HM Government

Scoping report for the UK Vaccine Network

Options for investment in vaccines and vaccine technology for infectious diseases with epidemic potential

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CONFLICTS OF INTEREST

Two of participants in the Delphi panel had received funding from previous rounds of UKVN. One on the development of adenovirus-based vaccines to various priority diseases and one for a vaccine manufacturing hub (see appendix 1 for further details). One member of the advisory group (George Warimwe) was a recipient of UKVN funding for development of a vaccine for Rift Valley Fever virus. The lead authors of the report declare no conflicts of interest.

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Abbreviations

ACT-A	Access to COVID-19 Tools Accelerator
AMC	Advance Market Commitment
APC	Advance Purchase Commitment
AVAREF	African Vaccine Regulatory Forum
AVMI	African Vaccines Manufacturing Initiative
BARDA	Biomedical Advanced Research and Development Authority (US)
BBSRC	Biotechnology and Biological Sciences Research Council (UK)
BMGF	Bill and Melinda Gates Foundation
CCHF	Crimean-Congo Haemorrhagic Fever
CDMO	Contract Development and Manufacturing Organisation
CEPI	Coalition for Epidemic Preparedness Innovations
DARPA	Defense Advanced Research Projects Agency
DCVM	Developing Country Vaccine Manufacturer
DHSC	Department of Health and Social Care (UK)
DRC	The Democratic Republic of the Congo
DTRA	Defense Threat Reduction Agency (US)
EDCTP	European and Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
EPI	Expanded Program on Immunisation
EPSRC	Engineering and Physical Sciences Research Council (UK)
EUA	Emergency Use Authorisation
EUAL	Emergency Use Assessment and Listing
EVD	Ebola Virus Disease
FCDO	Foreign, Commonwealth and Development Office (UK)
FDA	Food and Drug Administration (US)
GLoPID-R	Global research collaboration for infectious disease preparedness
GMP	Good Manufacturing Practice
HERA	European Health Emergency preparedness and Response Authority

HFRS	Haemorrhagic Fever with Renal Syndrome
HPS	Hantaan virus Pulmonary Syndrome
ICG	International Coordinating Group
ICMRA	International Coalition of Medicines Regulatory Agencies
IDEP	Infectious Disease of Epidemic Potential
IHR	International Health Regulations
IMI	Innovative Medicines Initiative
IP	Intellectual Property
JCVI	Joint Committee on Vaccines and Immunisation (UK)
LIC	Low-Income Country
LMIC	Low- and Middle-Income Countries
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger RNA (ribonucleic acid)
MVP	Meningitis Vaccine Project
NIAID	National institute of Allergy and Infectious Diseases (US)
NIHR	National Institutes for Health Research (UK)
NITAG	National immunization technical advisory group
NRA	National Regulatory Authority
PATH	Program for Appropriate Technology in Health
PAVM	Partnerships for African Vaccine Manufacturing
PDP	Product Development Partnership
PEF	Pandemic Emergency Financing Facility (World Bank)
PHEIC	Public Health Emergency of International Concern
PIPF	Pandemic Influenza Preparedness Framework
RVF	Rift Valley Fever
SII	Serum Institute of India
TDDAP	Tackling Deadly Diseases for Africa Programme (FCDO)
UKHSA	UK Health Security Agency
UKVN	UK Vaccine Network
VMIC	Vaccine Manufacturing and Innovation Centre
WHO	World Health Organization
ZAPI	Zoonoses Anticipation and Preparedness Initiative

Executive Summary

INTRODUCTION TO THE PROBLEM

This report was commissioned by the UK Department of Health and Social Care to:

- Describe the current landscape of vaccine development against infectious diseases of epidemic potential (IDEPs), previously defined as 'priority diseases' by the UK Vaccine Network (UKVN);
- Consider lessons learnt from developing vaccines against Ebola and COVID-19;
- Review remaining technical gaps that might be targeted by future UKVN funding; and
- Propose optimal mechanisms for project funding to ensure value for money.

UKVN was established following the 2014-16 Ebola outbreak in West Africa and used an expert panel to develop a list of priority pathogens which cause IDEPs and for which vaccines should be developed.[1] This list covered 13 priority pathogens, including Disease X, any previously unknown pathogen capable of causing epidemic disease. There was recognition that excellent pre-clinical studies showing safety and immunogenicity of prototype vaccines in animals were not being translated into vaccines for use in humans. UKVN specifically aimed to progress vaccines for priority diseases through to early phase clinical trials so that they were available for scale up and emergency use in the event of future epidemics.

APPROACH

We report findings that were identified through (i) a review of the current literature, (ii) stakeholder interviews and (iii) an expert panel. Interviewees were drawn from low- and middle-income country (LMIC) manufacturers, research funding organisations, donors, and academic and policy research. The expert panel was assembled to suggest areas that should be priorities for future rounds of UKVN funding and to identify technical gaps in development of vaccines for priority diseases.

The panel of 13 included experts from countries relevant to priority diseases (Democratic Republic of Congo (DRC), Malaysia, Nigeria), representatives from funding agencies (Wellcome Trust, the Coalition for Epidemic Preparedness Innovations) and scientists with relevant expertise (in viral vaccines, mRNA vaccines, protein-based vaccines, manufacture of vaccines, epidemiology). The aim was to achieve consensus regarding the importance of perceived technical gaps in vaccine development and the availability of alternative sources of vaccine development funding, using the Delphi method.[2,3]

PROGRESS TOWARDS VACCINES AGAINST PRIORITY DISEASES 2016-2021

UKVN allocated £107M towards the development of vaccines against priority diseases through Innovate UK, the National Institute for Health Research (NIHR), the Engineering and Physical Sciences Research Council (EPSRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). Vaccine projects were developed for the 12 priority pathogens identified at a species level, which included investments in platform technologies that could be used to develop vaccines for Disease X. These platforms included the Chimpanzee adenovirus platform which was eventually used to develop the University of Oxford/ AstraZeneca vaccine against COVID-19.

Although clinical trials were mentioned in the title or abstract of 33 of the 78 projects funded by UKVN, only 7 clinical trials were registered during the period. These trials focussed on 4 of the 12 pathogens on the priority list (Zika, Chikungunya, Middle East Respiratory Syndrome (MERS) Coronavirus, and Rift Valley Fever). All of these trials used the same chimpanzee adenovirus vaccine platform. Limitations of this analysis are that: (i) it includes only trials registered in international databases; (ii) it includes trials that may have been registered but are not yet completed; (iii) completion of a trial does not necessarily mean that an effective vaccine has been developed, although it is a necessary step along the pathway, (iv) it is possible that clinical trials were mentioned in titles and abstracts as a

future goal of projects and were not directly part of the project funded. Internationally, over the same period, most clinical vaccine trials for priority diseases were directed against Ebola, Chikungunya and Zika. This pattern reflects the historical trend of responsive vaccine development after the outbreak has occurred. Q fever was the only priority disease for which no clinical trial was started or completed between 2016-2021.

THE CURRENT FUNDING LANDSCAPE FOR VACCINES AGAINST PRIORITY DISEASES

The Coalition for Epidemic Preparedness Innovations (CEPI) has provided large-scale and sustained funding for the development of vaccines against IDEPs since it was established in 2017. While their focus is on vaccine development for diseases on the World Health Organization (WHO) blueprint list, they are also funding work on antibody treatments and the development and manufacturing of vaccines in LMICs. CEPI is currently investing millions of dollars in the development of vaccines against epidemic diseases, with a focus on 7 diseases, all of which are on the UKVN priority list. It is also by some distance the largest single contributor of research funding for vaccine development globally including for epidemic diseases, although most of its investments currently are focused on COVID-19 vaccines. CEPI's future ambitions range from increasing diagnostic, testing, vaccine manufacture and clinical trials capacity in LMICs to developing 'universal' coronavirus vaccines (Table 1).

Pathogen	Number of vaccines	Funding committed (US$)
COVID-19 (Disease X)	14	1446.3m
Lassa	6	246.9m
MERS	5	159.1m
Nipah	4	93.6m
Chikungunya	3	58.5m
Rift Valley Fever	2	22.0m
Marburg	1	8.4m

Table 1. CEPI's current portfolio of vaccine development (September 2021)

The European Union invested in the development of Ebola vaccines through its Innovative Medicines Initiative, but its epidemic preparedness funding has been mainly focused on the early detection of, and co-ordinated response to, emerging diseases. It has funded a clinical trials network in sub–Saharan Africa through its European and Developing Countries Clinical Trials Partnership (EDCTP) but it has not been a strong funder of clinical trials for vaccines against UKVN priority diseases during 2016-2021.

The USA is a major funder of human trials of vaccines against priority diseases, mainly through the National Institute of Allergy and Infectious diseases (NIAID) and the US army. It is not clear whether these projects are well connected with the downstream commercial manufacture of vaccines. The Gamaleya Institute in the Russian Federation has tested adenovirus-based vaccines against a variety of priority diseases. In addition, a few Chinese companies (Sinovac Biotech, Cansino and Beijing Institute of Biological Products) have tested vaccines against priority diseases.

Among large commercial vaccine companies (Sanofi, Pfizer, MSD and GSK) only MSD had invested significantly or with notable success in vaccines for epidemic diseases prior to the COVID-19 pandemic. The situation has changed in important ways since late 2019: Pfizer (with BioNTech) now have a major stake in mRNA vaccine development; and Sanofi and GSK have made significant investments in mRNA vaccine development albeit with varying degrees of success to date. Historically low interest in investing in IDEP vaccines could be due to the relatively small and unpredictable market for these products or a desire to avoid the political issues that often accompany an outbreak. Some smaller companies (e.g. Valneva, Themis Bioscience, Moderna, Emergent Biosolutions) have shown a sustained interest in vaccine development against several priority diseases, possibly because CEPI funding has created a market 'pull' for these products. None are UK-based companies.

THE CURRENT VACCINE LANDSCAPE FOR PRIORITY DISEASES

Commercially licensed vaccines have been produced for only one UKVN priority disease (Ebola). Since 2015, two different Chikungunya vaccines have been tested in phase 3 clinical trials. Two different vaccines have been tested against each of Zika and MERS in phase 2 trials. For Rift Valley Fever there is one vaccine at phase 2 and one at phase 1. There is a DNA vaccine platform which has been tested for two different hantaviruses, one at phase 1 and one at phase 2. Among the remaining pathogens on the UKVN list, a few (Lassa, Nipah, Marburg) have vaccines that are being/have been tested at phase 1; for others (Q fever, plague), no new vaccines have been tested in humans since

2015. As the vaccine landscape has changed since the UKVN list was first drawn up there is a strong argument for reviewing which pathogens should be included. A case could certainly be made for the removal of Ebola, and perhaps Chikungunya, from the UKVN list.

In terms of types of vaccines being developed there is a clear swing away from inactivated and attenuated vaccines and towards vaccine platforms based on other viruses (Measles, adenoviruses) or mRNA. These platforms offer advantages in terms of scalability and reproducibility of vaccine manufacture, processing and storage. Recent experience with COVID-19 has highlighted the potential of these types of vaccine platforms for rapid development during an epidemic but relevant expertise remains concentrated in high income countries and the timeline to the emergence of mRNA vaccine manufacturing capacity in LMICs was estimated by interviewees as at least 5-10 years.

LESSONS LEARNT FROM VACCINES DEVELOPED AND DEPLOYED IN PREVIOUS EPIDEMICS

The West African Ebola Virus Disease (EVD) epidemic in 2014-16 highlighted the need to develop processes for the emergency approval of prototype vaccines. The earlier that vaccines can be delivered the more use they are in controlling the epidemic and the best time to vaccinate is before the epidemic begins. A large outbreak in the DRC in 2018 has shown that market-shaping initiatives can generate sustained 'pull' for a new vaccine and that global stockpiling of vaccine candidates for rapid deployment is useful in emergencies. However, the Ebola vaccine story is atypical because the vaccine was already at an advanced stage of development in 2013 and it benefited from exceptional investment by Gavi. In addition, responses to subsequent outbreaks in DRC have highlighted that vaccine stocks alone are not sufficient to protect the population, even in countries experienced in dealing with Ebola. Healthcare infrastructure, trust in national and local authorities, political stability and community engagement are all essential for successful rollout of vaccines during an outbreak.

The response to COVID-19 has in many ways transformed the picture in terms of vaccine development, which is now occurring at unprecedented speed. mRNA and viral vector candidates (the Pfizer and AstraZeneca products respectively) were brought to licensure in less than 6 months, and regulators in the UK and other high-income countries have responded to the crisis by introducing new, accelerated procedures to ensure approval much more quickly than in the past – although speed of turn-around in LMICs has been much more variable. The pandemic has also, however, highlighted that even if regulatory approval for new vaccines is fast-tracked, a lack of 'surge capacity' can severely limit manufacturing capability. Furthermore, the benefit of vaccination has been seen primarily in countries with stable political systems, well established healthcare infrastructure, high public acceptance of vaccination and advanced capabilities in specific technical areas (e.g. vaccine procurement and delivery of adult vaccination programmes). Countries without these features have not been able to procure vaccines in sufficient volume to meet demand in a timely fashion and have experienced low vaccine uptake even after vaccines became available. Finally, the COVID-19 response has benefited from spending at exceptional levels by high income countries effectively guaranteeing markets for new vaccines through advance purchase agreements on a scale that bears little resemblance to the historical picture for other diseases.

INNOVATION GAPS

A consensus outcome of the expert panel was that the UK had strengths in key strategic areas including clinical trials, epidemiology, and viral vector platforms. There was a firm recommendation to invest in future development of mRNA-based vaccines. However, the panel noted that expertise in mRNA vaccine platforms was not well developed in the UK and that intellectual property restrictions could limit the potential application of this platform for commercial vaccine development. Detailed investigation of intellectual property (IP) issues was beyond the scope of this report but we note that a key patent, relating to modified nucleotides to improve vaccine efficacy, which underpins both the Moderna and Pfizer BioNTech COVID-19 vaccines, is due to expire in 2023.[4]

The panel agreed with the previous UKVN assessment that funding should push vaccine research beyond small-scale academic development towards phase 2 clinical trials. Arguably, one of the reasons that the UK could produce vaccines rapidly in response to COVID-19 was that, at the time the pandemic began, clinical trials for a vaccine against another coronavirus (MERS) had already been initiated. The gap from 'lab bench to clinic' remains, however. The government has recently announced the launch of a Vaccine Evaluation Centre, including expanded capacity at the UK Health Security Agency (UKHSA), to support risk assessments for future SARS-CoV-2 variants and efficacy testing for new vaccines – although the focus of this new Centre appears to be exclusively on COVID-19. However, there is uncertainty regarding the long-term future of the much larger Vaccine Manufacturing and Innovation Centre (VMIC), launched in 2018 with the goal of helping to move promising vaccines developed by UK researchers and small, and medium-sized enterprises to production. The panel recognised that scaling up the manufacture of upstream vaccine reagents was also a priority. It is also important to note, however, that the presence of a stringent national regulatory authority (the Medicines and Healthcare products Regulatory Agency –

MHRA) in the UK made a key contribution to accelerating late-stage development and deployment of COVID-19 vaccines.

Both the panel and the stakeholder interviews identified particular challenges in LMICs including inability to 'compete' with multinational companies, shortcomings of local regulatory authorities, lack of capacity to scale-up vaccine manufacturing and the need for technology transfer, particularly for mRNA vaccines. Interviewees consistently emphasised the importance of investing in countries with well-developed regulatory and manufacturing ecosystems for greatest impact. A landscape analysis carried out by Foreign, Commonwealth and Development Office (FCDO) in 2021 found that no single African country currently possesses both a national regulatory authority with sufficient capabilities, and an established vaccine manufacturing facility (using any platform) to enable vaccine licensing and manufacturing at scale. Initiatives such as the African Vaccine Regulatory Forum (AVAREF) are helping to build critical capacity, and the UK has technical expertise to offer in this space, building on MHRA's track record.

The expert panel observed that many of the diseases on the UKVN priority list were zoonoses emerging from wildlife or livestock. They recommended, therefore, prioritising the development of animal vaccines where these were likely to reduce the probability of an epidemic in humans.

Other technical gaps highlighted by the panel included the identification of appropriate animal models for the testing of new vaccines, the standardisation of diagnostic tests to demonstrate whether a pathogen was present, and immunological protection from disease. Finally, the panel recommended pursuing technical advances to vaccines to improve thermostability and broaden their routes of delivery. The 11 technical gaps identified by the panel are listed in Figure 4.

FINANCING AND GOVERNANCE OF VACCINE DEVELOPMENT AND DEPLOYMENT

Vaccine developers for epidemic priority diseases must reckon with the reality that, except for COVID-19, there will be no commercially viable market for most of these vaccines over the long term. To tackle market failure, the UK has invested substantially in vaccine development and deployment through CEPI and Gavi, among others. However, these investments are not integrated end-to-end for UKVN priority pathogens because Gavi is primarily focused on endemic diseases and because, beyond the subset of diseases for which there are vaccine stockpiles, there is no agreed mechanism governing vaccine procurement, global distribution and deployment in emergencies. Without sufficient join-up in the development and deployment pathways, there is a significant risk that UKVN, and indeed wider UK, investments in IDEP vaccine development will not materially improve population health, and will not deliver value for money. Only a combined push-and-pull approach for the public good, through a partnership focused on specific, priority diseases is likely to offer a viable route to vaccine development and production at a price affordable to LMICs. The Meningitis Vaccine Project (MVP), in which the UK invested heavily between 2010-18, provides a potential model. An alternative may be to adapt or extend the remit of COVAX (to which the UK is also a significant contributor) but this remains speculative during the ongoing pandemic.

WHERE COULD UKVN FUNDING HAVE MOST IMPACT?

Taking into account the global landscape for vaccine development for priority diseases it is clear that future UKVN funding will need to be carefully targeted to avoid duplicating efforts elsewhere, and to maximise the likelihood that investments will actually result in deployment and uptake of vaccines in an epidemic. Vaccine platform technologies, and particularly mRNA vaccines, have been a major step forward during the COVID-19 pandemic, though this follows many years of prior development. The challenge for UKVN2 will be to maintain key skills and build capacity for the next 'Disease X' while producing usable vaccines for the existing threats to human health.

Previous UKVN funding produced good progress and yielded prototype vaccines for priority diseases. There is clear potential for follow-on funding for vaccines and platforms that have demonstrated progress. The focus should remain on pushing vaccines up to phase 2 trials and encouraging these to occur in countries and populations where outbreaks are more likely. However, vaccines for Ebola, Zika, Chikungunya, Nipah and Lassa fever are already in late-stage clinical trials or have several different developments already well-funded by CEPI. Developing new vaccines from scratch for these diseases would not be the most efficient use of UKVN funds. There are strategic reasons for maintaining expertise with coronaviruses so, although there is already one very good UKVN MERS candidate and 5 CEPI-funded MERS vaccines in the pipeline, support for coronavirus research should continue. There is still a need for vaccines against Crimean-Congo Haemorrhagic Fever (CCHF), Q fever and Plague and some potential for a Marburg vaccine, although it is not clear to what extent current Ebola vaccines will cross protect against this disease. For hantaviruses, there needs to be careful thought about which hantavirus(es) should be targeted and which population the vaccine will eventually protect.

Beyond that, the highest impact from UKVN funding may come from improvements in thermostability and ease of delivery of vaccine platforms, optimisation of their large-scale manufacture, and by following up phase 1 and 2 trials completed in the UK with local trials in the target populations at risk of infection. This would be best achieved by interacting with local and international clinical trials networks such as the EDCTP. Finally, there is some value to having standardised diagnostic and immunological tests for the effectiveness of vaccines against priority diseases and for these standards to be agreed at an international level. Here the UK has existing strengths and influence through the National Institute for Biological Standards and Control.

FUNDING MODELS

Research funding tends to follow block grant, competition or commissioned research models. Most UK research funding operates on a competitive basis with some core funding for strategic research institutes such as Porton Down or the Pirbright Institute. Commissioned research is rarely used in the UK but international examples of its effective use would be the MVP in sub-Saharan Africa, or DARPA in the USA, where a programme manager coordinates the end-to-end pipeline of a scientific programme by commissioning research groups to work on specific aspects of the overall project. The most appropriate funding model for UKVN2 would depend on the phase of research being funded. Competitive funding calls would maintain a pool of interested researchers developing a broad range of new ideas, but for end-to-end development of a vaccine pipeline there are clear advantages to the commissioned research model. This would allow freedom to operate, with respect to IP, and ease of scalability to be built into vaccine projects from the start.

