as the infectious agent most-likely to cause the next global epidemic[9]. The Global Virome Project[10] aims to increase understanding of the diversity and ecology of viral threats, providing data for public health interventions against future pandemics.	Further investigations into the families of viruses most likely to contain *unknown* epidemic-causing pathogens will help direct pre-emptive research
Evaluation of vaccine efficacy and identification of immune correlates of protection	**Lack of good animal models** Good animal models will be natural hosts for the virus, and share routes and outcomes of infection similar to those in humans[11]	**MERS-coronavirus** (MERS-CoV) only infects primates, bats and camelids. Non-human primates and camelids exhibit very different pathologies to humans upon infection, and are	**The WHO** identified a need for better understanding of animal models in its R&D Blueprint [15].	There is need for a FANG-like organisation to coordinate the development of animal models for all pathogens on the WHO R&D Blueprint list of priority diseases, as well

	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) [12,13]	expensive and difficult to use [4]. Vaccines for **filoviruses** are usually tested in rodent models, despite the viruses causing limited disease in these species [14].	**The Filovirus Animal Non-Clinical Group** (FANG) aims to use clinical data from filovirus disease outbreaks in humans to guide animal model development [16].	as general research into the properties and use of animal models. Neither the WHO or FANG are yet to produce a record of their work on 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. **The WHO R&D Blueprint** identifies a need for platforms that expedite data sharing [15]. **The GloPID-R Data Sharing Working Group** has released a framework for data sharing during outbreaks [17]. **The International Severe Acute Respiratory and Emerging Infection Consortium** (ISARIC) provides a platform for researchers to share protocols and data tools [18]. The **WHO's Pandemic Influenza Preparedness Framework** has developed a system for the sharing of influenza viruses with pathogenic potential [19]. **GlaxoSmithKline**[20], the **Global Alliance for Genomics and Health**[21], and the **Biomarkers consortium**[22] are pioneering data transparency models.	There is need for a governing body to lead pre-negotiations between R&D stakeholders, pharmaceutical companies, national governments, humanitarian organisations and academics to facilitate timely sharing of data and materials [23,24]. Upon the start of an outbreak, this organisation should set up a central database to collect information on routine care practices and outcomes [24]. The Pandemic Influenza Preparedness Framework should be

				expanded to other threats.
All	**Time required/deceleration in R&D responses due to lack of funding**	Early pre-clinical development of **EBOV** vaccines was slowed by a lack of funding [1].	**Platform technologies** (Section _) 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 [25]. 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. **Pro-active pre-emptive approach** [25] Requires increased incentivisation to progress development of vaccines against potential viral threats through to the clinical stage. **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[26]), that has been used in recent outbreaks in Guinea and the Democratic Republic of Congo [27,28].	Need for a global governing body that will receive funding from governments and traditional funding bodies, review vaccine development proposals and chose the best candidates to invest in [25]. The money contributed by each country should correlate with the expected benefits and be directed to relevant disease targets [25].

	Lack of understanding/appreciation of risk leading to lack of incentive	The lack of known of severe clinical consequences associated with **Zika virus** hampered vaccine R&D [4]. Appreciation of the potential global threat from **MERS-CoV** was delayed for about a year [4].	**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.	

Table 2: Challenges of clinical development

Stage	Challenge	Examples	Solutions	Recommendations
Phase II Phase III	**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[4] Incidence of **Zika** cases has declined – will be difficult to move to Phase II/III before the disappearance of the virus from endemic regions[4] The epidemiology and sporadic nature of **Nipah and Chikungunya virus** outbreaks makes large scale clinical trials	**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[4]. **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 [31,32]. **Human challenge**, only with pathogens that cause mild symptoms e.g. Zika virus [33]	

		logistically challenging – no clinical trials for NiV of CHIKV vaccine candidates have begun [29,30].		
	Lack of infrastructure in developing countries Examples[5,23,24]: • Challenges in setting up clinical sites with the administrative, research, clinical and laboratory infrastructure and workforce to conduct trials • Lack of information of 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	Current outbreak of **EBOV** in the Équateur province of Democratic Republic of Congo has 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. (Section___). Before the 2014 outbreak, EBOV-affected countries had little experience in running clinical trials or for the review of complex clinical trial protocols[34].	**Assess current research and public health capacities and invest in infrastructure** [23] Capacity strengthening efforts should not be limited to services that solely benefit study participants, and should benefit the local population as a whole [24]. **Strengthen clinical research capacity and sustainable health systems in developing countries** 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[35]. The International Vaccines Task Force (IVTF) was created to produce recommendations to facility sustainable clinical research capacity in low- and middle-income countries[35]. **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 [34]. **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 [36].	Recommendations for strengthening clinical research capacity are defined in 'Money & Microbes: STRENGTHENING CLINICAL RESEARCH CAPACITY TO PREVENT EPIDEMICS', a review by the IVTF[35] and 'Integrating Clinical Research into Epidemic Response: The Ebola Experience'[24], an independent review by the National Academies of Sciences, Engineering and Medicine.