CONCLUSIONS

Findings from this report suggest that:

- Advancing vaccines for priority diseases into phase 2 trials is an efficient next step at this point.
- Follow on funding is likely to be effective for research projects where good progress has already been made but the increasingly complex nature of vaccine development beyond Phase I suggests that a coordinated investment model should be considered. In this model a technical programme manager oversees the end-to-end vaccine process and only commissions new research if there is a reasonable chance that phase 1 trials will be conducted within a 3-5 year period. The coordinator acts both as a gatekeeper and as a facilitator to ensure that projects progress beyond laboratory studies. A strategy that focuses on a small number of vaccine candidates for each disease rather than a 'shotgun' approach against one or two high profile diseases is likely to be more efficient.
- There remain a number of clearly identifiable technical gaps in vaccine development and manufacture (mRNA vaccines, optimisation of scale up, GMP production, enhancing thermostability, alternative delivery routes, rapid deployment of vaccine and upstream component manufacturing, identifying relevant animal models, standardised diagnostic and immunological tests for pathogen detection and vaccine efficacy). These are likely to be filled through competitive calls via Innovate UK, EPSRC, BBSRC, and NIHR.
- There is a strong case to review the UKVN priority list regularly and adapt it as necessary, removing pathogens for which vaccines are now available and adding pathogens which are emerging threats. This report has carried out a limited review, but a more in-depth analysis would be warranted, considering, in particular, the potential for overlap with work already being supported by CEPI.
- For some diseases funding vaccines for livestock and wildlife may be more effective than developing a human vaccine programme if it could reduce the probability of spill over epidemics.
- There is a sound rationale for investing in clinical trial networks in LMICs to carry out phase 2 trials in target populations once vaccine safety in UK volunteers has been established.
- Transfer of technology and manufacturing know-how is strategically compelling and could be achieved by working with colleagues in FCDO and across government to ensure that the commitment to technology transfer to LMIC manufacturers is integrated into all vaccine development funding agreements signed by technical bodies (e.g. CEPI) to which the UK is a major funder.
- Enhancing links between the MHRA and regional or continental regulatory initiatives (e.g. AVAREF in Africa) would promote alignment between National Regulatory Agencies and develop local capacity which is essential for rapid deployment of vaccines in an emergency.
- A cross-departmental review could be considered to assess the extent to which existing UK investments and activities in health system strengthening and epidemic preparedness (through, for example, TDDAP, the UK Public Health Rapid Support Team and UKHSA's work on IHR strengthening) support robust IDEP surveillance capacity and readiness

for vaccination delivery in target countries, with proposals for improvements where necessary.

- A competitive call could be considered to evaluate governance structures at CEPI and Gavi, and identify ways in which the UK could leverage its funding contributions to strengthen strategic alignment between these organisations in support of IDEP vaccine development and deployment. We note, however, that given the life cycle on funding replenishments these changes may take time to come into effect.
- A competitive call could be considered to explore legacy options for COVAX, examining the extent to which its institutional architecture and operating model could be repurposed, in due course, to promote late-stage development for other epidemic diseases, and exploring the options presented by other frameworks, including the Pandemic Influenza Preparedness Framework (PIPF).
- A competitive call could be considered to evaluate the extent to which equitable access provisions, applied to vaccines supported by technical bodies that the UK funds (including CEPI), are met in practice, and explores the levers available to the UK to strengthen these provisions in future.

Three further considerations cut across all of the opportunities for investment. The first is the need for capacity development in target LMICs, in areas such as clinical trials, surveillance for IDEPs, regulatory capacity and vaccine manufacturing. Partnership working with UK funders such as Wellcome, MRC and NHIR, all of which have developed valuable experience in fostering successful scientific careers in Africa and Asia, could support this. Secondly, development of R&D, manufacturing, regulatory and related capacity is closely interconnected and for this reason it would make sense to geographically focus investments in countries where the UK already has strong relationships, and where there is sufficient existing capacity to maximise return on investment. Finally, successful late-stage development and deployment hinges on a very wide set of skills spanning epidemiology and surveillance, clinical trials, manufacturing, national regulation, health systems for deployment, acceptability by local populations, vaccine finance mechanisms and governance/response systems for international allocation. To optimise onward investments within UKVN2 it would be prudent to incorporate expertise in some, if not all, of these areas within the advisory structure of the programme.

1 Introduction

IDEPs pose a genuine threat to human health and economic stability. Vaccines have tremendous potential to prevent, control or attenuate these diseases in all countries, including Low- and Middle-Income Countries (LMICs).

The UK is an innovative leader in the science of vaccine development and the UK government plays a leading international role in supporting vaccine development and shaping vaccine delivery in LMICs through its substantial funding for CEPI and Gavi, the Vaccine Alliance, respectively. The end-to-end development of vaccines leads from discovery to delivery through outbreak response (see Figure 1) and failure at any point in this pipeline undermines all successful work undertaken upstream.

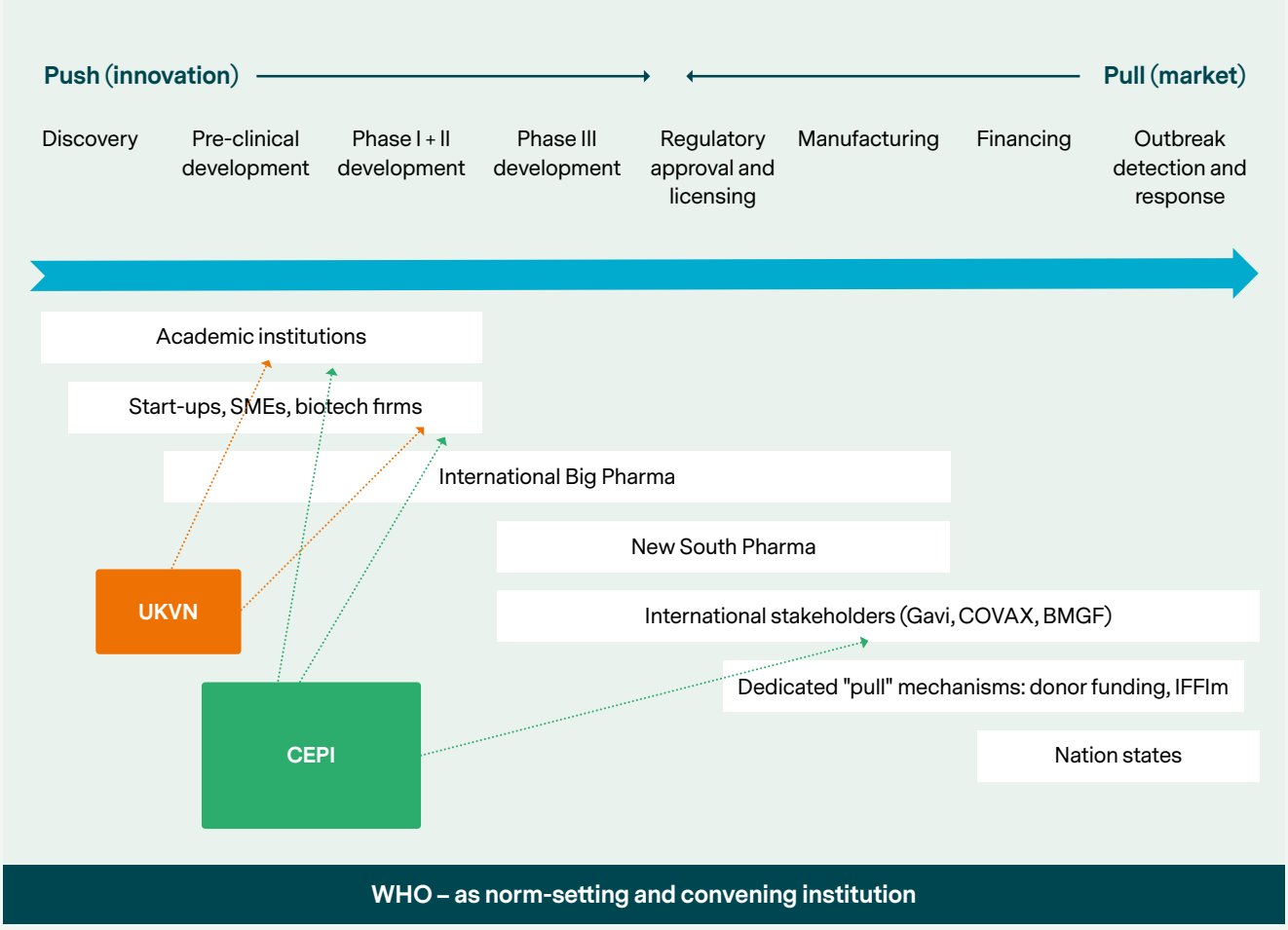


Figure 1. Schematic of the end-to-end pipeline for vaccine development, manufacture and delivery.

IDEPs are more frequently found in LMICs and these are precisely the settings where the lack of resources and an abundance of competing health problems confound usual market incentives for vaccine development. Creating a successful end-to-end development pathway, therefore, means connecting the push-funding that drives discovery

and early clinical development (by reducing costs and shortening development timelines) to the pull-funding that generates international and local demand (and thereby revenues arising from production) and pulls the vaccine through late clinical development and manufacture.

This report examines the role of UKVN in the context of this pathway, taking account of the tremendous advances in development, manufacture and delivery of vaccines for SARS-CoV-2. It has a primary focus on identifying propitious technical advances and opportunities in the push-mechanism of vaccine development. The report also examines structural, economic and institutional advances and opportunities in the pull-side of the development process to encourage a complete vaccine pipeline for WHO blueprint IDEPs. Throughout the report we will attempt to illustrate specific diseases where these advances are closer to completion and where targeted investments may lead to a complete pipeline. A central principle, underpinning our analysis, is the need to ensure prompt and equitable access to vaccines for IDEPs, at prices that are affordable to LMIC governments.

APPROACH

We report findings that were identified through (i) a review of current literature, (ii) stakeholder interviews and (iii) an expert panel. This mixed-methods approach was used because the development, production and deployment of vaccines for epidemic diseases is evolving at speed and many of the most important innovations are not yet well captured in the scientific literature. Literature sources were similarly diverse and spanned peer-reviewed publications to a large body of grey literature (including analytical reports, strategy and implementation documents, and annual reports from key stakeholders including CEPI, Gavi and the BMGF). Interviewees were sampled in snowball fashion and drawn from LMIC manufacturers, representative bodies, research funding organisations, donors, and the worlds of academic and policy research. While we attempted to sample interviewees purposively, we could not be comprehensive because the range of stakeholders involved in late-stage vaccine development, manufacturing and deployment is very diverse and time available for research for this report was limited.

The expert panel was assembled to identify technical gaps in development of vaccines for priority diseases and suggest areas that should be considered as priorities for future investment by UKVN. The panel of 13 included experts from countries relevant to priority diseases (Democratic Republic of Congo (DRC), Malaysia, Nigeria), representatives from funding agencies (Wellcome Trust, the Coalition for Epidemic Preparedness Innovations or CEPI) and scientists with relevant expertise (in viral vaccines, mRNA vaccines, protein-based vaccines, manufacture of vaccines, and epidemiology). The aim was to reach consensus regarding the importance of perceived technical gaps in vaccine development and the availability of alternative sources of vaccine development funding, using the Delphi method.

THE SCOPE OF INFECTIOUS DISEASES OF EPIDEMIC POTENTIAL

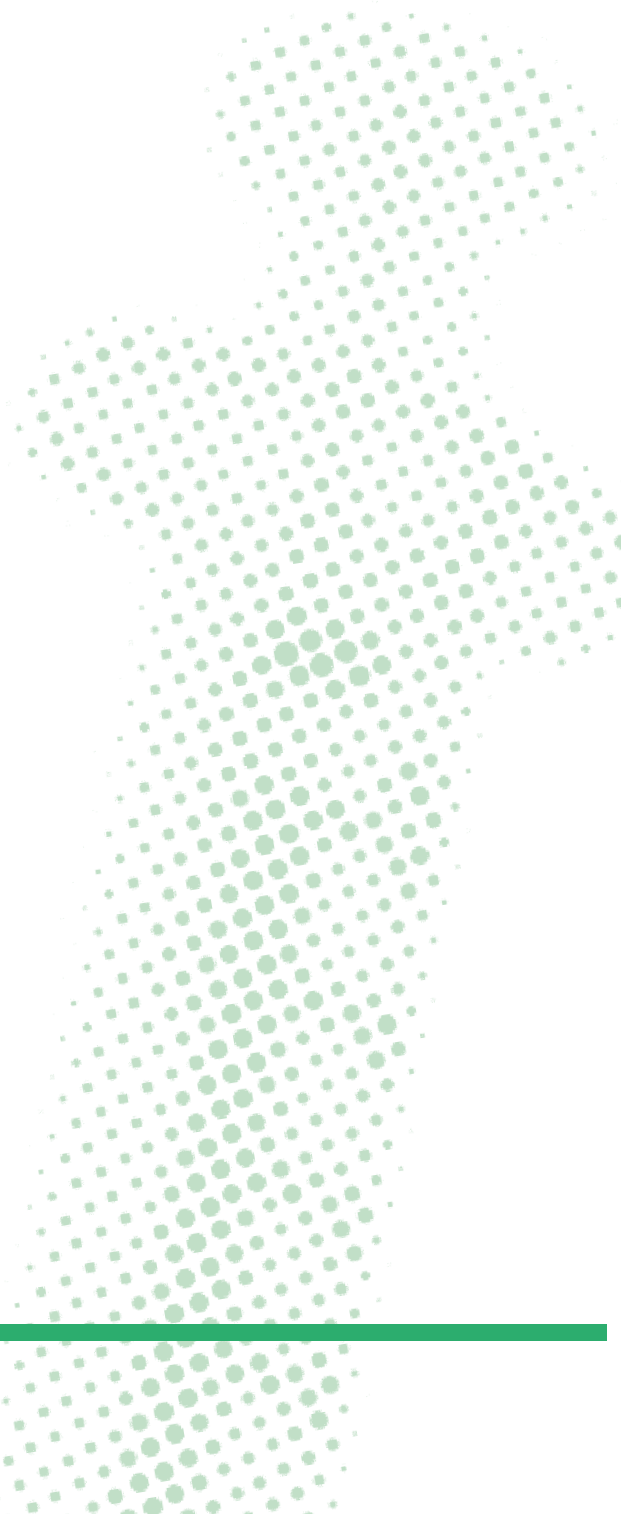
This section will provide an overview of need in terms of the epidemiological distribution and impact of epidemic diseases, drawing on evidence from the published literature. We will consider which countries are at greatest risk of epidemic disease (drawing on epidemiological evidence) and how, in summary terms, these risks map against capacity to develop and deploy vaccines. We will also indicate some of the key characteristics of a vaccine for a disease of epidemic potential that would be likely to facilitate uptake in a LMIC.

IDEPs are by their nature sporadic and although many have caused large outbreaks in the past there are often long inter-epidemic periods during which there is no detectable disease. During these periods it is hard to maintain momentum towards vaccine development as resources are often demanded by what seem to be more pressing needs.[5] The fundamental problem for new vaccines for IDEPs is that they can only be tested for efficacy when there is an ongoing outbreak. However funding is not usually available to produce high quality vaccine batches before an outbreak occurs. This was exemplified by the Ebola outbreak in West Africa that started in 2015 where vaccines were available too late to make a major impact on the course of the outbreak. Vaccines are preventative and take time to stimulate a maximum immune response. They work best if given before the disease outbreak has started because as well as preventing illness, most vaccines reduce the likelihood of becoming infected, and therefore reduce transmission of the pathogen. The two options for epidemic diseases are to stockpile vaccines and transport them to areas of need in the face of an outbreak, or to manufacture only in the case of need. Historically, stockpiling has been the only option practised because there has been no financial incentive to manufacture vaccines for epidemic diseases as the affected populations are relatively poor. The concept of stockpiling vaccines was very much associated with UKVN in the past with the vision being that international funders would commission stockpiles of vaccines which would be distributed in response to an outbreak.[1] Following the COVID19 outbreak and the emergence of mRNA-based vaccine approaches the alternative option, where vaccine facilities for the production of mRNA are established and these are used in response to whichever pathogen has emerged as more feasible.

Unlike vaccines based on inactivated or attenuated virus, or viral proteins, where each virus and protein would have slightly different optimal production characteristics, the

production of mRNA would be a much more defined process which could use a core manufacturing process. Therefore, provided that mRNA vaccines were validated and licensed against priority diseases there is some potential for a 'just in time' manufacturing model to be used.

Whether a stockpile or 'just in time' manufacturing model is used no vaccine provides instant protection. Immune responses to immunisation generally take several weeks to optimise protection and full protection may also require a schedule of multiple doses given over several months. This is why vaccination ahead of an outbreak is more effective than vaccination during an outbreak. Good epidemiological information to establish 'at risk' populations is therefore vital if vaccines are to have their full impact in preventing disease.



2 Summary of progress towards vaccines for epidemic diseases from research funded by the UK and other actors

DIRECT FUNDING FROM UK VACCINE NETWORK

UK Vaccine Network (UKVN) spent £107M on the development of vaccines for 12 priority epidemic diseases over the period 2016-2021. Funding had a specific focus on (i) late-stage preclinical development and early-stage clinical development of vaccine candidates for the priority pathogens, (ii) development of novel vaccine platforms and manufacturing techniques to enable vaccines against unknown pathogens to be developed faster and to improve accessibility and delivery of vaccines in LMICs, and (iii) associated technologies and epidemiological work that would support effective vaccine deployment in an outbreak.

DHSC has already published annual progress reviews of the programme for 2016-2018[6] and for 2018-19[7] so here we will just highlight some of the main findings of these reports and a description of the current progress towards vaccines for the priority diseases.

UKVN funded 78 projects, including 16 projects which had follow on funding.7 These projects ranged from preclinical studies to phase 1-2 clinical trials and vaccine manufacturing hubs. Funding was administered by Innovate UK (£65.2M), EPSRC (£16.9M), NIHR NETSCC (£14.7M), BBSRC (£5.4M) and NIHR-CCF (£5M). Although it is important to note that studies funded by UKVN did include all of the priority pathogens, clinical trials of prototype vaccines have been conducted for only a few of these diseases (Table 1). Although 33 projects mentioned clinical trials in the title of the project or the abstract, clinical trials for vaccines against only four pathogens could be linked to UKVN funding. This included a phase 1 trial by Themis Bioscience (Austria) for a measles virus-vectored Zika vaccine, phase 1 trials for vaccines against Rift Valley Fever, Zika, MERS Coronavirus and a combined Chikungunya/Zika vaccine using the chimpanzee adenovirus platform by the University of Oxford. It is notable that the MERS vaccine was the basis for the rapid development of the SARS-CoV-2 vaccine used against COVID-19.

There are clear limitations to this analysis: it was limited to examination of the title and abstract of projects funded by Innovate UK, BBSRC, EPSRC and NIHR (NETSCC and CCF); the period covered includes the pandemic, where it is reasonable to expect that research by the groups with an interest in epidemic diseases would have either been redirected towards SARS-CoV-2 or severely disrupted by COVID-19; projects may have mentioned clinical trials even though the funded project may have focused on pre-clinical research and did not include plans for a clinical trial; and the indirect effects of training junior researchers and maintaining expertise in this area were not measured. During this period, UK researchers did also conduct clinical trials of vaccines against Chikungunya and Ebola, mainly with the chimpanzee adenovirus or modified vaccinia virus platforms, using other funding sources. CEPI has reported committing up to $19M to Oxford University's Lassa, MERS and Nipah vaccines using the chimpanzee adenovirus platform.

One of the ideas behind the original UK Vaccine Network was to uncouple the vaccine development process from the 'boom and bust' in vaccine research funding that accompanies a major disease epidemic. Generally vaccine research funding is plentiful during and immediately after an epidemic but relatively scarce during inter-epidemic periods. This boom-and-bust picture is clear in the overall record of international vaccine trials over the 2016-2021 period during which most clinical trials were conducted for vaccines against diseases with recent epidemics, including Ebola (75 trials of which 10 were phase 3), Zika (19 trials) and Chikungunya (16 trials).

	Number of projects*	Number mentioning Clinical trials in abstract	UKVN Clinical trials Registered (2016-2021)	UK Trials (other funder, 2016-2021)	Other Clinical trials (2016-2021)
Zika	17	9	2	0	19
Ebola/Marburg	8	6	0	1	10**
Lassa	7	4	0	0	2
CCHF	7	4	0	0	1
Chikungunya	5	3	1	2	16
Rift Valley Fever	5	1	2	0	2
Plague	5	3	0	0	1
Q Fever	5	0	0	0	0
MERS	2	1	2	0	5
Hantavirus	2	1	0	0	4
Nipah	2	1	0	0	1
Diagnostics	3	0	-	-	-
Vaccine formulation or platform	5	0	-	-	-
Epidemiology	5	0	-	-	-
Others	7	0	-	-	-

Table 2. Summary of the number of projects funded for specific pathogens in UKVN and other funders (2016-2019). Grant funding data was from BBSRC, EPSRC NIHR (NETSCC and CCF) and Innovate UK.

* some projects included multiple pathogens e.g. Ebola/Marburg, Ebola/Lassa or Chikungunya/Zika. 'Others' indicates projects where there was no specific pathogen target but where vaccine could impact on several pathogens, for example vaccines preventing virus transmission in mosquitoes.

** for Ebola, only phase 3 trials are listed. Clinical trials data were compiled from ICTRP (WHO), Clinical trials.gov (USA), and the EU Clinical trials register.

THE CURRENT FUNDING LANDSCAPE FOR VACCINES AGAINST PRIORITY DISEASES BEYOND UKVN FUNDS

Coalition for Epidemic Preparedness Innovations (CEPI)

Since the West African EVD outbreak that started in 2015 other international agencies have also targeted the development of vaccines against epidemic diseases (Table 2), most notably CEPI, to which the UK government was the largest single contributor in 2020.[8] CEPI was founded in 2017 and has taken a strategic and systematic approach to the development of vaccines for diseases on the WHO blueprint list. CEPI has published a plan for 2022-2026, predicated on financial commitments of up to US$3.5 billion, which aims to reduce global epidemic and pandemic risk – although it is unclear how far this fund-raising goal will be met. This plan incorporates (i) optimisation of COVID-19 vaccines and the production of universal coronavirus vaccines, (ii) development of vaccines against Chikungunya, Lassa, Nipah, MERS, Rift Valley Fever and additional clinical trials for Ebola vaccines, (iii) working with regulators and manufacturers and clinicians to produce a clinical trials network to respond to new threats, (iv) production of prototype vaccines against representative pathogens from critical viral families using platform vaccines and testing these in phase 1 clinical trials, (v) establishing networks for lab capacity, assays and pre-clinical models and developing national and regional collaborations in support of

Pathogen	Phase			Licensed/ approved
	1	2	3	
Ebola	+	+	+	4
Chikungunya	1	2	2	
Zika	9	2		
MERS	2	2		
Rift Valley Fever	1	1		
Hantavirus	1	1		
Lassa	2			
Marburg	2			
Nipah	1			
CCHF	1			
Plague	0			
Q fever	0			

Table 3. Summary of progress developing vaccines against priority diseases 2016-2021, assessed according to the number of different vaccines in phase 1, 2, and 3 clinical trials respectively.

this, and (vi) supporting full ownership of the vaccine development, testing and manufacturing process by LMICs.[9] In addition to the development of vaccines CEPI also plans to invest in the development of clinical treatments, e.g. monoclonal antibodies, that can be used in managing an outbreak.

CEPI is well funded and internationally recognised and has developed an initiative (COVAX) for the distribution of COVID-19 vaccines to LMICs. It is likely that the COVAX initiative will be a major focus of CEPI funds over the next 5 years and it has the potential to strengthen CEPI's ability to support deployment of epidemic vaccines in LMICs, if it goes well. CEPI has also committed to developing other COVID-19 vaccines with improved product profiles such as single dose vaccines and vaccines with improved thermostability and is also funding research to develop broadly effective vaccines that would work against other betacoronaviruses.

CEPI is committed to standardising tests, regulations and clinical trial methodologies and to ensuring vaccine manufacturing is closer to the site of the outbreak. Currently CEPI sees itself primarily as a funder of clinical development on the pathway to licensing. For earlier and later stages in the pipeline (discovery and distribution) it sees itself as a 'facilitator'. This has resulted in a 'shotgun' approach to vaccine funding where many vaccines against the same disease are progressed through pre-clinical development in parallel. It is less clear what will happen when more than one CEPI-funded vaccine reaches clinical development. As noted in chapter 6 of this report, the long-term commercial viability of any vaccine product is critically dependent on the mechanisms that are put in place to maintain demand for vaccines during inter-epidemic periods.

The European Union (EU)

The EU has invested in epidemic infectious disease research through its Horizon programme but also through specific projects. COVID-19 has stimulated fresh interest in pandemic preparedness and the EU is in the process of putting in place mechanisms to deal with future emerging disease threats such as a standing EU advisory committee on health threats and crises. Other proposed advances include co-ordinated research and development and co-ordinated early response measures to disease threats. Specifically, for epidemic preparedness, the EU (like the UK) is part of the Global research collaboration for infectious disease preparedness (GLoPID-R network). It also funds the EDCTP which involves partnerships to strengthen capacity of countries in sub-Saharan Africa to respond to infectious disease threats. EU funding is directed more towards co-ordinated surveillance and response to epidemics in general, for example the RECOVER and PREPARE programmes, than to a specific list of diseases. This allows flexibility in the response to disease but, due to its reactive nature, it is not well suited to the development of vaccines which have relatively long development times. There are pockets of EU funding that are linked to diseases of relevance to the UKVN priority list, for example the Zoonoses Anticipation and Preparedness Initiative (ZAPI) project funded under the wider Innovative Medicines Initiative (IMI). This has targeted three pathogens, Middle East respiratory syndrome coronavirus (MERS-CoV), Schmallenberg virus and Rift Valley Fever virus and has particularly focused on vaccines, antibody design and 'surge manufacturing capacity'. However it is currently unclear how many of these products are related to human, as opposed to livestock health. Certainly, Schmallenberg virus does not infect humans. The wider IMI is well funded (€5.3 billion) but covers 173 projects ranging from Alzheimer's disease, through cancers, to zoonoses. A search of the IMI projects database with the keyword 'epidemic' returns 13 projects. 10 of these are related to Ebola or other filoviruses, including projects aimed at developing diagnostic tests.

Company	Country	Priority Disease	Type/Platform
Valneva	Austria	Chikungunya, Disease X (SARS-CoV-2), Zika	Inactivated virus
Themis Bioscience	Austria	Lassa, MERS, Chikungunya, Zika	Measles platform
Beijing Institute of Biological Products	China	Disease X (SARS-CoV-2)	Inactivated virus
CanSino Inc	China	Disease X (SARS-CoV-2)	Human adenovirus (Ad5)
Sinovac	China	Disease X (SARS-CoV-2)	Inactivated virus
Shanghai Zerun Biotechnology	China	Disease X (SARS-CoV-2)	Recombinant protein
Clover Biopharmaceuticals	China	Disease X (SARS-CoV-2)	Recombinant protein
CureVac	Germany	Disease X (SARS-CoV-2)	mRNA platform
IDT Biologika	Germany	MERS coronavirus	Recombinant virus vector
Bharat Biotech International Ltd	India	Disease X (SARS-CoV-2), Chikungunya, Zika	Inactivated virus
Biological E Ltd	India	Disease X (SARS-CoV-2)	Protein
S K Bioscience	South Korea	Disease X (SARS-CoV-2)	Recombinant protein
GSK	UK	Ebola	Chimpanzee adenovirus
AstraZeneca	UK/Sweden	Disease X (SARS-CoV-2)	Chimpanzee adenovirus
Moderna	USA	Zika, Disease X (SARS-CoV-2), Chikungunya	mRNA platform
Merck	USA	Ebola	VSV platform
Gritstone Bio	USA	Disease X (SARS-CoV-2)	Self-amplifying mRNA
Novavax	USA	Disease X (SARS-CoV-2)	VLP
Auro vaccines	USA	Nipah	Recombinant protein
Emergent Biosolutions	USA	Lassa, Chikungunya, Zika	VLP, inactivated virus
VBI Vaccines	USA	Disease X (SARS-CoV-2)	VLP
Johnson and Johnson (Janssen, BV Nordic)	USA (Belgium, Denmark)	Ebola, Disease X (SARS-CoV-2), Lassa, MERS, Nipah	Human adenovirus, MVA
Pfizer (BioNTech)	USA (Germany)	Disease X (SARS-CoV-2)	mRNA platform
Inovio Pharmaceuticals	USA	Disease X (SARS-CoV-2), Lassa, MERS	DNA

Table 4. Companies producing or developing vaccines against priority diseases. Abbreviations: MVA = modified vaccinia virus Ankara; VLP = virus-like particles; VSV = vesicular stomatitis virus.

Vaccine development funding from other national governments

In the USA, the National institute of Allergy and Infectious Disease (NIAID), Biomedical Advanced Research and Development Authority (BARDA), Defense Threat Reduction Agency (DTRA), and U.S. Army Medical Research Institute of Infectious Diseases are all involved in developing vaccines against IDEPs. Other active nations include the Russian federation, through the Gamaleya Research Institute of Epidemiology and Microbiology and China, through the companies Sinovac Biotech, Cansino and Beijing Institute of Biological Products. Within the nations of the EU, pre-clinical vaccine development is highly active but clinical trials are mainly linked to private companies or universities. University Medical Center Hamburg-Eppendorf, University of Oxford, and University of Vienna have all conducted clinical trials of vaccines against priority pathogens. India has acted as a manufacturing hub for COVID19 vaccines but has also developed vaccines against some priority diseases. Manufacture is mainly through private companies.

Vaccine development from Companies

Many companies are now producing vaccines against priority diseases (Table 3). During the pandemic many companies have focussed on the production of vaccines against COVID-19. This is likely to be sustained as long as the pandemic continues. A few companies appear to have longer term interests in developing vaccines against IDEPs. These include Moderna, Valneva, Themis, Emergent Biosolutions, Inovio, Bharat Biotech and the Janssen subsidiary of Johnson and Johnson. Some of these companies are exploiting a particular platform technology e.g. mRNA in the case of Moderna or the measles vaccine platform in the case of Themis. Most of these long-term commercial developers have received at least some funding from NIAID or CEPI, or both, for vaccines against IDEPs. There are 4 big vaccine companies that collectively hold 90% of the market share for human vaccines (Pfizer, Sanofi, MSD and GSK). It is notable that these companies are not well represented in the development of vaccines against epidemic diseases. Both GSK and Sanofi have previously had abortive attempts at developing vaccines against particular IDEPs but these projects currently appear to be mothballed. MSD did produce a Vesicular stomatitis virus (VSV)-based vaccine for Ebola which is licensed. Pfizer has rapidly developed a vaccine for 'Disease X' (COVID-19) but mainly because of an existing partnership with the German biotechnology company, BioNTech, with which it was developing a mRNA-based influenza vaccine at the time the pandemic started.

3 Current vaccine position for UKVN priority diseases

Progress in the development of vaccines against priority diseases has been heterogeneous since the UKVN was established. For some diseases, such as Ebola, there has been substantial progress; for others, such as CCHF, there has been hardly any movement. This chapter provides an overview of the current position of vaccine development, by disease, for pathogens on the WHO's Blueprint priority list.

Ebola/Marburg

The Ebola outbreak that started in West Africa in 2015 was a major driver of vaccine development. At present, Merck has a licensed vaccine (Ervebo®) which is approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) and is based on a genetically engineered RNA virus (VSV) backbone. This vaccine was evaluated in a clinical trial in the West African EVD outbreak and, although it is not commercially marketed in the USA, it is stockpiled in the event of an outbreak and is made available to specific categories of people at high risk of coming into contact with the virus.[10] This vaccine is currently in use as part of the response to the current EVD outbreak in North Kivu in the DRC. In addition, the EMA has licensed a vaccine from Janssen which is based on a prime/boost adenovirus 26/MVA (Zabdeno/Mvabea) vaccine regimen for use in exceptional circumstances. China has approved an adenovirus-based Ebola virus vaccine (Ad5-EBOV) made by CanSino and the Russian Federation has approved a combined Adenovirus/VSV based Ebola vaccination regime (GamEvac-Combi) for emergency use. Another vaccine that is at phase 3 development is a chimpanzee adenovirus vaccine (cAd3-EBO Z) currently owned by GSK.

Currently-licensed vaccines for Ebola have only been evaluated against one strain, the *Zaire ebolavirus* species, which caused both the West African outbreak and a subsequent outbreak in DRC. Three other virus species in the *Ebolavirus* genus are known to cause disease (Sudan, Bundibugyo, and Taï Forest viruses). In addition, a virus in the same family, *Marburgvirus*, was also targeted for vaccine development by UKVN. *Marburgvirus, Sudan ebolavirus* and *Bundibugyo ebolavirus* have all have previously resulted in epidemic clusters of disease with high case fatality (Table 4).

Taï Forest ebolavirus has only been reported in one person who developed a self-limiting disease with dengue-like clinical signs after close contact with two dead chimpanzees affected by the virus.

Most of the current vaccines express antigen for a single Ebolavirus species but the MVA boost for the Janssen vaccine contains Nucleoprotein for Taï forest virus and glycoprotein from Marburg, Zaire and Sudan ebolaviruses. There are no data on the degree of protection afforded by this vaccine against any virus other than *Zaire ebolavirus* in humans. However, it is possible that this vaccine would also provide some cross protection against the species included in the vaccine. A phase 1 trial, sponsored by NIAID, was completed in March 2019 looking at, among other indicators, antibody responses to filovirus antigens using this vaccine but the results of this study have not yet been made public.

UKVN research funded a multivalent Zaire/Sudan/Marburg vaccine using the chimpanzee adenovirus platform but to date that vaccine has only been tested in rodents.[11] A *Zaire ebolavirus* vaccine using the chimpanzee adenovirus platform has been tested in phase 2 trials by GSK and a Marburg vaccine with a chimpanzee adenovirus vector was tested in phase 1 trials in work sponsored by NIAID and the US military (Clinical trial number: NCT03475056). There is, therefore, good evidence that a cross protective vaccine against different filoviruses is possible and testing to phase 2 is achievable. However, although Zaire, Sudan and Bundibugyo ebolaviruses and Marburg virus can all occur in the same large-area outbreaks, they are sporadic and often do not occur in the same place at the same time (Table 4), so phase 3 testing of multivalent vaccines in a single trial is nearly impossible.

Virus	Country	Year	Cases	Deaths	Case fatality (%)
Zaire ebolavirus	Zaire (now DRC)	1976	318	280	88%
	Gabon	1994	52	31	60%
	Zaire (now DRC)	1995	315	250	79%
	Gabon	1996	60	45	75%
	Gabon	1996	37	21	57%
	RC	2001	57	43	75%
	Gabon	2001	65	53	82%
	RC	2002	143	128	90%
	RC	2003	39	25	64%
	DRC	2007	264	187	71%
	DRC	2008	32	15	47%
	DRC	2014	66	49	74%
	Guinea, Sierra Leone, Liberia	2014-2016	28,646	11,323	40%
	DRC	2018	54	33	61%
	DRC, Uganda	2018-2020	3,470	2,287	66%
	DRC	2020	130	55	42%
Sudan ebolavirus	Sudan	1979	34	22	65%
	Sudan	2000	425	224	53%
Bundibugyo ebolavirus	Uganda	2007	149	37	25%
	DRC	2012	36	13	36%
Marburg ebolavirus	Germany	1967	29	7	24%
	DRC	1998-2000	154	128	83%
	Angola	2005	374	329	88%

Table 5. Filovirus outbreaks with >25 cases. RC=Republic of the Congo, DRC= Democratic Republic of Congo. Data from CDC. Prior to 2014 Zaire Ebolavirus single outbreaks had affected less than 320 individuals.

CEPI currently partners with Africa CDC (funded by the African Union) to deploy the Janssen Ad.26/MVA filo vaccine in DRC. It does not currently list any new Ebola vaccines in its development portfolio.[12] The EU has funded development of Ebola vaccines through the Ebola+ programme in its €230M Innovative Medicines Initiative launched in 2014. It also contributed €6M to the deployment of Ebola vaccine in DRC in 2019, in partnership with CEPI. The EU funds the EDCTP which includes 16 African and 14 European countries and supports the testing of vaccines against emerging diseases as part of its remit. NIAID provided funding for vaccine trials in response to the Ebola outbreak in West Africa in 2014-2018. Although it has also funded vaccine trials, NIAID has focussed more on drug and monoclonal antibody treatments for cases during outbreaks.

Given the widespread use of Janssen vaccine in DRC and the fact that there are several other vaccines which have been licensed for Zaire ebolavirus the potential for UKVN funding to advance new vaccines into field trials is small. Potential areas where there are technical gaps include validating vaccines for Marburg, Sudan and Bundibugyo viruses in human studies as well as testing of effective multivalent vaccines.

Zika

Although Zika was first described in 1947 and subsequently detected in various countries in Micronesia (2007) and the Pacific (2013-14), it was the 2015 outbreak in Brazil that first linked infections to effects on the developing foetus. Mosquito-borne transmission for the virus has been detected in 87 countries around the world and is associated with congenital abnormalities in newborn children and with Guillain-Barré syndrome in adults. Surveillance has recorded a marked drop in cases of Zika in recent years. From a peak of 2119 cases in 2016, the EU reported 74 cases in 2019,[13] Brazil reported 273,904 cases in 2016 but only 18,941 cases in 2020.[14,15] Most other countries in Central and South America have reported fewer than 1000 cases in 2021. There is some evidence that the virus exists in two lineages, African and Asian, and that the African lineage results in more severe pathogenesis, causing abortion rather than teratological effects in the foetus.[16,17]

Although there is as yet no licensed vaccine, Zika vaccines have been tested in more clinical trials than any other disease except Ebola. There have been 19 clinical trials which have studied inactivated vaccines (NIAID-Sanofi), DNA vaccines, mRNA vaccines (Moderna), Virus-like particles, viral vectors and live attenuated vaccines. Of these, two have progressed to phase 2 trials, a DNA vaccine sponsored by NIAID (trial completed in 2019) and a mRNA vaccine developed by Moderna (trial currently recruiting, due to end in 2023). The decline in circulation of the virus in previously affected areas may have reduced the urgency of this research and indicate that natural exposure results in immunity. It is possible that the outbreaks that emerged in 2015 in South America were caused by the arrival of a new pathogen in immunologically naïve populations. If Zika follows the pattern of other arthropod transmitted diseases it is likely that there will be periodic epidemics with long inter-epidemic periods where disease is less detectable.

The 2015-2017 Brazilian Zika outbreak occurred simultaneously with funding calls for the UKVN and consequently a lot of Zika projects were funded. Zika is related to other arthropod transmitted pathogens (Dengue, Yellow Fever, Japanese encephalitis, West Nile, Japanese encephalitis, Tick-borne encephalitis), some of which have well established vaccines. UKVN funded 19 projects related to Zika vaccines, although some of these targeted multiple pathogens or targeted arthropod-transmitted disease in general. Two Zika-associated clinical trials were supported with UKVN funding. One was a phase I trial of a measles virus-vectored Zika vaccine developed by the Austrian biotechnology firm Themis (NCT02996890). The other was a phase I trial of a Zika virus vaccine using the chimpanzee adenovirus platform developed by University of Oxford (NCT04015648). This trial also included a trial for a Chikungunya virus immunogen using the same platform in the same trial. Since the other two Zika vaccines that have reached phase 2 use different platforms there is some argument in favour of progressing this vaccine also to phase 2.

Chikungunya

Chikungunya is another arthropod transmitted pathogen which has resulted in large epidemics. Two different vaccines have progressed to phase 3 trials. One is a live attenuated vaccine manufactured by Valneva (VLA1553, supported by CEPI), the other is an inactivated vaccine manufactured by Bharat Biotech International Limited (India, also funded by CEPI). Other vaccines have reached phase 2 trials, including vaccines based on the measles virus platform (Themis, Austria, supported by CEPI) and virus like particles (Emergent Biosolutions, USA). Vaccines based on mRNA (Moderna) and chimpanzee adenovirus platforms have both reached phase 1 trials. The chimpanzee adenovirus vaccine was funded by UKVN.

Given the late-stage development of other vaccines for Chikungunya and extensive funding by CEPI there seems little incentive to continue to fast track development of the chimpanzee adenovirus vaccine by UKVN in the near future.

MERS coronavirus

Arguably it was the existing clinical trial programme for a MERS coronavirus (MERS-CoV) vaccine based on the chimpanzee adenovirus platform that gave UK researchers a head-start in developing a new vaccine against COVID-19. At a national level, countries with a high burden of MERS are wealthy so, in principle, there should be a significant market for vaccination. In general terms there is a strategic question as to whether the focus of MERS vaccine development should be on products administered to camels (from which most human cases reported to date have originated) as opposed to humans. However, given the rapid spread of COVID-19 and the evidence from the South Korean outbreak of MERS which occurred in a hospital setting in 2015, there is a strong case for progressing this vaccine and maintaining stocks of vaccine for healthcare workers most at risk of contact with affected individuals. Two MERS vaccines have reached phase 2 trials, a DNA vaccine tested in South Korea by Inovio Pharmaceuticals and the BVRS-GamVac vaccine developed by the Russian Federation based on a human adenovirus platform. Vaccines using the MVA (University of Hamburg) and Chimpanzee adenovirus platform (University of Oxford, UKVN funded) are both at the phase I clinical trial level. In addition, CEPI is funding pre-clinical development of a recombinant protein-based vaccine to MERS-CoV.