	Ethicality	Highest strength data is generated by randomised, double-blind, placebo-controlled trial. This is not always ethically acceptable in the epidemic setting[34]. **EBOV** vaccine trials were challenged by ethical concerns over whether to include a control arm[1].	**Other randomised controlled designs** can collect clinical data to provide evidence for analysis[34]. The solution reached in the rVSV-ZEBOV ring vaccination trial was to randomise primary cases into immediate versus delayed [37]. Adaptive clinical trial design will allow changes to placebo groups based on ethical considerations and results. The WHO has reported a Guidance for Managing Ethical Issues in Infectious Disease Outbreaks [38]. **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 (PHEIC), 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 [34,39,40]. 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 [41].	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 [24].
	Societal mistrust of foreign entities conducting clinical trials leading to challenges in patient recruitment Due to ineffective community awareness, sensitisation and education programmes[5].		**Community engagement in research and response** Engage local people in research, particularly key opinion leaders and scientists, including local healers as well as religious leaders in discussions of clinical trials [23]. **Education and consent** Participants should be informed about all aspects of the protocol before consent [23,42]. 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 [43].	International and national research institutions, and humanitarian organisations should identify social science experts to lead efforts in engaging local communities and identifying key community representatives [24].

Licensing	**Lack of efficacy 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[44] Two years after the first trial, rVSV-ZEBOV is still not licensed [45].	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[44]: **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 [34] **The WHO Emergency Use Assessment and Listing Procedure (EUAL)**[46]. Aims to provide guidance to UN procurement agencies and Member States on the use of vaccines during public health emergencies.	
	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 developing countries do [47]. Two years after the first trial, **rVSV-ZEBOV** is yet to be licensed in any	**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 [47]. Works in collaboration with the European Medicines Agency (EMA) Article 58 procedure [50]. **Streamlined processes**[23,34] Countries should: a. Align requirements of regulatory submissions for product review from manufacturers, so there is	

		country. Russia and China are the only countries to have licensed EBOV vaccines, both based on limited preclinical and clinical trials and neither of which are promoted by the WHO [14]. **H1N1 Influenza outbreak**: Each country's national regulatory authority imposed its own requirements for vaccine approval [48,49] – had an impact on efficacious donation and distribution from manufacturers[23].	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 response, address regulatory science issues and identify areas for streamlining [51].	
All	**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) expediate approval of vaccines when efficacy trials are not possible or ethical[52]	The use of different immunological assays in different clinical trials during the **EBOV** outbreak hindered the comparison of immunogenicity induced by different vaccine candidates [3] The methodology used for assays measuring humoral immunity following vaccination against **Chikungunya virus** varies widely across studies [30]	**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) that should permit comparison of humoral responses [53] The Filovirus Animal Non-Clinical Group (FANG) have developed a standardised ELISA assay that has approval from the FDA [16,54]. In general, there should be a push towards use of common protocols [23].	Need for an organisation like FANG that develops standardised reference reagents and protocols for a range of viral threats.

		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 [5]		
	Lack of regulatory preparedness Need to accelerate regulatory review and access to products during epidemics		**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 [55–57]. **Communication** between regulatory agencies to define requirements of product review submissions (see 'Regulation disparity between countries') – 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 [34]. Countries should identify experts in negotiation of clinical trial and material transfer agreements before the onset of an epidemic [24]. **Vaccine platform technologies** will reduce the number of regulatory procedures required for each new vaccine	The WHO should continue to facilitate connections between national authorities and vaccine manufacturers, and experts in the field of clinical trial design[24].
	Cost of vaccine development, production and clinical trial conduct for unknown commercialisation potential	Moving from preclinical to clinical development is an expensive step [14]. Funding for **LASV** vaccine R&D is insufficient as incentives to invest are not clear – disease is endemic in an	**Protection for manufacturers against product liability claims [23,48].** 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[15] **Involve stakeholders in clinical trial design** [1]	

		under-resourced West African region [5]		
	Time		**Platform technologies (Section_)** Will allow limited but useful Phase I studies to begin before identification of the antigen **Lessons from the EBOV outbreak** Clinical trials during the EBOV outbreak proceeded relatively quickly. Reasons for this included [1]: 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	

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