There have been three large-scale outbreaks caused by coronaviruses since 2001 (SARS-CoV, MERS-CoV and SARS-CoV-2) which suggests there are strong strategic reasons to maintain a pipeline and expertise in coronavirus vaccine development.

Hantavirus and Lassa

Hantaviruses and Lassa fever are both viruses that have rodents as reservoir hosts. Lassa is largely contained in West Africa and although around 80% of people exposed to the pathogen have no clinical signs, in severe cases infections can be lethal. Although case fatality is relatively low, 100,000-300,000 people are infected annually resulting in significant public health burden in countries where the virus is endemic.

Only two Lassa fever vaccines have reached phase 1 clinical trials: one trial used the measles virus vaccine platform (Themis) and was completed in 2021; the second trial used a modified VSV platform, funded by International AIDS Vaccine Initiative, and this has just started recruiting participants.

CEPI is investing US$249M in the development of 6 Lassa vaccines using different platforms including the University of Oxford Chimpanzee adenovirus platform. Therefore, although Lassa is an important neglected tropical disease, there is likely to be little additional benefit in extra UKVN funding at this time.

Hantavirus infections are caused by several related viruses and tend to occur in people in close contact with rodents or rodent droppings. There are two types of clinical disease, hantavirus pulmonary syndrome (HPS), which mainly affects people in the Americas, and haemorrhagic fever with renal syndrome (HFRS), which occurs worldwide. Case fatality is low, and as human-to-human transmission is rare, human cases rarely occur in clusters. There have been two phase 2 clinical trials of vaccines against Hantaan virus since 2016, both using a DNA-based vaccine funded by the US army. There has also been a single NIAID-funded trial of a DNA vaccine to Andes virus. Andes virus results in HPS and Hantaan virus results in HFRS.

Rift Valley Fever (RVF)

Rift Valley fever is a mosquito transmitted pathogen of livestock which can infect humans and causes severe disease in a minority of infected individuals. Handling meat and aborted foetuses from affected animals is a major risk factor in disease.[18] Outbreaks have been reported in 31 African countries since 1968.[19] Compared to other outbreak diseases on the WHO list, outbreaks of RVF are relatively predictable, and are associated with rainfall events.[20] Rift Valley fever is another focus for vaccine funding for CEPI who have invested US$22M in the preclinical development of two live attenuated vaccines. Clinical trials have been carried out for both inactivated and live attenuated virus by the US army. Phase 1 trials have also started with a chimpanzee adenovirus platform vaccine produced by University of Oxford.

Epidemiology for RVF in most countries is poorly described due to intermittent surveillance and because most infected individuals have mild (if any) clinical signs. This complicates vaccine testing and deployment. If public health authorities cannot observe the problem, there is little incentive to vaccinate for prevention. There is a stronger case for livestock vaccines especially for large cattle ranches which are common in affected areas. However, to be economically viable veterinary vaccines must be considerably less expensive than human vaccines, which reduces the incentive for commercial vaccine development.

Nipah

Nipah is a bat-vectored pathogen that has caused large outbreaks in Malaysia and Bangladesh. CEPI has invested US$118.6M in vaccines against Nipah, including the chimpanzee adenovirus platform. However, to date, only one of these has reached clinical trials in humans, a recombinant protein vaccine jointly developed by Auro vaccines and PATH. This trial is currently recruiting participants for a phase 1 study.

There would be a strong case for vaccination of farmers in areas affected by Nipah but there is also a strong argument for epidemiological control measures (targeting farm practices, for example) to reduce the risk of outbreaks occurring in the first place.

Crimean-Congo haemorrhagic fever

CCHF is a tick transmitted livestock pathogen which causes disease in humans and can also spread from person to person resulting in clusters of cases. It has caused outbreaks in the Balkans, Turkey, Afghanistan, Pakistan, Kazakhstan, Mauritania and the Russian Federation. There is currently only one vaccine which has reached clinical trials, a formalin inactivated vaccine that has been tested in phase 1 trials in Turkey.

Q fever and Plague

Q fever is a human disease caused by a bacterial pathogen *(Coxiella burnetii)* that is carried by livestock. The disease was originally reported in Australia in 1935 but has now been widely documented elsewhere

including in the USA, UK and European countries.[21] There was an outbreak in the Netherlands 2007-2009 that affected more than 4000 individuals.[22] Currently most infections with severe clinical disease are controlled by antibiotic use. There is some evidence of antibiotic resistance developing in the bacterial pathogen but it is currently rare.[23] In 2014, the US army sponsored a phase 2 vaccine trial using an inactivated vaccine but there have been no new clinical trials reported since then.

Plague is another bacterial outbreak disease, caused by *Yersinia pestis,* for which vaccines are not currently commercially available. Most recent large scale plague outbreaks have occurred in Africa. Transmitted by fleas on rodents, cases are more common in small towns and agricultural communities than in larger towns. There are concerns about emergence of antibiotic resistant strains of the pathogen[24] which may make control by vaccination more attractive. Clinical vaccine trials have mostly been reported before 2015 but there is evidence of revived interest more recently. Both NIAID and a Chinese company (Lanzhou Institute of Biological Products Co., Ltd) have tested recombinant protein vaccines. There have also been promising pre-clinical developments using a range of different approaches[25] including a human adenovirus prototype vaccine that has been shown to work in non-human primates.[26] In 2021, the Oxford Vaccine Group commenced a Phase 1 trial against plague using the chimpanzee adenovirus vector used in AstraZeneca vaccine for COVID-19, and in the US, a recombinant rF1V candidate is due to move to phase 2 trials in 2022 with funding from the Department of Defense.

Disease X

Disease X represents the newly emerging, previously unknown pathogen that results in epidemic disease. An example would be SARS CoV-2, the cause of COVID-19. Although it is not possible to prepare vaccines for a pathogen without knowing its identity, it is possible to put in place platform technologies that can be rapidly adapted to a new pathogen. The investment in platform technologies from previous UKVN funding has been justified by the rapid development of a COVID-19 vaccine and is clearly world leading. Another approach, which has been targeted by CEPI, is proposing the approach of generating 'libraries' of vaccine candidates targeting viruses within specific families of viruses. At this stage it is unclear which families will be targeted but based on the WHO priority lists, coronaviruses and flaviviruses are likely to be the top of the list based on previous outbreaks.

Should the priority list be revisited?

Many of the pathogens on the priority list have reached the clinical trial stage during the period since UKVN was first set up. However licensed vaccines have only been produced for two diseases: Ebola and COVID-19 ('Disease X'). Examining the clinical trials carried out and the pipeline of vaccines for priority diseases funded by other organisations, particularly CEPI, there is a strong argument for reviewing the prioritisation of epidemic diseases to focus future funding more efficiently. There is also likely to be a continuing need to review the priority list as the epidemiological profile, and particularly antimicrobial resistance patterns, for known pathogens shift. Although the focus of the priority list has been on viral diseases, the emergence of extensively drug resistant variants of known bacterial pathogens may strengthen the case for investment in vaccines for these agents.

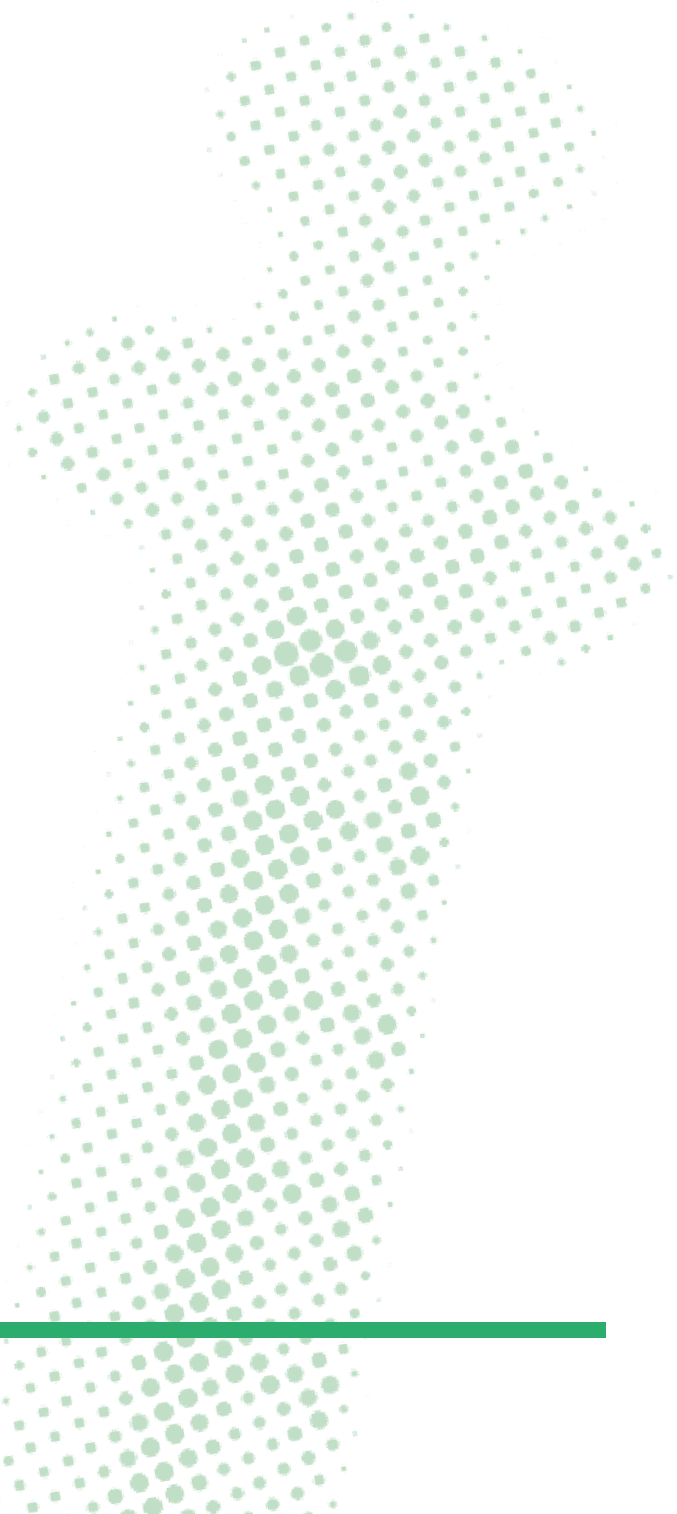
Focusing on viral infections on the current list, it is likely that, even without further UKVN funding, clinical trials for vaccines against Zika, Chikungunya, MERS, Nipah, RVF and Lassa fever will be completed within the next 3-5 years. Over the same period, Q fever and plague are likely to remain controlled by antibiotic use in most places but the need for vaccine development long term remains. Unlike most of the pathogens on the UKVN list, Hantavirus is not a single species of pathogen and does not usually cause large outbreaks of disease making it hard to identify a target population for the vaccine beyond agricultural workers. CCHF currently provides a niche for vaccine development in that few vaccines have been developed to the pathogen despite epidemic potential. However, the risk of a narrow focus on a small number of diseases is that although there is likely to be good progress towards a vaccine there is insufficient flexibility to cope with the next Disease X. The experience of the past 20 years suggests that Disease X is most likely to be a coronavirus (Like SARS-CoV-1, MERS-CoV and SARS-CoV-2), a flavivirus (like West Nile and Zika), an alphavirus (like Chikungunya) or a filovirus (like Ebola). In animals there is further evidence that bunyaviruses (like Schmallenberg, related to RVF) also have potential for epizootic spread.

The potential impact of recent Innovations in vaccine design

Historically vaccines for viral disease have either been inactivated virus or live attenuated vaccine strains produced by passage of the virus in animals or cell lines. DNA vaccines have been shown to work in some animals but have been disappointing in humans. The major advances in vaccine technology in the past few years have been related to the use of viral vectors (mainly with VSV or adenovirus platforms) and vaccines using lipid encapsulated mRNA. Both these options offer considerable advantages over traditional methods of vaccine design in terms of ease of production and flexibility. Instead of having to optimise manufacturing

processes from the beginning with each new vaccine it is now possible to take a modular approach to modify a 'platform' vaccine technology to produce the new vaccine. For both approaches, but for mRNA production especially, the manufacturing process can be standardised between immunogens so that it is theoretically much easier to make more than one vaccine using a common vaccine manufacturing process/plant.

mRNA-based vaccines have been in development for many diseases for some time, but the COVID-19 pandemic has highlighted the speed and flexibility of the approach in the face of a previously unknown pathogen. We are therefore in a 'gold-rush' situation with respect to IP relating to the new technologies. Indeed, the largest barrier to future implementation of the new approaches to vaccination is likely to be restrictions on licensing. The degree to which these will really hamper the exploitation of the mRNA platform is currently unclear.



4

Lessons from developing, manufacturing and delivering vaccines against SARS-COV-2, Ebola and other epidemic diseases: What have we learnt?

In this chapter, we consider lessons from the experiences of vaccine development, manufacture and deployment for Ebola and SARS-CoV-2 for other IDEPs. Although other epidemic diseases have caused outbreaks since 1999 (e.g. West Nile, SARS CoV, MERS CoV, Chikungunya and Zika) the 2014-16 Ebola outbreak in West Africa was a catalyst which focussed funding and research attention in this area.

In the case of SARS CoV-2, the virus that causes the disease COVID-19, the speed of vaccine development has been unprecedented and has demonstrated that it is possible to rapidly develop, test and manufacture at scale effective vaccines. A central theme running through this chapter is the need to take an ecosystem-based approach, recognising the closeness of interconnections between vaccine research and development, local regulatory and manufacturing capacity, and ability to deploy vaccines rapidly and equitably at scale.

VACCINE DEVELOPMENT

Analyses at the time of the West African EVD outbreak in 2014-16 identified the gap between academic, laboratory-scale testing of immunogens in animals and the implementation of clinical trials and commercial vaccines as a major barrier to solving the problem represented by epidemic diseases.[1] The vaccine world was quick to respond to the Ebola epidemic, with rapid development of vaccines based on platform technologies (VSV, Adenovirus and MVA). However, although the epidemic lasted until 2016 and allowed testing of prototype vaccines, the vaccines developed were available too late to have a major impact on case numbers.[27] One of the most positive outcomes from the EVD outbreak in West Africa was the development of a process for the rapid approval of clinical trials in emergency settings. This has great relevance for all of the priority diseases on the UKVN list as any vaccine developed will, after initial safety testing, be tested in this sort of emergency outbreak setting.

Following the 2014-16 outbreak there was another large EVD outbreak in the Democratic Republic of the Congo (DRC) which started in 2018. In this case, due to both the scientific progress made in previous outbreaks, and the availability of a novel financing mechanism (see Box 1), vaccines were available to be deployed at scale. The use of an Advance Market Commitment (AMC – a financing mechanism we address in more detail in chapter 6) helped to create sufficient market 'pull' to allow for the accumulation of a stockpile of near-to-use vaccines in preparation for an outbreak. This provided the basis for deployment of the vaccine in DRC in 2018. However, the circumstances under which this AMC were developed were unusual: the catastrophic effects of the 2014-16 epidemic helped create a strong political imperative for action on Ebola in a way that has not been seen for other IDEPs. Furthermore, as Box 1 shows, there was already a candidate vaccine at a late stage of development around which to structure the AMC, because of extensive public investment in early-stage research over many years. Importantly, a large portion of this funding came from BARDA and had been contributed to help mitigate a perceived biosecurity risk for the United States, rather than to aid prevention among populations in Africa where all outbreaks to date had originated. In general, however, commercial incentives to vaccine development for IDEPs are weak.

Box 1

Using an advance market commitment to overcome commercial barriers to Ebola vaccine development

Late-stage development and regulatory approval of the rVSV-ZEBOV vaccine for Ebola offers a case study of the potential power of AMCs to overcome commercial barriers to vaccine development for epidemic diseases. However, it also emphasises that AMCs are primarily late-stage tools, depend heavily on public investment (often over many years) for their success, and that even with large financial incentives, pathways to regulatory approval, and ultimately to market, are long.

Although outbreaks of EVD had occurred intermittently since its discovery in 1976, the scale and scope of the West African outbreak in 2014-16 altered global perceptions of the risk associated with epidemics of the virus. In late 2014, drawing on global interest, Gavi approved an AMC for Ebola vaccine to pay up to $300m for doses of a WHO-approved product, and up to an additional $90m to support vaccination delivery and health system recovery from the effects of the epidemic.[28] This offer was made to all manufacturers with candidate vaccines at phase 1 or later, but on condition that (i) the manufacturers submitted their vaccine for licensure by a defined date in 2017, (ii) that they applied for a WHO Emergency Use Assessment and Listing (EUAL), and (iii) that partner firms agreed to the creation of a vaccine stockpile to support future epidemic response.[28] The new AMC was announced at a time when there were at least 10 candidate vaccines and treatments in various stages of development, many of which had benefited heavily from government funding at earlier stages in the development process, particularly from Canada and the United States.[29]

One of these candidates, rVSV-ZEBOV (originally developed in Canada), was rapidly advanced through phase 1, 2 and 3 trials during the West African epidemic, with positive findings from a ring vaccination trial carried out in Guinea by 2015.[30] rVSV-ZEBOV trials took place in partnership with the pharmaceutical firm, Merck, but again depended on significant public sector investment, including a further $175m from BARDA to support vaccine production and regulatory validation of Merck's manufacturing facilities for the vaccine in Germany. Gavi reached an agreement with Merck to provide investigational doses for their stockpile in 2016, but it was not until an outbreak in the Democratic Republic of Congo in 2018 that this stockpile was first used, and final regulatory approval from the European Medicines Agency and US Food and Drug Administration was not granted until late 2019.

MANUFACTURING

The involvement of a state or commercial vaccine manufacturing company has been key to the progression of vaccines beyond academic proof of concept scale. The scale of the COVID-19 problem suggests that for this disease the vaccine market is likely to be fairly stable for some years, however, this will ultimately depend on the duration of immunity afforded by current vaccines and the possibility of vaccine escape strains developing. Vaccine manufacture is also complex, involving at least three distinct processes each demanding specialised knowledge and skill sets:

- Drug substance production (upstream): the biological process of vaccine production from cell cultures
- Vaccine formulation (downstream): harvesting and purification of the drug substance
- Fill and finish: formulation of the vaccine, including additional ingredients (excipients) to bolster the immune response that it generates

Manufacturing of new vaccine products is constrained by factors including: (i) the stability of supply chains for essential input materials; (ii) timelines to production of a finished product; (iii) technical know-how; (iv) the need for consistency in production to ensure product quality; and (v) brute production capacity. Supply chain stability has proven a particular challenge for COVID-19 vaccine manufacture because of the scale of demand but, for any epidemic disease vaccine, the precise scope and type of input needs will be platform-dependent (Figure 2).

Platform	Manufacturing requirements			
Viral Vector	· Bioreactor bags · Single use assemblies · Cell culture media	· Bioreactor bags · Single use assemblies · Cell culture media	· Vials · Caps/stoppers · Excipients	
Protein subunit	· Bioreactor bags · Single use assemblies · Cell culture media	· Single use assemblies · Filters · Chromatography consumables	· Vials · Cap/stoppers · Excipients · Adjuvants	
RNA	· Bioreactor bags · Single use assemblies · Plasmid DNA templates	· Single use assemblies · Filters · Chromatography consumables	· Vials · Caps/stoppers · Lipid nanoparticles	· Dry ice · Frozen storage
Inactivated vaccine	· Bioreactor bags · Single use assemblies · Cell culture media	· Single use assemblies · Filters · Chromatography consumables	· Vials · Cap/stoppers · Excipients · Adjuvants	

Figure 2. Examples of key supply chain requirements and challenges by stage of vaccine production and platform type, for candidate COVID-19 vaccines (adapted from 31).

The global distribution of manufacturing capacity

A full analysis of the global vaccine manufacturing landscape is beyond the scope of this report[i], but the COVID-19 pandemic response has demonstrated with alarming clarity just how skewed the global distribution of manufacturing capacity and – for some of the newer technologies – expertise, now is. The global vaccine manufacturing base remains highly concentrated in a small number of firms predominantly in high income countries,[32] although manufacturing capacity in China and India is growing at pace and – by number of doses produced – now exceeds the total elsewhere. In 2019, four firms accounted for 90% of global vaccine production by revenue, reflecting a similar level of concentration at the buyer end where high income country governments and multilateral organisations such as Gavi and UNICEF are key purchasers. Indeed, in 2020, high income countries accounted for 82% of the global vaccine market by revenue, despite purchasing just 20% of the vaccines produced.[33]

The practical implications of this geographical skew can be seen not only in the concentration of production of COVID-19 vaccines among high income country companies, but also in supply chain vulnerabilities exposed by COVAX's reliance on vaccines manufactured by the Serum Institute of India (SII). When production capacity at the SII was temporarily redirected to meet local demand, during the large wave of Alpha variant cases of COVID-19 in India in April-June 2021, there was no manufacturing capacity available to compensate for this redirection and supplies to COVAX and high-income countries alike fell markedly. Similar export restrictions have been applied in the past, notably during the H1N1 epidemic in 2009, for example.[34] The global imperative to diversify the geographical distribution of manufacturing capacity is therefore strong.

The need for technology transfer and sharing of know-now

Since the beginning of the pandemic, investment by pharmaceutical firms to ramp up manufacturing capacity alongside clinical development (scaling-up) and to form partnerships with contract development and manufacturing organisations (CDMOs) to increase overall production capacity (scaling-out) has satisfied demand in high-income countries. Progress in LMICs has lagged far behind, and especially so in Africa.

The African Union and the African Centres for Disease Control and Prevention (Africa CDC) have led intensive efforts since 2020 to bolster continent-wide manufacturing capacity and investment through the Partnerships for African Vaccine Manufacturing (PAVM) initiative.[35] There is some evidence that this is bearing fruit through memoranda of understanding agreed between pharmaceutical companies and local producers: Aspen now produces the J&J COVID-19 vaccine and Egypt's Vacsera has an agreement in place to produce the inactivated COVID-19 vaccine developed by Sinovac, for example.[36] However, these initiatives depend for their success on the willingness of companies to support technology transfer. At the time of writing none of the major pharmaceutical companies producing WHO-approved vaccines had shared technology with a mRNA vaccine regional hub in Africa that was announced in 2021,[ii] although a partner in this hub has succeeded in reproducing Moderna's COVID-19 vaccine.[37] The first six recipient countries for mRNA vaccine technology under the hub have recently been announced – in Egypt, Kenya, Nigeria, Senegal, South Africa and Tunisia.[38] Company engagement with the COVID-19 Technology Access Pool (C-TAP) has been similarly sluggish.[iii] Recently announced partnerships between BioNTech, the Institut Pasteur de Dakar in Senegal, and with the Rwandan government to develop upstream through to fill-finish manufacturing capacity for mRNA COVID-19 vaccines in these countries do, however, include provisions for technology transfer further down the line.[39] Given the reluctance of key industry players to support technology transfer to date there is already evidence that other actors, including in China and Russia, are beginning to move in to support manufacturing capacity development in selected LMICs.

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i. We understand that a number of global and regionally focused analyses of the vaccine manufacturing landscape are either underway or pending publication, including work led by CEPI, PATH, the Wellcome Trust and FCDO (the latter focused on scoping investment opportunities to support vaccine manufacturing in Africa).

ii. In June 2021, the first of a series of regional hubs was announced as a partnership between a South African consortium comprising Biovac, Afrigen Biologics and Vaccines, a network of universities and the Africa Centres for Disease Control and Prevention (CDC), with support from WHO and the Medicines Patent Pool (MPP).For further details please refer to: https://www.who.int/news/item/21-06-2021-who-supporting-south-african-consortium-to-establish-first-covid-mrna-vaccine-technology-transfer-hub [accessed 04/11/2021]

iii. C-TAP, which is hosted by the WHO, was originally established in May 2020 and works through partners including the MPP and Unitaid to secure access to technology and know-how relating to vaccines, therapeutics and other COVID-19 innovations. For further details please refer to: https://www.who.int/initiatives/covid-19-technology-access-pool [accessed 04/11/2021].

In the case of SARS CoV-2, as with Ebola, vaccines built on platforms have been more effective and more rapidly developed than the traditional approaches of attenuated and inactivated virus. It is likely that this is due to the vaccine 'product' being the same irrespective of the antigen triggering the immune response. The production process of making mRNA or Adenovirus vectors is the same whatever the 'payload' carried by the platform. In contrast, the more traditional approaches require growth conditions for virus vaccine stocks to be adapted specifically for each the new pathogen. There have been some COVID-19 vaccines based on the inactivated virus model, for example the Sinovac vaccine. However, in general, other approaches have been more efficient in producing effective vaccines at speed.

However, scaling-up manufacturing capacity globally, using these platforms, depends on the presence of relevant, local technical know-how – a barrier long-recognised by developing country vaccine manufacturers.[40] Manufacturing mRNA vaccines at scale requires new capacities to be developed in LMICs and a key constraint to widening vaccine access throughout the pandemic has been the concentration of expertise in just a few high-income countries. This is less likely to apply for protein subunit or viral vector vaccines for which there is a more established track record of development and production in LMICs and for which existing capacity may be repurposed to some extent. Interviewees for this report acknowledged that development of sustainable mRNA manufacturing capacity in Africa at sufficient scale to meet continental demand is at least 5-10 years away given additional human resource, training and technology transfer requirements to support it.

Strategies for promoting early knowledge-sharing are urgently need to help overcome the shortfall in global manufacturing capacity.[41] Although some of the key actors in vaccine development already apply access conditions (notably CEPI),[42] both the precise terms and the effectiveness of these is unclear and there is scope to strengthen the conditions to drive knowledge-sharing, for example, as recently highlighted in the CEPI mid-term review.[43]

Developing surge capability for manufacturing in the event of an epidemic

It has also become clear that 'surge capacity' in vaccine manufacture for epidemic response is a key challenge as existing vaccine plants tend to be otherwise occupied, and new production lines for vaccines can take 6-12 months to come online with appropriate regulatory approval. Most future epidemics for diseases on the UKVN priority list are likely to demand smaller vaccine batches for shorter periods than COVID-19. There is, therefore, both a commercial challenge of sustaining vaccine manufacturing capacity during inter-epidemic periods when demand is low, and a technical challenge in maintaining workforce expertise and systems at an appropriate level when skills are not being used at the same level. Interviewees for this report universally asserted that 'mothballing' production capacity was impractical because of the risk of eroding workforce knowledge and expertise. This was also an important reason for enthusiasm for newer platforms that could be switched between production of vaccines for endemic disease and epidemic diseases relatively quickly.

The track record for sustaining high-quality, surge manufacturing capacity is less than encouraging. The WHO Global Action Plan for influenza has, since 2006, helped promote the development of production capacity for pandemic influenza vaccines (with sites worldwide, including in Africa), but the success of this approach has been predicated on the existence of a seasonal flu market that helps maintain a baseline level of demand, ensure workforce skills can be maintained, and keeps production facilities 'warm'.[44] Similarly, in the United States, BARDA has invested in production flexibilities principally for pandemic influenza preparedness,[45] and some of this capacity has been used to try to meet near-term COVID-19 vaccine production needs. However, quality control has proven problematic in some of these facilities, and it is not clear whether or how it is possible to sustain surge capacity for vaccine production given the specialised nature of the processes involved.

On the other hand, the COVID-19 response has shown that CDMOs in LMICs such as the SII can scale vaccine manufacturing of new vaccine at pace. So it is certainly possible for this problem to be solved in response to a sudden demand for vaccine manufacture. There is a question over whether India is the most strategically appropriate place for a vaccine manufacturing hub for priority diseases. However, the answer to this question would depend to some extent on the disease and the target population for vaccination. It is necessary either to enable local vaccine manufacturing of some vaccines, e.g. mRNA vaccines, or to improve vaccine stability to facilitate distribution.

REGULATORY ISSUES

Availability of clinical information to inform regulatory evaluation has been a long-standing problem in development of vaccines for epidemic diseases. Clinical data on efficacy is often not available because – in the absence of an outbreak – there are insufficient cases to support phase 3 evaluation. This, then, means evaluation during an outbreak, for which ethical challenges may be significant.[46] However, a series of important innovations emerged in the context of the West African EVD outbreak that have transformed the picture for vaccine development for epidemic diseases (Box 2). Key lessons to emerge include the need for pre-designed and pre-approved

study protocols, the use of prior agreements with potential study sites, and accelerated pathways for joint ethical approval for clinical studies across participating countries; but there are also considerations around trial design and implementation.[47]

Box 2

Overcoming barriers to clinical evaluation of vaccines for epidemic diseases

One of the principal paradoxes in licensing vaccines for epidemic diseases is that, to be useful, they should be licensed before an epidemic occurs; however, before the epidemic takes off there are insufficient cases to conduct a successful Phase 3 study so support licensure. When an epidemic does occur, it becomes difficult to undertake an individually-randomised Phase 3 study because denial of a potential vaccine benefit appears socially unacceptable. Experiences in evaluation of the rVSV-ZEBOV vaccine in West Africa, and in the COVID-19 response, point to a range of potential solutions, including the compression of normal timescales for phase 1-3 trials.[30] For the rVSV-ZEBOV vaccine, phase 1 recruitment was scaled up to generate sufficient numbers for phase 2 without the need for sequential recruitment of participants for this next step.[30] For the Pfizer-BioNTech and Oxford/AstraZeneca COVID-19 vaccines, combined phase 1/2 and phase 2/3 trials were carried out on compressed schedules to allow safety and efficacy evaluation much more quickly than would conventionally be the case.[48,49]

The design of the rVSV-ZEBOV trials, using a ring vaccination approach, also allowed important ethical and statistical requirements to be met by enabling recruitment of sufficient participant numbers to ensure statistical power, by ensuring that all participants were ultimately vaccinated (some immediately, some with a delay), and by including controls but without the use of placebos as is commonly the case for therapeutic trials in stable settings.[50] Finally, practical measures were important in pushing trials for rVSV-ZEBOV to conclusion. These ranged from recruitment of a mixture of staff cadres (including university students) and use of scaled-up good clinical practice training, through to cold chain strengthening and infrastructure investment to support delivery in settings without reliable access to electricity and water.[51]

In many LMICs, the general barriers to approval of new vaccines include limitations to regulatory capacity, although there have been improvements in capacity in recent years. A survey of National Regulatory Authorities (NRA) in Africa, for example, found that none of those included had sufficient in-house expertise to cover the full range of regulatory functions required to bring a drug safely and sustainably to market, with particular deficits around pharmacovigilance and post-marketing surveillance.[52] The WHO currently lists NRAs in only Ghana and Tanzania as operating at a superior level of maturity for vaccines but neither country is a vaccine manufacturer. In the ASEAN region, India, Indonesia, Thailand and Vietnam, all vaccine manufacturing sites, currently qualify at equivalent level.[53] Processes and timelines to regulatory approval can also vary markedly across countries,

increasing the risk of delays and potentially of failure at this stage, and spanning everything from the structure and level of detail in document submissions, through activities needed to meet Good Manufacturing Practice (GMP) requirements, to processes for post-approval changes (which matter for vaccines to address new variants).[54]

There have also been significant improvements in global and regional regulatory coordination in recent years. Globally, the International Coalition of Medicines Regulatory Agencies (ICMRA), of which the MHRA is a member, has acted as a forum to support collaboration between NRAs throughout the pandemic.[55] Regionally, initiatives such as AVAREF,[56] created in 2006 with WHO support and Gates Foundation funding, have helped to improve regulatory alignment and to strengthen oversight of interventional clinical trials being conducted in Africa. AVAREF brings together NRAs and Ethics Committees across the continent. It played an important role in the response to the West African EVD outbreak in 2014-16 by providing a convening point for joint reviews of clinical trial applications, bringing together regulators, ethics committees and trial sponsors.[57]

National-level changes in response to COVID-19 have been more striking. Regulatory agencies in Europe and the United States shortened timelines for approval to a matter of days and were prepared to do so based on preliminary trial data (although the approach to handling this information, including the extent to which analysis was performed by regulatory bodies in-house, varied from country-to-country) but with an understanding that Emergency Use Authorisations (EUAs) were granted with an assumption of rolling review.

VACCINE DEPLOYMENT

Although a full analysis of the health system capabilities needed to deliver vaccines for epidemic diseases at scale in LMICs is beyond the scope of this report (for further details please see appendix 3), interviewees for this report repeatedly emphasised that, *without sufficient capacity for these countries to absorb new products, funding invested in upstream development is very unlikely to be translated into meaningful population health impact.* We have seen that the response to the Ebola outbreak in DRC in 2018 benefited both from the presence of a vaccine candidate that was already near-to-use, and a financing mechanism that helped neutralise disincentives to late-stage development. It also depended, however, on the capability to rapidly and equitably deploy the vaccine in affected areas.

The region of DRC most affected by the Ebola outbreak of 2018 had ongoing issues with violence, a fragile healthcare infrastructure and poor trust of the local population in national and local government.[58]

In common with many other LMICs, the DRC also had no prior experience of delivering vaccination at scale to adults. Only around 10% of countries in the WHO Africa and South East Asian regions had any prior experience of adult vaccination programmes before the pandemic, all from hepatitis B and influenza vaccine deployment, and this has proven a significant impediment to delivery of COVID-19 vaccination.[59] The implementation of effective mass vaccination in the face of the outbreak in DRC faced substantial social, political and infrastructure barriers, and although the vaccine rollout was widely viewed as successful, it depended on significant past experience of managing epidemic disease outbreaks in DRC, as well as intensive support from international actors, neither of which may be present to the same degree elsewhere (see Box 3). The experiences with Ebola highlight the fact that vaccines are a first step towards effective disease control, but they need to be supported by community engagement, an effective healthcare infrastructure and trust that the vaccine is needed and effective in the local population.

For SARS-CoV-2, it is clear that the benefit of vaccines has been most rapidly realised in countries with developed healthcare systems and a high degree of public trust. Part of this may be due to 'vaccine nationalism' but it is also true that in other parts of the world, including areas that would be targets for vaccines for other epidemic diseases on the UKVN priority list the political commitment, the infrastructure and public acceptance needed to support mass vaccination in the adult population is less certain.

Finally, although there is evidence to suggest that at current production rates there should be sufficient supply to meet modelled demand to the end of 2021,[67] procurement of COVID-19 vaccines by LMIC governments to cover the remaining 80% of their eligible populations (i.e. beyond the COVAX offer) is far lower than is needed to ensure high coverage in these countries. The reasons for this are complex, but are linked to slow release of supporting funds by multilateral development banks (MDBs) and stringent regulatory requirements imposed as a condition for financing by the World Bank, in particular, and the difficulty of securing loan financing on international markets for countries with lower international credit ratings.[68] However, there is also evidence that a move to bilateral supply agreements with pharmaceutical companies, rather than pooled procurement, has also undermined the ability of many LMICs to vaccinate larger proportions of their populations. This is despite a long track record of successful pooled procurement for vaccination in some regions, notably the Americas – where the Pan American Health Organization's revolving fund has made major contributions to raising routine childhood vaccination coverage.[69]

Box 3

Vaccination delivery in the Democratic Republic of Congo

Vaccine delivery in the Democratic Republic of Congo (DRC) is shaped by the enormous scale of the country, at more than 2m km^2; the challenging nature of the terrain, especially in outlying areas; and the size and cross-border mobility of its population. It is also influenced by the political and economic context for health service delivery: DRC has one of the smallest per-capita health spending allocations in the world; households contribute by far the largest share of spending on health nationally; the health sector is heavily donor-dependent; and it has been subject to chronic insecurity.[60] The UK is one of many donors with a significant presence in DRC and it currently contributes over £50m directly to support health system strengthening in-country, including for routine immunisation delivery.

Day-to-day delivery challenges in DRC are considerable. While there is, in theory, a clear process for movement of vaccine stock from the central warehouse in Kinshasa to clinic level, in reality supply chain disruptions due to security issues, breakdowns in electricity supplies and in transport links, and the limited number of trained health service staff mean that the quantity of viable vaccine at facility level is often insufficient to meet demand.[61] Although population-level data on health service delivery is available through the national health management information system (DHIS2), this does not provide individual-level information on vaccine dose delivery to allow monitoring on the model of systems implemented in neighbouring Rwanda recently.[62] Recruitment and retention of trained staff to deliver vaccines is also problematic, especially in outlying areas.[61]

The response to the 2018-20 Ebola outbreak in North Kivu nevertheless illustrates what can be achieved in delivering vaccinations even to some of the most remote areas of the country and, in this case, a region affected by active conflict. By the time the outbreak was declared over in June 2020, there had been almost 3,500 cases and around 2,200 deaths. The government-led response mobilised hundreds of local responders to carry out contact-tracing, as a result of which some 300,000 contacts were identified and vaccinated using a ring-vaccination strategy. Directly employing local health workers also helped to build trust in the response and in the vaccine itself – an especially important intervention given well-documented issues of mistrust in previous Ebola outbreaks.[63] Delivery was complicated by the supply chain challenges outlined above, but also by the exacting storage requirements for rVSV-ZEBOV, which must be kept at -60 to -80oC to ensure viability. Among other interventions, cold chain maintenance was supported by use of portable cool boxes originally developed for transporting polio vaccines, and the use of a new cold storage network at facility level, with donor and agency support.[64]

The 2018-20 outbreak was the tenth that had been recorded in DRC since Ebola was first discovered in 1976. Successful deployment of control measures, including vaccination, was built on lesson-learning from past outbreaks and improved institutional preparedness globally, especially following the 2014-16 West African outbreak. These factors were important contributors to the success of the response and they cannot be taken for granted in the event of future IDEP outbreaks elsewhere. Moreover, the very low coverage rates for COVID-19 vaccination in DRC to date, linked partly to distribution challenges but also to potent vaccine scepticism, illustrate the need for tailored approaches for the introduction of each new vaccine to ensure uptake.[65,66]

5 Identifying technical gaps for future vaccine development

DELPHI ANALYSIS

To identify technical gaps and set priorities for future vaccine development, an expert panel was established and a Delphi methodology used to reach consensus opinions (Appendix 1). The basis for this approach is to select a panel with a broad range of expertise relevant to the problem and then use an iterative process to arrive at a consensus opinion. All panellists are invited to justify their opinions at each round of the process and anonymous comments from other panel members are available to panellists in future rounds. The advantage of the approach is that it allows asynchronous consideration of a problem (or series of problems) by a panel of experts but reduces the possibility of any one expert dominating the panel.[2,3,70]

The expert panel used for the Delphi analysis included in this report had 13 experts which included representatives from different funding agencies (Welcome trust, Coalition for epidemic preparedness Innovations), UK scientists with expertise in relevant areas (Viral vaccines, mRNA vaccines, protein-based vaccines, manufacture of vaccines and epidemiology) and scientists from a range of different countries relevant to the priority disease list (Democratic Republic of Congo, Malaysia, Nigeria). The panel was asked to suggest areas that should be priorities for future rounds of UK vaccine network finding and to identify technical gaps in development of vaccines for priority diseases. The Delphi process required panel members to score technical gaps identified for importance to future vaccine development and identify whether there was existing funding from other (non UKVN) sources to investigate the problem. Based on these scores, panel opinions were categorised into four categories according to whether members considered them to be important/less important or well-funded/poorly funded (Figure 3). Consensus was reached when at least 70% of panel scores were in the same category, and at least 50% of panel members provided an opinion.

Clinical trials, epidemiology and viral vector platforms for vaccines were identified by the panel as strategic areas where the UK had existing strengths. Among areas where there was a recommendation to invest in future development, the development of mRNA-based vaccines

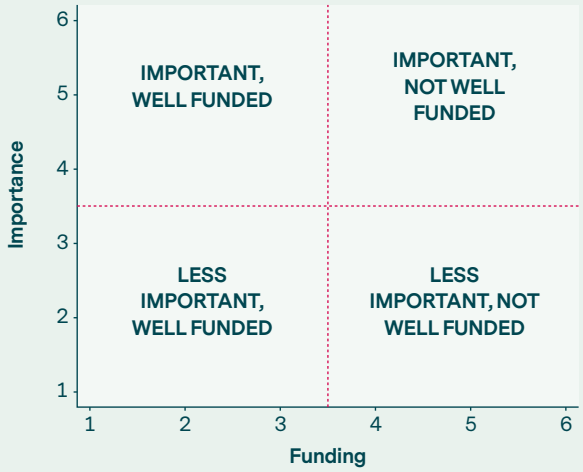

Figure 3. Scoring matrix used to categorise panel opinions. Consensus was reached when 70% of panel opinions were in the same sector of the graph.

was included. However, the panel members noted that the existing expertise in mRNA vaccine platforms was not UK-centric and that there was existing intellectual property that could limit the potential application of this platform for commercial vaccine development. A detailed review of the intellectual property relating to mRNA vaccines is beyond the scope of this report. However, a recent academic review suggests that a key piece of intellectual property, a patent that specifically relates to the use of modified nucleotides as a method of preventing unwanted immune responses to mRNA (and which is sublicensed to both Pfizer-BioNTech and Moderna) runs out in 2023. As vaccines that are developed through the next cycle of UKVN funding are likely to reach commercial use after this date it may be that this perceived problem is historical. Furthermore, the holders of current patents may be willing to license the technology for specific uses (as evidenced by the competing mRNA vaccines for COVID-19 from different companies). A suggestion for future rounds of funding would be that: (i) applicants for future funding for any vaccine platform should explain how they have or will obtain freedom to operate as part of the funding process (and this criterion is included in the evaluation of which projects should be funded); or (ii) DHSC should

commission further investigations into whether there is sufficient 'freedom to operate' for any funding of mRNA vaccines as a platform.

TECHNICAL GAPS WHERE THE EXPERT PANEL REACHED CONSENSUS

The expert panel reached consensus on 11 of the 25 technical gaps that they considered (the consensus list is given in Figure 4; the full list of 25 gaps can be found in appendix 1). In all cases they were areas which the panel felt were important but poorly funded. Two of the gaps related to the overall strategy for funding of vaccines, the panel agreed that the strategy started by previous UKVN funding of providing funding to progress to clinical trials was still important and still underfunded. Arguably one of the reasons that the UK could pivot to produce COVID-19 vaccines rapidly is that at the time of the outbreak clinical trials to another coronavirus (MERS) were at an advanced stage of preparation. The second area that the panel reached consensus was the recommendation that, where appropriate for the disease, DHSC should consider

Technical Gap
Overarching
Funding to allow vaccines to progress to completion of phase 2 clinical trials even during inter-epidemic periods.
Vaccines for livestock and wildlife for zoonotic diseases.
Manufacture and deployment
Funding to enable and improve GMP vaccine manufacture at scale for prototype vaccines.
Research into deployment of rapid production platforms for vaccines.
Research into deployment of rapid production platforms for input materials (plasmids, linear DNA, enzymes, nucleotides, formulation ingredients).
Funding for GMP production facilities (including LMICs)
Knowledge transfer especially for RNA vaccines (LMICs)
Technical improvements to vaccines
Development of vaccines with alternative delivery routes (e.g. oral or nasal)
Vaccines that are stable at 40 °C
Testing and immunology
Identification of animal models relevant to vaccine development for priority diseases
Standardised diagnostic tests for priority diseases.

Figure 4. Technical gaps on which the expert panel reached consensus.

funding research into vaccines for the same disease in livestock and wildlife species. The rationale behind this was that if humans were at risk of being infected by spill over from other species, then reducing disease in the reservoir has a positive impact on human health.

The remaining technical gaps could be grouped into three priority areas: Manufacturing and deployment, technical improvements to vaccines, and testing and immunology. Of these the greatest number of gaps were related to the large-scale production of vaccine candidates for clinical trials. At a basic level this included funding for GMP-compliant production facilities including in LMICs but also extended to improving GMP manufacture at scale for prototype vaccines. The panel recognised that rapid scale-up of production was necessary and there was a suggestion that research into rapid production platforms for both vaccines and input materials (plasmids, linear DNA, enzymes, nucleotides and formulation ingredients) should be prioritised. Some of these priorities reflect

recent experience with COVID-19 vaccines where shortages of key components were seen as bottlenecks in the vaccine development process.

The gap from lab bench to clinic remains, however. The UK government has recently announced the launch of a Vaccine Evaluation Centre, including facilities at UKHSA to support risk assessment for future SARS-CoV-2 variants, and efficacy testing for new vaccines – but the focus of this centre appears to be exclusively on COVID-19.[71] While the UK had invested up to £200M in the Vaccine Manufacturing and Innovation Centre (VMIC) with the goal of promoting advancement of promising vaccines to production, the long-term status of this facility is now unclear.[72] There was a specific suggestion from panel members that MHRA should consider a 'platform master file' for the acceleration of approval of vaccines using a common platform. Further work will be needed to ensure that there is efficient communication and commissioning of research related to the VMIC facility, and that those involved in vaccine development are able to effectively draw on the resources and opportunities it will provide.

For the wider deployment of rapid production facilities there are different problems depending on whether this is aimed at LMICs or high-income countries. The argument for investing in facilities that could rapidly scale-up manufacture of vaccines against emerging diseases is clear. Local production of vaccines is particularly attractive as it would mitigate risks associated with vaccine nationalism, storage and transport. However, developing manufacturing plants in LMICs presents several challenges in the areas of infrastructure (supply of raw materials), regulatory capacity (approval of vaccine batches made from rapid deployment facilities) and public perception (safety of vaccines from facilities that are regarded as new and untested). The panel also reached consensus that technology transfer to LMICs, particularly with respect to mRNA vaccines, should be prioritised, although this should be considered in the wider context of the freedom to operate with respect to the mRNA vaccines platform.

For technical improvements to vaccines, the panel reached consensus on two topics, that approaches that improve the thermal stability and route of delivery should both be improved. These improvements are likely to have the most impact if they are combined with existing vaccine platforms. However, a vaccine that has both a new platform and a new method of stabilisation or delivery would present a greater regulatory challenge.

Finally, for testing and immunology, the panel felt that there were gaps in the identification of appropriate animal models for some of the pathogens on the priority list. For many of these pathogens pre-clinical research will take place during inter-epidemic periods so there will be limited potential for testing efficacy in human subjects. Related to this was the suggestion that there should be improved standardisation of reagents and diagnostic tests for priority diseases. These include international serological standards that could be used to compare vaccine strategies and the degree of cross protection for circulating strains, but also the diagnostic tests used for disease surveillance. One panel member argued that the development of diagnostic tests and vaccines should be coordinated so that it would be possible to determine the extent of disease circulation even in a vaccinated population.

6 Financing vaccines for epidemic diseases

In its first round, the UKVN's stated focus was to "support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases of epidemic potential".

The network's role statement also explicitly recognises that because of the geographical focus of many epidemic diseases in LMICs, market incentives for companies to develop candidates against these diseases are often lacking.[73] However, as preceding chapters have shown, funding allocation in the UKVN's first round was overwhelmingly focused on upstream support for R&D, and predominantly in the UK. In this chapter we show that, without appropriately structured financing mechanisms it is very unlikely that vaccines developed for IDEPs can be brought sustainably to market. We then consider some interventions to strengthen commercial incentives for late-stage vaccine development, and some that explicitly de-link development from market sales.

CAN MARKETS FOR EPIDEMIC DISEASE VACCINES EVER BE SUSTAINED?

The brute reality is that sustainable demand for vaccines for IDEPs on the current priority list cannot be guaranteed without assurance of revenues for manufacturers. The inherently high-risk nature of this kind of product development and costs of R&D and manufacturing make investment without promised returns prohibitive. A recent analysis of vaccine development for infectious diseases in the period 2000-2020 found an overall probability of success[iv] of around 40% (irrespective of the vaccine type) for industry-sponsored programmes, but this figure obscures large variations between diseases and for a number of epidemic diseases (e.g. SARS, MERS, Zika) no approved vaccine yet exists.[74] Documented rates of progression through clinical trials for vaccines (any infectious disease) in other studies are as low as 6-11%.[75,76] Technical risks for development of vaccines for epidemic diseases are compounded by extraordinary financial costs, estimated in a recent economic modelling study[v] at a minimum of $2.8-3.7B to advance at least one new vaccine for each of the 11 WHO blueprint diseases from preclinical to the end of phase 2a trials.[77] Taken together, risk of failure and financial cost are strong disincentives for companies to invest.

For epidemic diseases – as for vaccines in general, even in high income settings – incentives to invest are also reduced by low perceived return on investment (ROI). As current data on the epidemiology of epidemic diseases show (see chapter 1), these are products for which the principal markets are in LMICs and especially low-income countries (LICs). Epidemic diseases predominantly affected the poorest populations who, by definition, are least able to pay. In addition, epidemic diseases may emerge or re-emerge only sporadically, providing no long-term market for companies to meet.[78] The occasional nature of disease outbreaks is also likely to drive vaccine prices up, reducing accessibility to the most vulnerable populations. Finally, post-development testing and evaluation requirements are often considerable, and where vaccines may be used outside an outbreak context, there may also be considerations around integration into the routine national vaccination schedule. If so, this long-term market can exert a strong incentive to manufacturers who would otherwise be reluctant to invest in development costs.[79]

GENERATING SUFFICIENT DEMAND FOR VACCINES FOR EPIDEMIC DISEASES

Given the size of the commercial barriers to development of vaccines for epidemic diseases, where might we look for solutions? Although the unprecedented success

iv. Defined in this particular study as progression from phase 1 to regulatory approval in at least one country.
v. This study considered 141 preclinical candidates for DEP vaccines for WHO blueprint diseases, identified in discussion with stakeholders at CEPI.

of vaccine development for COVID-19 (an emerging infectious disease, after all) looks encouraging, the practical lessons that can be drawn from this experience for other epidemic diseases are limited. The circumstances for COVID-19 vaccine development have clearly been exceptional. Public and private actors have proven willing to accept far higher levels of investment risk than would normally be the case because of global nature of the crisis and the scale of the potential market. Key actors have also concurrently combined intensive 'push' funding (e.g. Operation Warp Speed in the US) with incentives to spur production that match anticipated market size worldwide (e.g. the COVAX AMC, the Access to COVID-19 Tools Accelerator (ACT-A)). Markets on this scale are highly unlikely to exist in LMICs facing epidemic disease outbreaks in future. Similarly, the creation of captive markets (e.g. tourists and military personnel) for regular vaccination against some infections are unlikely to offset even a fraction of the cost of vaccine development.[80]

Market-shaping initiatives

Shaping is an increasingly common intervention to promote development of products for which there is no well-functioning market exists.[vi] The mechanisms for which there is the most extensive track-record are advance purchase- and advance market commitments (APCs and AMCs). APCs guarantee markets for a specific product through contracting with an individual company and have been used extensively by high income countries during the pandemic in purchasing COVID-19 vaccines directly from pharmaceutical companies.[81]

AMCs, by contrast, guarantee markets for vaccines developed to predefined specifications. In doing so, they allow room for competition between vaccine developers in a way that APCs cannot. Pioneered by BARDA in the US, the first global AMC was introduced in 2009 to help bring a series of late-stage pneumococcal vaccines to market. There is economic evidence to suggest that APCs are more efficient at promoting late-stage development for near-to-use products, but that AMCs offer clearer benefits for early-stage development (see Box 1 earlier in the report).[82] Both approaches usually depend on a defined exit strategy to guarantee donor engagement: in other words, that subsidies will not be required on an ongoing basis.

Variations to the basic AMC model have emerged to meet prospective markets for different diseases (appendix 2). Recent economic modelling suggests that, whatever the disease, the most efficient AMC structure depends heavily on (i) the technology under consideration and (ii) the stage of development of that technology.[83] Benefit-based models offer advantages for epidemic diseases by accounting for the societal and global value of vaccines against these diseases, as well as health-related costs. However, benefit-based models would still depend heavily on donor financing because most LMICs purchasing vaccines would not be able to buy doses unless they are available at, or near to, cost price.[82]

COVAX is a very particular kind of AMC that – by bringing 'push' and 'pull'-funding actors together and using staggered financial contributions according to the income status of participating countries – has tried to support global access to COVID-19 vaccines at costs affordable for LMICs. The limitations of this model have, however, become increasingly apparent. Among many other issues, COVAX has struggled to mobilise donor funding; efforts to procure vaccinations in a timely way have been undercut by high income countries reaching prior agreements directly with manufacturers on preferential terms, and by an export ban imposed by the Indian government earlier this year; and dose delivery has sometimes occurred in a haphazard and unpredictable way, obliging LMICs in some cases to make direct-to-manufacturer deals and effectively paying twice for vaccines. Delivery to LMICs continues to lag a very long way behind stated targets, although COVAX has committed to a significant acceleration over the coming months.[84,85]

De-linking vaccine development from market sales

A third approach – de-linkage – explicitly separates investment in R&D from market prices and sales volume as a means of recouping costs. Product Development Partnerships (PDPs) offer one route for de-linking and have been combined with pull funding to support roll-out where target prices are unattractive to private sector actors, most successfully for the Meningitis Vaccine Project (Box 4).

Although other approaches – including product development portfolios and prizes – have been suggested (see appendix 2), these are unlikely to address the fundamental market barriers to epidemic disease vaccine development outlined above.

In this chapter, we have seen that the COVID-19 experience has been exceptional for an emerging pathogen. High-income countries generated sufficient market demand through APCs to drive development even for unproven vaccine candidates. We cannot expect a similar situation for IDEPs in future. The most financially viable long-term solution for IDEP is, in our view, a combined push-pull mechanism similar to the MVP but this will require sustained, and substantial

vi. Market-shaping typically takes one of three forms: (i) interventions designed to reduce transaction costs for market players so that they are more likely to engage in it; (ii) providing better information; or (iii) transferring financial risks away from current and potential new players in a market to encourage them to participate. The types of intervention described in this section – APCs and AMCs – both fall in category (iii).

funding commitments in the medium-term. AMCs, which have been used with some success to spur late-stage development for EVD and pneumococcal vaccines, offer an alternative route. For both PDPs and AMCs, however, governance and financing structures will need to be tailored closely to the disease (and particularly the development status of vaccine candidates), and further analytical work is needed to understand the viability of alternative PDP or AMC structures for IDEPs from the priority list where vaccine candidates are nearer to use. Short of these options, and in light of the UK's major financial contributions to COVAX, UKVN could consider commissioning work to explore legacy options for this Facility and the extent to which it could be adapted to support IDEP vaccine development in the future.

Box 4

Product development partnerships to develop priority vaccines at low cost: MenAfriVac

The Meningitis Vaccine Project (MVP) was set up in 2001 using $70m seed grant from the Bill and Melinda Gates Foundation to fund development of a vaccine for Neisseria meningitidis serogroup A through a partnership between WHO and PATH. It is an example of a combined push-pull initiative that did successfully deliver a low-cost vaccine suitable for field use but was, nevertheless, dependent on third party financing for roll-out. The UK contributed around £5.8m to MVP between 2010 and 2018.

Funding for the MVP was provided upfront to support late-stage development of candidate products, but also enable technology transfer to the Serum Institute in India, to enable large-scale production of a final vaccine. Importantly, consultation with in-country partners, prior needs assessment and economic analysis were all used both to determine the desired type of product (specifically – a single-dose monovalent Meningitis A conjugate vaccine for use in 1-29-year-olds in sub-Saharan Africa) and to set a final price per dose to LMIC partners of $0.40. The combination of set final price and projected R&D costs proved unattractive to private sector pharmaceutical partners, so MVP funds were instead used to build a multi-national collaboration to develop and produce the vaccine.[86,87]

The success of this approach depended on the identification of three actors willing to contribute, at affordable rates, critical technologies for the vaccine, but also on MVP's investment in capacity-building for both participating NRAs but also laboratory and surveillance networks to support clinical trials.[87] However, substantial additional funding has been required from Gavi to enable rollout of the vaccine in sub-Saharan Africa. Difficulties in ensuring long-term donor funding emphasise the vulnerability of programmes of this kind even where a successful product has been developed. In addition, the MVP model depended on use of 25m doses per year for at least 10 years – an uptake level that is unlikely to apply for many IDEPs.[88]

7 Governance and coordination of vaccine R&D, epidemic preparedness and response

In this chapter, we shift focus to consider the missions and capabilities of entities involved in epidemic disease vaccine development, vaccine use for prevention, and in epidemic preparedness and response more specifically, the extent to which these align, and areas where change might lead to improvements in system performance.

The UK is a significant financial contributor to many of the leading actors in this space: it was the largest single contributor to the WHO's core voluntary contributions fund in 2018-19 and has recently announced a further uplift in support; it has so far pledged around £250m to support CEPI's work in developing COVID-19 vaccines; and has pledged £1.65bn to Gavi in its 2021-25 replenishment round. A central theme running through this chapter is the need for closer attention to epidemic preparedness in LMICs – an area that has achieved greater prominence since the West African EVD epidemic but is frequently neglected between epidemic cycles.

GOVERNANCE AND COORDINATION OF R&D FOR VACCINES AGAINST EPIDEMIC DISEASES

Global governance for emergency preparedness and response is labyrinthine and there is currently no formal coordination mechanism governing R&D for epidemic disease vaccines worldwide, although CEPI has come to assume the dominant position in this space. The WHO Blueprint provides a framework for identifying priority diseases against which to develop countermeasures. It has also provided an organising focus for research communities around specific diseases both in the UK and elsewhere – including for COVID-19.[89] However, it has no formal role in driving progress on research against Blueprint priorities, nor in monitoring the collation and distribution of funding or identifying outstanding gaps. In the absence of pooled funding, there may also be significant delays in mobilising funds for research that has been identified as a priority under the Blueprint, including during emergencies.[90] Notwithstanding CEPI's pre-eminent position in financing vaccine R&D, these deficits contribute to the risk of duplication in research efforts under 'peacetime' conditions, and even where consensus priorities emerge in the context of emergency response, funders need time to issue their own calls, and to evaluate submitted proposal before releasing funds for research.[90] Finally, and importantly given the zoonotic origins of IDEPs and transmission potential from animal reservoirs or hosts, the focus of the Blueprint and of key actors in R&D including CEPI continues to be restricted to vaccine development for humans.

As the experience of the pandemic has shown, the number of stakeholders in vaccine development and delivery for preventive purposes is very large, and each is quite different in terms of capability and agility. Table 4 (appendix 4) sets out the remit and financial contributions to vaccine development and deployment of some of the major scientific actors (including academia), country governments, private organisations and multilateral institutions. The picture is complicated, and dynamics differ regionally. In Africa, for example, there are important brokering and coordination efforts underway led by the African Union and Africa CDC to bolster late-stage development and manufacturing for COVID-19 vaccines. These have the potential to be transferred to vaccine technologies for other pathogens in the future. These activities are occurring in coordination with WHO, but the degree of support from pharmaceutical companies remains in question.

The landscape for vaccine development and deployment is dominated by two actors – CEPI and Gavi. The creation of CEPI in 2017 has transformed the picture for early vaccine development for IDEPs, especially by comparison with the level of support available for development in other fields including diagnostics and therapeutics. CEPI was created partly in response to coordination problems identified during the West African EVD epidemic in 2014-

16, and in addition to its financial heft, it has contributed policy innovations including a 'no regrets' approach that helped greatly reduce development times for new COVID-19 vaccines. CEPI was able to initiate vaccine development for a number of candidates for COVID-19 very quickly – in fact as early as the end of January 2020[91] – and currently has a portfolio of 14 COVID-19 vaccines including major financial contributions to the AstraZeneca and Moderna vaccines already in use. However, the status of its wider portfolio for epidemic diseases is much more mixed, with just one vaccine at phase 3 (Valneva's Chikungunya vaccine), one at phase 2 (Inovio for MERS), and progress across the portfolio set back by delays linked to COVID-19.[92] In addition, it focuses exclusively on vaccines for human use, with no funding currently allocated to animal vaccine development.

Gavi has traditionally focused on vaccines for endemic disease although it has developed dedicated financing mechanisms for Ebola vaccines. It offers support according to strictly defined country eligibility criteria (a number of countries that are vulnerable to epidemic diseases either have or will shortly transition out of Gavi support, including Vietnam and Kenya). Although CEPI and Gavi co-lead COVAX with the WHO, outside the context of COVID-19 the degree of strategic alignment in their activities is unclear. Neither organisation currently has board-level representation from the other, for example. The UK does currently hold board-level seats at both organisations, with the potential to advocate for more joined-up support for IDEP vaccine development.

A number of key actors (BMGF, CEPI and the Wellcome Trust – though CEPI makes by far the largest financial contribution) apply specifications regarding access to medicines as a pre-condition of funding for R&D. However, we do not yet have a clear view of the extent to which these access provisions, determined in advance, affect the final accessibility of vaccines developed using this funding; the record for COVID-19 vaccines is certainly far from encouraging. Given the scale of the UK's contributions to CEPI, UKVN should consider commissioning work to evaluate the effectiveness of equitable access provisions tied to funding for vaccine research, and ways in which they can be strengthened for IDEPs given that affected populations reside principally in LMICs.

GOVERNANCE OF EPIDEMIC DISEASE PREPAREDNESS AND RESPONSE

Epidemic preparedness

Global and country-level support for epidemic preparedness has long been piecemeal – the political incentive to action declines between epidemic cycles. The International Health Regulations (IHRs) set out in broad terms the expectations of signatory states for actions in handling public health events and emergencies – but also in the maintenance of core surveillance and response functions to respond to pathogens. Elsewhere, there is now a plethora of actors engaged in strengthening epidemic preparedness and response in high-income settings (e.g. the Global Health Security Initiative[vii]), and across high-income and LMIC settings (e.g. the Global Health Security Agenda[viii]). The latter now has a broad membership of over 70 countries and mechanisms for supporting IHR activities such as Joint External Evaluations (JEE) of country capacity to prevent, detect and rapidly respond to an epidemic. However, this and other initiatives to strengthen LMIC capacity have suffered from a chronic under funding over many years – a shortcoming identified as in need of urgent action by the most recent annual reports from both the Global Preparedness Monitoring Board, and the Independent Panel for Pandemic Preparedness and Response.[89,93]

A striking aspect of the COVID-19 response was the move to create wholly new structures – in the form of ACT-A and more specifically COVAX – to drive global efforts to develop, produce and distribute countermeasures against the disease, despite the existence of the Pandemic Influenza Preparedness Framework (PIPF). The PIPF is a partnership agreement bringing together WHO with member states, industry and other actors to support strengthening of country surveillance systems. It includes provisions to strengthen the access of LMICs to vaccines against novel strains of flu through several mechanisms, including the agreement of advance supply contracts with manufacturers, to try to assuage concerns over restricted access to countermeasures that arose during the H1N1 outbreak in 2009.[94] Although global influenza surveillance systems have contributed in important ways to the COVID-19 response, adaptations to the PIPF to enable its use in supporting development and rollout of countermeasures for COVID-19 was not prioritised in the early stages of the pandemic. Considering how and where existing architectures, including COVAX and the PIPF, can be better used in preparing for and responding to future epidemics should be a central part of the lesson-learning

vii. For further details, please refer to: http://ghsi.ca/ [accessed 20/10/2021]
viii. For further details, please refer to: https://ghsagenda.org/ [accessed 20/10/2021]

from the current pandemic, and are areas in which we would suggest UKVN commission original analytical work. This work could consider a menu of options including strengthened strategic alignment between CEPI and Gavi (leveraging the financial contributions the UK makes to both organisations), or identifying whether and how (and for which IDEPs) specific, integrative financing and governance mechanisms such as COVAX or the PIPF could be repurposed to provide strengthened incentives to late-stage vaccine development, and ensure equitable access to products in the event of an epidemic.

Epidemic response: deployment of countermeasures

National governments naturally take a primary role in response to domestic outbreaks, but for those epidemics which have risks of spill over to other countries, global response mechanisms are fragmented and continue to be organised primarily around individual pathogens. The IHRs provide an overarching framework governing action on events that may constitute a potential public health emergency of international concern (PHEIC) and specify the norm-setting role of the WHO within this. Under the IHRs, signatory governments are required to inform the WHO of all within-border events that might constitute a PHEIC, and to engage with partners to tackle outbreaks if they cannot be contained locally.

However, practical capacity to respond to a potential PHEIC is limited by a number of factors including (i) the effectiveness of surveillance systems and ability of states to identify outbreaks of concern in a timely fashion; (ii) the willingness and speed shown by national governments in declaring outbreaks of concern; (iii) funding constraints; (iv) coordination problems; and (v) ready access to countermeasures. The WHO naturally occupies a central role for (ii), (iii) and to some extent (iv). However, its scope for action is limited by three factors (i) the small size of the Contingency Fund for Emergencies (the dedicated funding mechanism used to provide the organisation with flexibility to respond quickly in the event of an emergency – which can release up to $500,000 within 24 hours to finance immediate responses),[95] (ii) the diversity of actors with a stake in vaccine deployment, and (iii) the variation in requirements for successful deployment depending on the epidemic characteristics and the nature of the vaccine product concerned.[96] Emergency financing for epidemic responses in LMICs continues to be a major challenge across the board: the World Bank's Pandemic Emergency Financing Facility (PEFF), developed specifically to tackle this, demonstrably failed to release bond funding in a timely and effective way for both the Ebola response in DRC in 2019, and the COVID-19 response globally in 2020.[97]

Partly in recognition of the need for better coordination and speedier access to countermeasures in the event of epidemics, the International Coordinating Group (ICG) on Vaccine Provision now plays a central role in overseeing responses to country-level requests for vaccines for a specific set of pathogens.[ix] Set up in 1997 in the wake of a large cross-country meningitis outbreak in Africa, the ICG is hosted by the WHO and works in partnership with UN agencies and NGOs to assess and respond to country requests for vaccine deployment according to predefined criteria, with the aim of releasing supplies in-country within 10 days of an initial request for assistance. The ICG's remit currently covers deployment for the oral cholera vaccine and for vaccines against Ebola, meningitis and yellow fever, and depends on use of vaccine stockpiles (see Box 5) to ensure speed of delivery.

The appropriateness and design of stockpiles depends heavily on the vaccines concerned and the epidemiology of the pathogens they target. For emerging pathogens without a recognised vaccine amenable to stockpiling, governance mechanisms are more *ad hoc* as experiences during the pandemic have demonstrated. Leaving aside widely publicised failings in the speed and comprehensiveness of both national and global responses to the emergence of SARS-CoV-2,[101] equitable distribution of new vaccines for COVID-19 has become the defining challenge of the pandemic – but the wider lessons to be learnt from the COVAX experience remain unclear. COVAX has had to shape its organisation and role 'mid-flight' and has been chronically under-funded since its inception. Reliance on a traditional financing model, based on donor-contributions, has led to difficulties in raising the amount of funding required to support vaccine procurement to meet existing commitments (which amount to coverage for 20% of LMIC country populations), at a time when many high income countries with greater purchasing power than COVAX have been prioritising procurement to meet domestic demand.[102]

ix. The ICG has four founding members: the WHO (which also provides the secretariat function for this group), Medecins sans Frontieres, the International Federation of Red Cross and Red Crescent Societies, and UNICEF. See for further details: https://www.who.int/groups/icg/about [accessed 04/11/2021].

Box 5

Stockpiling IDEP vaccines for rapid deployment

Stockpiles have become the preferred route for storage and deployment of vaccines for a subset of IDEPs. Although the ICG manages a majority of these, other examples do exist including global and country-level stores of smallpox vaccine, the WHO's Pandemic Influenza Preparedness (PIP) framework under which flu vaccines are stockpiled for emergency response globally, and monovalent oral polio vaccine – managed jointly by WHO and the Global Polio Eradication Program (GPEI).[98] A key advantage of the stockpiling approach is that it overcomes time constraints imposed by regular manufacturing and procurement processes – the ICG can simply call on existing stocks, mostly held at manufacturing sites, on-demand with UNICEF stepping in to procure within the 10-day timeframe for response.

While the track record for deployment through the ICG and other mechanisms suggests that it is rapid and effective, establishing and maintaining a stockpile is not straightforward. Stockpiles can usually only be maintained at relatively small scales and are best suited to pathogens for which outbreaks are likely to be small and contained. Funding even for the established stockpiles depends heavily on Gavi support for eligible countries, and potentially unstable revolving funds at WHO for those that are not Gavi-eligible. The durability of a stockpile also depends on characteristics of the vaccine in question (in particular, its stability, shelf-life and effectiveness), and the ability to manufacture additional supplies at short notice. Finally, criteria for release of vaccines need to be clearly specified.[99] For Ebola, for example, current ICG criteria dictate that vaccination should be used only for healthcare workers and others at immediate risk of contracting the virus, through a ring vaccination strategy. However, consensus on the appropriateness of this strategy is not absolute, especially given our evolving knowledge on long-term consequences of infection in those who contract the virus.[100] All of these features mean that stockpiling is likely to be practical only for a subset of epidemic disease vaccines – specifically, those for which there is already a near-to-use or already established vaccine, for known pathogens for which key epidemiological characteristics are understood, and for which reasonably robust surveillance systems are either already in place, or implementable relatively quickly.

8 UNVN2 purpose: connecting UK strengths to LMIC needs

In this chapter, we bring together key themes from the report to make the case for where we believe UKVN support – both in terms of funding, and through wider engagement – could achieve the greatest impact in terms of vaccine development for epidemic diseases.

We also consider possible funding models, starting with conventional research grant models, but also reviewing the advantages offered by some innovative approaches to promote biomedical innovation developed in the United States and elsewhere.

WHERE COULD UKVN FUNDING HAVE THE MOST IMPACT?

Taking into account the global landscape for vaccine development for priority diseases and the expert opinion from the Delphi analysis it is clear that future UKVN funding will need to be carefully targeted to avoid duplicating effort made elsewhere. This is especially important because the list of actors involved in supporting vaccine research is dynamic and new players are emerging – including the newly established European Health Emergency preparedness and Response Authority (HERA), modelled on BARDA.[x] Vaccine platform technologies and the demonstration that mRNA vaccines can be quickly and effectively tested and used has been a major step forward which has been many years in development. The challenge for the next round of UKVN will be to maintain key skills and build capacity for the next emerging 'Disease X' while producing useful vaccines for known threats to human health.

Our panel of experts considered that the UK was a leading nation in several key areas of vaccine development, such as clinical trials and certain viral vaccine platforms, though some of the technologies of the future are not currently UK-centric. Ultimately, vaccines are mainly being developed against diseases that do not currently exist in the UK. Therefore, testing them in their target populations in phase 2 clinical trials, will involve funding work overseas.

Overarching technical gaps are outlined in chapter 5 but it is also clear that specific challenges are present for different diseases in the priority list. Ebola, Zika, Chikungunya, Nipah and Lassa fever already have vaccines in late-stage clinical trials or several different vaccine approaches well-funded by CEPI and other funders. While there remain some technical challenges, developing new vaccines from scratch for these diseases through UKVN2 would not be an efficient use of funds. However, phase 2 trials in populations that would eventually be the targets for vaccination, where previous UKVN funding has progressed vaccines to phase 1/2 trials in the UK, would be worthwhile: there would be important opportunities to identify contextual issues in vaccine deployment early on, as well as improving buy-in from local populations for products that they had participated in developing.

For CCHF, Q fever and plague there is currently potential for vaccine development although with the latter two pathogens the diseases can currently be controlled using antibiotics. For hantaviruses, there needs to be careful thought about which hantavirus(es) would be targeted by any new vaccine and which population the vaccine was eventually intended to be used in.

Beyond that, the highest impact from UKVN2 funding, therefore, would come from the improvement of existing vaccine platforms or their large-scale manufacture, or by following up the phase 1 and 2 trials completed in the country of vaccine development with local trials in the target populations most at risk of infection. This would be best achieved by interacting with local and international clinical trials networks, and the UK has a strong track record of supporting relevant capacity in countries where IDEP outbreaks are likely, including in Gambia, Kenya, Malawi, Nepal, Thailand, Vietnam and Uganda among others. Finally, there is some value to having standardised

x. HERA's remit is not yet fully specified but appears likely to include horizon scanning functions, funding for research and development into new vaccines, and support to development of relevant manufacturing capacity including addressing production bottlenecks that have been identified through the COVID-19 response – see: https://ec.europa.eu/commission/presscorner/detail/en/IP_21_4672 [accessed 04/11/2021]

immunological tests for the effectiveness of vaccines and for these standards to be agreed at an international level. This was also recognised as a technical gap in the expert panel evaluation.

Investment in vaccine research is, however, unlikely to translate into sustained impact in prevention and control of epidemic disease without support for number of additional areas, including (i) LMIC manufacturing and deployment capability; (ii) financing for vaccine development and deployment; and (iii) global governance of R&D and epidemic preparedness and response. The UK is already an important player in each of these areas but there is scope for more to be done both bilaterally and through partnership working globally – and UKVN can support this in several ways. Firstly, our findings underscore the importance of sustained commitment to health system strengthening, to which the UK already makes substantial contributions both for general health and for emergency response through, for example, FCDO's Tackling Deadly Diseases for Africa Programme (TDDAP), the UK Public Health Rapid Support Team (PHRST) and the UK Health Security Agency's work on IHR strengthening. There is scope – for example through a cross-government programmatic review – to consider the extent to which these activities support the development of robust surveillance systems to identify IDEP outbreaks quickly, readiness to receive and deploy new vaccines in partner countries, and ways in which activities in these areas can be strengthened to bolster preparedness for future outbreaks.

Secondly, although building LMIC manufacturing and regulatory authority capability will require sustained investment over time beyond the capacity of any single donor, there are specific areas where the UK, and UKVN, are well-positioned to provide support. The UK is a major donor to CEPI and should evaluate the extent to which equitable access provisions in funding agreements from this organisation ultimately result in technology and know-how transfer to LMIC partners – strengthening these mechanisms where appropriate. The UK has also assumed – through the MHRA – a leading position in regulatory innovation to accelerate approval for new vaccines. There is valuable expertise arising from this that could contribute to regulatory strengthening elsewhere through engagement activities such as training courses, exchange visits, or partnership working with AVAREF. Impact is likely to be greatest in countries with which the UK already has strong bilateral relationships – for example some of those supported through the TDDAP programme.

Finally, we have highlighted above the need for better integration between the activities of CEPI and Gavi (outside the framework of COVAX) – an issue that straddles questions of financing and governance for vaccine development and deployment. There would be considerable benefit from a more detailed analysis than was possible for this report, of synergies between the roles of these two organisations in supporting end-to-end vaccine development for IDEPs, possible legacy options for COVAX, and recommendations to ensure UK investments in these actors achieve best value for money.

HOW COULD UKVN MAXIMISE RETURN ON INVESTMENT?

Research funding around the world tends to fall into three different models. Block grants such as core funding of facilities and research centres deemed essential to capacity in certain areas. Competitive funding, where either a problem or general areas of research is outlined and researchers are invited to propose a plan of research to solve that problem. Finally commissioned research where a manager is appointed to solve the research problem and they then commission specific researchers to carry out part of the work towards solving that problem on a contract basis.

What little evidence there is comparing the effectiveness of these different funding approaches suggests that the block grant model favours innovation for younger researchers at the start of their careers and the competitive funding approach favours innovation from more established researchers.[103] There is some evidence that the competitive model can skew funding decisions towards certain types of institution independent of the quality of the research proposed.[104] Most vaccine research funding within the UK falls within the competitive funding description with funding administered through UKRI through one of the research councils or innovate UK. There are also pockets of block funding such as Porton Down, the Animal and Plant Health Agency (APHA) and BBSRC institutes, such as The Pirbright Institute. Examples of commissioned research in the UK are rare although Innovate moves some way towards this in its funding contracts for research.

Internationally the best know example of research funding from commissioned research would be the DARPA, a research agency of the US Department of Defence.[105] The model used by this agency is that a programme manager is recruited to the agency with a very specific technical idea. This individual is appointed on a 3-5 year contract and solicits research proposals for steps along the overall programme after careful study of the research landscape in the area of the topic. These are sent for review but the programme manager has the final say about which projects are funded. Accepted proposals are used as the basis of research contracts and contractors are required to make frequent (3 month) progress reports. Contracts are subject

to revision and cancellation dependent on research progress. Sometimes there can be more than one parallel contractor working on the same step of an overall programme but only the most promising project is taken forwards. CEPI have incorporated some elements of this contracting model, for example, by commissioning the development of 6 competing vaccines for Lassa fever. The evidence from DARPA is that the commissioning model can be very effective but requires substantial faith in the programme manager.

Finding for UKVN was mainly through Innovate UK, which ran both start-up and follow-on projects to develop vaccines all the way through to early clinical trials. This was an effective way to allocate funds to a broad range of scientifically good projects aimed at eventual commercial use. Inevitably, there is a risk that companies funded eventually go out of business, or use the specific example of the call to fund underlying technology that is aimed at a more commercial market than epidemic diseases. It is interesting that the only organisation that managed to record clinical trials relating to UKVN funding was a university, not a commercial organisation.

For the next round of UKVN funding we would suggest that the DHSC considers very carefully the specific goal of the research when it decides the mechanism for funding. If the priority is to continue to develop vaccines against all the priority pathogens on the UKVN priority list, or to solicit the best solution to a defined problem such as improving the thermal stability of existing vaccines then a similar funding mechanism to last time would be appropriate. The main suggestion arising from analysis of previous funding rounds would be to ring-fence some of the funding for the more 'neglected' diseases on the list such as CCHF, Q fever and Plague. Otherwise there is a risk that the majority of projects will focus on coronavirus in the same way that the majority of projects focussed on Ebola and Zika in previous funding rounds. If the plan is to target development of vaccines against a small number of specific pathogens to phase 1/2 level then with limited funds a commissioned research model may be more efficient. This would allow an integrated consideration of IP, market, testing, vaccine production, and standardised tests as a single programme with separate contractors fulfilling different parts of the project.

9 Conclusions

The full, global social and economic costs of COVID-19 are hard to quantify but have by any measure been enormous. The global economy contracted by around 3.5% in 2020 according to estimates from the International Monetary Fund. The severity of the economic downturn was also markedly greater in LMICs than in high income countries. Recovery is likely to be slow and uneven, with the most sustained effects anticipated in LMICs.[106]

However, although case fatality rates have varied from country to country, and over time during the pandemic, recent analyses suggest a relatively low rate for COVID-19 overall by comparison with those typical for some other diseases on the priority list, notably EVD.[107,108] The social and economic implications for a large-scale outbreak of a more deadly pathogen are therefore likely to be drastic. The imperative for vaccine-led preparedness for future IDEP outbreaks is strong.

In preceding chapters, we have described a mixed picture in terms of vaccine development for IDEPs on the priority list to date but shown that there has been a move away from inactivated and attenuated vaccines towards vaccine platforms based on other viruses (measles, adenoviruses) or mRNA, platforms that offer clear advantages in terms of scalability and reproducibility of vaccine manufacture, processing and storage. Development of new vaccines for COVID-19 has drawn on these technologies – some of which stemmed directly from work funded by UKVN in its first round – and has occurred at unprecedented pace under pressure of the pandemic. It has also depended on a host of innovations in the manufacturing and regulatory worlds, including unprecedented acceleration of regulatory approval processes and an acceptance of rolling review based on emerging data from stringent regulatory authorities. However, much of the expertise and capacity to support these developments has remained concentrated in high income countries, and success has depended on major and often high-risk investments from high income country governments in untested vaccine candidates. APCs signed directly with manufacturers by these governments have undermined commitment to COVAX and contributed to marked inequities in the global distribution of vaccines.

The pandemic response, combined with experiences from more localised epidemics in recent years – including Ebola outbreaks in West Africa and the DRC – have highlighted a series of areas where investment is needed to support vaccine development and rollout. *Without adequate attention to these areas, it is very unlikely that UKVN investment in IDEP vaccine research will lead to meaningful impact either in reducing the risk of outbreaks occurring in the first place or reducing the risk of spread.* Firstly, equitable rollout of vaccines in the event of an epidemic depends not just on having a near-to-use product available, but crucially on prompt recognition of need, the state of the readiness of country health systems to receive new vaccines, and public acceptance of new medicines. Prompt recognition of emerging threats hinges on the presence of robust infectious disease surveillance systems, which are found in few of the countries that are vulnerable to IDEP outbreaks. Country capacities to procure and deploy COVID-19 vaccines are emerging as two of the key factors limiting ability to ensure protective levels of vaccine coverage for populations in LMICs. Overcoming this will require a sustained commitment to strengthening vaccination delivery systems in LMICs, building on existing UK support for health system strengthening, and improved approaches to population engagement and demand-generation to support rapid introduction of new vaccines.

Secondly, while high-income countries have scaled-up production capacity and delivery capability remarkably in the last 18 months to meet COVID-19 vaccine requirements, LMICs have not been able to follow this lead. Tackling this problem in LMICs will require, firstly, long-term investment in manufacturing capacity in LMICs embedded in existing industrial, business and R&D ecosystems, and backed up by a robust commitment to early technology transfer, technical support especially for the newer vaccine technologies, and importantly regulatory system strengthening. The UK has expertise and technical capabilities to offer in some of these areas, notably given the MHRA's performance during the pandemic. The FCDO is also currently

scoping opportunities to support investment in vaccine manufacturing in Africa.

Thirdly, commercial barriers to vaccine development for epidemic diseases are substantial. The sole example to date of successful epidemic disease vaccine development using a market-shaping approach – Gavi's AMC for Ebola – worked because there was a relatively late-stage product available that had already received substantial public investment over many years. We argue that a more realistic model for vaccine development for these diseases, that accounts for market failure and is better able to cap prices at an affordable level for LMICs, would be to combine push and pull approaches through a partnership model for a smaller number of specific, priority diseases. This is a model that, through the MVP, the UK has previously funded.

Finally, the governance landscapes for vaccine R&D, preventive use of vaccines and emergency deployment are fragmented – particularly in the domain of epidemic preparedness. While CEPI's role in promoting development has been transformational for COVID-19, its remit has expanded far beyond that for which it was originally established, and it is arguably still too early to form a clear judgement regarding performance across the wider portfolio of epidemic disease vaccine candidates. In addition, important gaps remain, especially at the interface between push and pull activities (exemplified by the division of labour between CEPI and Gavi, the latter of which in any case focuses on vaccines for endemic diseases). The UK is a major financial contributor to many actors in the areas of vaccine R&D, epidemic response and vaccine deployment, and there is scope to consider, in more detail than is possible in this brief report, whether these investments are driven by an efficient, integrated strategy or are pursuing disintegrated short-term goals within discrete scopes of interest.

A recurrent theme throughout this report is the recognition that, although vaccine development is often thought of in linear terms, there are in reality numerous points of interaction and interdependency between vaccine development, manufacturing and regulation, vaccine delivery and the overarching mechanisms by which these are governed. Without a systemic approach to support each of these areas, it is unlikely that UK investments in innovation will lead to durable improvements in prevention and epidemic response for epidemic diseases. However, effective solutions to the problems identified above require global cooperation in which the UK has an opportunity to take a leading role. Furthermore, concerted action in these areas is needed over the long-term – certainly beyond the five-year lifecycle of UKVN's next tranche of funding tranche.

Evidence presented in this report suggests the following potential options for further investment:

- Advancing vaccines for priority diseases into phase 2 trials is an efficient next step at this point.
- Follow on funding is likely to be effective for research projects where good progress has already been made but the increasingly complex nature of vaccine development beyond Phase I suggests that a coordinated investment model should be considered. In this model a technical programme manager oversees the end-to-end vaccine process and only commissions new research if there is a reasonable chance that phase 1 trials will be conducted within a 3-5 year period. The coordinator acts both as a gatekeeper and as a facilitator to ensure that projects progress beyond laboratory studies. A strategy that focuses on a small number of vaccine candidates for each disease rather than a 'shotgun' approach against one or two high profile diseases is likely to be more efficient.
- There remain a number of clearly identifiable technical gaps in vaccine development and manufacture (mRNA vaccines, optimisation of scale up, GMP production, enhancing thermostability, alternative delivery routes, rapid deployment of vaccine and upstream component manufacturing, identifying relevant animal models, standardised diagnostic and immunological tests for pathogen detection and vaccine efficacy).These are likely to be filled through competitive calls via Innovate UK, EPSRC, BBSRC, and NIHR
- There is a strong case to review the UKVN priority list regularly and adapt it as necessary, removing pathogens for which vaccines are now available and adding pathogens which are emerging threats. This report has carried out a limited review but a more in-depth analysis would be warranted, considering in particular the potential for overlap with work already being supported by CEPI.
- For some diseases funding vaccines for livestock and wildlife may be more effective than developing a human vaccine programme if it could reduce the probability of spill over epidemics.
- There is a sound rationale for investing in clinical trial networks in LMICs to carry out phase 2 trials in target populations, once vaccine safety in UK volunteers has been established.
- Transfer of technology and manufacturing know-how is strategically compelling and could be achieved by working with colleagues in FCDO and across government to ensure that the commitment to technology transfer to LMIC manufacturers is integrated into all vaccine development funding agreements signed by technical bodies (e.g. CEPI) to which the UK is a major funder.
- Enhancing links between the MHRA and regional or continental regulatory initiatives (e.g. AVAREF in

Africa) would promote alignment between National Regulatory Agencies and develop local capacity which is essential for rapid deployment of vaccines in an emergency.

- A cross-departmental review could be considered to assess the extent to which existing UK investments and activities in health system strengthening and epidemic preparedness (through, for example, TDDAP, the UK Public Health Rapid Support Team and UK Health Security Agency's work on IHR strengthening) support robust IDEP surveillance capacity and readiness for vaccination delivery in target countries, with proposals for improvements where necessary.
- A competitive call could be considered to evaluate governance structures at CEPI and Gavi, and identify ways in which the UK could leverage its funding contributions to strengthen strategic alignment between these organisations in support of IDEP vaccine development and deployment. We note, however, that given the life-cycle on funding replenishments changes may take time to come into effect.
- A competitive call could be considered to explore legacy options for COVAX, examining the extent to which its institutional architecture and operating model could be repurposed, in due course, to promote late-stage development for other epidemic diseases, and exploring the options presented by other frameworks, including the PIPF.
- A competitive call could be considered to evaluate the extent to which equitable access provisions, applied to vaccines supported by technical bodies that the UK funds (including CEPI), are met in practice, and explores the levers available to the UK to strengthen these provisions in future.

Two further considerations cut across all of the opportunities for investment. The first is the need for capacity development in target LMICs. This is particularly apparent in the areas of clinical trials, surveillance for IDEPs, regulatory authorities and vaccine manufacturing. It would be appropriate to consider capacity development as a thread running throughout all investments. Scientific capacity development in LMICs has advanced considerably in the last decade and UK science funders, including Wellcome, MRC and NHIR have all developed valuable experience in fostering successful scientific careers in Africa and Asia. Collaboration with these partners may prove efficient in enhancing skills in the areas of vaccine development and licensure. The second issue is the geographical dispersion of investments. Strengthening the national regulatory authority improves a country's capacity to develop clinical trials rapidly, and strengthening trials capacity challenges the NRA to respond authoritatively to the results of those trials, generating a virtuous cycle of improvement and excellence in both domains. A similar argument can be made for co-investment in manufacturing capacity. Whilst in phase 2 vaccines should be developed in populations that are likely to be infected in future epidemics, serious consideration should be given to coordinating investments and training opportunities in a small number of countries in order to optimise the synergies that arise from raising capability in several domains simultaneously.

The existing successes of the UKVN programme have created new challenges for future investment that will push vaccine development towards its ultimate goal of preventing and controlling epidemics in LMICs. This onward process is substantially more complex than early clinical development, with a wider range of stakeholders from LMICs and HICs, from epidemiology and surveillance, clinical trials, manufacturing, national regulation, health systems for deployment, acceptability by local populations, vaccine finance mechanisms and governance/response systems for international allocation. To optimise onward investments within UKVN2 it would be prudent to incorporate expertise in some, if not all, of these areas within the advisory structure of the programme.

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Appendices

APPENDIX 1: DELPHI ANALYSIS

Method:

Expert opinion for identification of technical gaps for future vaccine funding for priority diseases was collected and processed using the Delphi method. Briefly, this involved the selection of a panel of experts with a broad range of perspectives to establish a consensus on where funding for the next round of the UK Vaccine Network would be most effective at progressing vaccine development and deployment for priority diseases. There were 13 experts on the final panel (Table A1.1) with diverse experience from funding agency managers (CEPI and Welcome Trust) to scientists in LMIC countries (Malaysia and Democratic Republic of Congo) to experts in vaccine design (mRNA and Virus based vaccine platforms).

	Government	Charities	Academics
Virology	Miles Carrol (PHE)		Sharifah Hassan (Malaysia)
Vaccines (protein)		Mike Whelan (CEPI), Charlie Weller (WT)	Polly Roy (LSHTM)
Vaccines (virus)			Sarah Gilbert (Ox)
Vaccines (RNA)			Robin Shattock (Imperial)
Vaccines (manufacture)			Nigel Titchener-Hooker (UCL), Nilay Shah (Imperial)
Vaccines (Zoonotics)	Bryan Charleston (Pirbright Institute)		Leopold Mulumba (DRC)
Epidemiology			John Edmunds (LSHTM)
Policy	Chikwe Ihekweazu (Nigeria CDC)		

Table A1.1. Experts who agreed to take part in the Delphi process. The panel was selected to represent diverse views. Abbreviations: PHE = Public Health England, CEPI = Coalition for Epidemic Preparedness Innovations, WT = Wellcome Trust, LSHTM = London School of Hygiene and Tropical Medicine, Ox = University of Oxford, DRC = Democratic Republic of Congo.

Experts completed a series of surveys aiming to define technical gaps and rank them based on their importance to future vaccine development and the availability of alternative funding for these gaps. Scores were recorded on a 6-point Likert scale for each criterion (Figure A1.1). On scoring scales for both questions, panel members had the option of selecting 'Don't know'. All surveys were sent to all panel members and remained open for a minimum of 7 days. The list of technical gaps suggested by the panel of experts was supplemented by suggestions from a literature review by the Delphi manager who subsequently took no role in ranking any suggestions. Panel scores were only processed when at least 50% of the 13 panel members who had agreed to take part in the process gave a score. For interpretation of consensus, scores were converted into a plot showing funding and importance ranked by each panel member (Figure A1.2). Plots were divided into 4 sectors based on scores. Consensus was defined as being reached when at least 70% of the scores for the panel were in the same sector of the graph. Technical gaps were removed from further consideration once consensus was reached. After initial scoring (survey 2) the panel members were asked to present arguments to support their position for all technical gaps for which consensus had not already been reached. These arguments were included in the final survey (survey 4) where the panel was asked to re-score all remaining gaps. All comments and scores shared between panel members were anonymous to prevent bias due to 'who' made the comment rather than the strength of the argument.

Six panel members contributed ideas to the first survey. Survey 2 also included an open question for gaps that the expert panel felt should be included but which had been missed. These were ranked during survey 3.

Eight panel members responded to survey 2 and 7 panel members responded to surveys 3 and 4. Data was collected with MS Forms, exported to Excel and graphs were generated in R using the RStudio interface and the ggplot2 library.

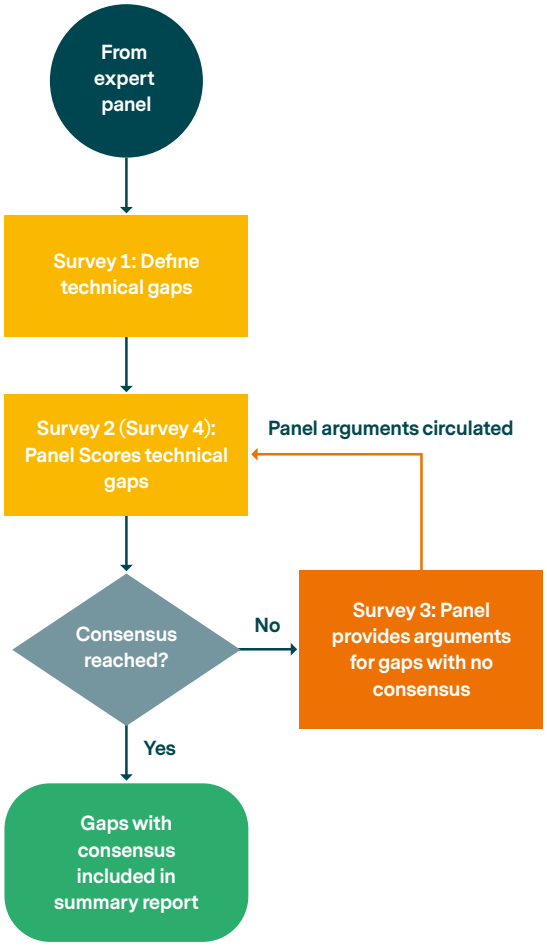


Figure A1.1. Summary of the workflow used by the Delphi process. Panel members completed a series of surveys aimed at reaching consensus on importance and funding of technical gaps for vaccine development. For gaps where no consensus score was reached after survey 2, panel members were asked to provide arguments to support their position (survey 3). These arguments were then provided to all panel members when the panel was asked to re-score the gaps (survey 4).

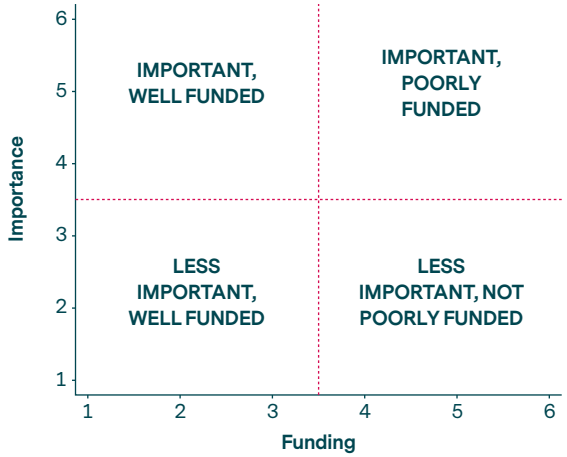


Figure A1.2. Data plot used to analyse expert panel opinions. Consensus opinion was recorded when 70% of panel member scores were in the same sector of the graph. A score of 6 on each axis corresponded to Important/poorly funded.

Results:

The UK has strengths in clinical trials and should develop expertise with mRNA vaccines.

Part of the initial survey asked the experts the question, *'What are the areas in vaccine development for priority epidemic diseases where you think the UK has a technical lead or should prioritise development of expertise for strategic reasons?'*. Responses to this question highlighted the expertise in the country relating to viral vectors, DNA sequencing, epidemiology and clinical trials. Areas that were mentioned where future investment was necessary included mRNA vaccines. Some respondents pointed out that the need for vaccine development was dependent on the pathogen and suggested that the priority list needed to be carefully considered with respect to where vaccines were viable options (Table A1.2). This point was also repeated by the panel with respect to some of the priority 'gaps' with the suggestion that some of these were bigger gaps for some pathogens on the priority list than others. One of the potential issues that emerged from panel considerations of questions about mRNA vaccines was how much freedom to operate there was with respect to intellectual property rights.

The UK has several companies that have the expertise to develop and manufacture vaccines for viral epidemic diseases, such as Oxford Vaccitech, AstraZeneca and GlaxoSmithKline. These represent a UK lead which should be strengthened whenever possible. On the other hand, long standing pathogens which have never emerged on a global scale, such as Nipah, will not change their behaviour just because of heightened pandemic awareness. Accordingly, the "list" should be considered carefully when prioritizing candidates for further development. Not all warrant the same attention.
The UK has good capability for the development of viral vectored vaccines. Nucleic acid (RNA) vaccine platforms need greater investment, the successful RNA platforms are currently linked to companies. Recombinant protein expression at scale may also need greater investment. Novel adjuvants would also provide greater freedom to operate.
Prioritise global disease burden intelligence. Prioritise improved in vitro assays capabilities and in vivo models.
UK technical lead areas in the mentioned priority diseases vaccine development is very evident in genomics, proteomics including of broad range of viruses, which should be exploited to sort out the above mentioned gaps. Outbreaks isolates' purified nucleic acids products should be needed for profound and specific studies through full sequencing and identification of target genes and proteins. The UK may take advantage of its own infrastructures such as the Welcome Trust genome center in Cambridge/Hinxton.
UK is strong in epidemiology. Also platform technologies are well advanced in the UK and should be prioritised. Finally, MHRA is in a somewhat unique position post Brexit and perhaps could think about developing a "platform master file".
The areas are: Vaccine design and constructs especially for mRNA vaccines, both conventional or self amplifying mRNA vaccines. This will include the (i) construction of the mRNA element, synthesis of the mRNA, purification and formulation (ii) Testing in-vivo and in-vitro. Animal BSL-3 for animal challenge is available but of restricted use. (iii) GMP manufacturing especially for human vaccines especially mRNA vaccines may need to be initiated in the country. Clinical trials in Malaysia can be easily conducted with approval from the Ethics committee of the Ministry of Health.

Table A1.2. Panel responses to the question: 'What are the areas in vaccine development for priority epidemic diseases where you think the UK has a technical lead or should prioritise development of expertise for strategic reasons?'

Consensus was reached for 11 out of 25 technical gaps included in the Delphi process.

Across all surveys a total of 24 technical gaps were rated for importance and availability of alternative funding by the panel. These ranged from fairly broad aspirational policy areas such as, 'Funding to allow vaccines to progress to completion of phase 2 clinical trials even during inter-epidemic periods' to specific technical gaps such as,' Vaccines that are stable at 40oC.' At the end of the Delphi process the panel reached consensus on 11 out of 25 technical gaps (Table A1.3). For all of these gaps the panel opinion was that they were important for vaccine development and poorly funded from other sources.

Key themes that emerged from the analysis were that there was still a need for funding clinical trials to phase 2, and the barriers around the optimisation and manufacture of vaccines. This particularly included LMIC settings where there was an additional need for knowledge transfer relating to mRNA vaccines.

Opinions among panel members who responded to the surveys were rarely unanimous even where consensus was reached.

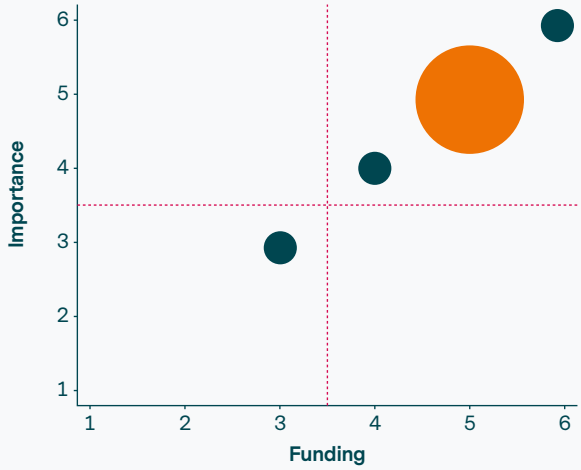
There were very few technical gaps where all the panel members opinions were consistent. At one level this is a sign that the expert panel was well chosen and represented a diverse range of opinions. However, it should be noted that not all panel members agreed with all consensus opinions. In fact, the only 'gap' where all experts who expressed an opinion agreed was for 'Funding to allow vaccines to progress to completion of phase 2 clinical trials even during inter-epidemic periods.' This was universally ranked as important and poorly funded. For the other gaps where consensus was reached 1 or 2 panel members disagreed with the consensus opinion, depending on the topic (Figure A1. 3). For 7 of these gaps panel arguments to support the scores given are available and vary depending on the topic. The most frequent argument against desirability of further funding was that CEPI was already supporting this activity. However this did not apply in all cases (Table A1.4). For 4 gaps consensus was reached without needing two rounds so no arguments were documented.

Topic	Technical Gap	Suggested by?	Consensus reached? (Y/N)
LMICs			
1	Funding for GMP production facilities (including LMICs)	Panel	Yes
2	Training/expertise for developing vaccines in humans (LMICs)	Panel	No
3	Knowledge transfer especially for RNA vaccines (LMICs)	Panel	Yes
4	Training of vaccine technologists	Panel	No
5	Funding of field work in high risk areas(epidemiology, novel isolates, in situ lab work including biological products such as blood plasma from outbreak survivors).	Panel	No
Deployment			
6	Research to produce multivalent vaccines that combine protection from epidemic diseases with protection from endemic diseases.	Literature review	No
7	Development of vaccines with alternative delivery routes (e.g. oral or nasal)	Literature review	Yes
8	Vaccines that are stable at 40 oC	Literature review	Yes
9	Funding to allow vaccines to progress to completion of phase 2 clinical trials even during inter-epidemic periods.	Literature review	Yes
10	Funding for public awareness and sensitisation (in terms of KAP=knowledge,attitude and practice).	Panel	No
Manufacture			
11	Funding to enable and improve GMP vaccine manufacture at scale for prototype vaccines	Panel	Yes
12	Research into deployment of rapid production platforms for vaccines.	Panel	Yes
13	Research into deployment of rapid production platforms for input materials (plasmids, linear DNA, enzymes, nucleotides,formulation ingredients).	Panel	Yes
Vaccine development and improvement			
14	Research to allow vaccines to be effective at lower doses.	Literature review	No
15	Identification of animal models relevant to vaccine development for priority diseases	Panel	Yes
16	Novel Adjuvants	Panel	No
17	Improved delivery of RNA vaccines	Literature review	No
18	Vaccines with faster onset of immunity	Literature review	No
19	Epidemiological surveys to identify high risk populations for vaccine trials	Panel	No
20	Vaccines for livestock and wildlife for zoonotic diseases	Literature review	Yes
21	Vaccines for wildlife for zoonotic diseases	Panel	No
Basic research underpinning vaccine development			
22	Research to understand the correlates of immunity for priority diseases	Panel	No*
23	Research to understand why some individuals and hosts are resistant to disease.	Panel	No
24	Standardised diagnostic tests for priority diseases.	Panel	Yes
25	Banking of pathogen field isolates to understand virus variability/improve vaccines	Panel	No

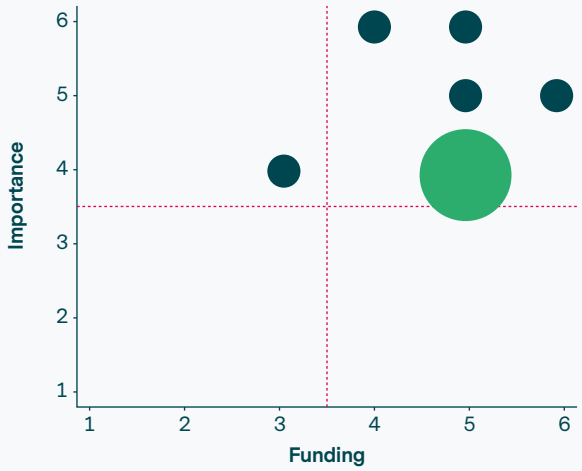
Table A1.3. Summary of technical gaps considered in the Delphi analysis and whether consensus was reached. *For topic 22 consensus was not reached because only 6 responses were received.

Funding to enable and improve GMP vaccine manufacture at scale for prototype vaccines.

Vaccines for livestock and wildlife for zoonotic diseases.

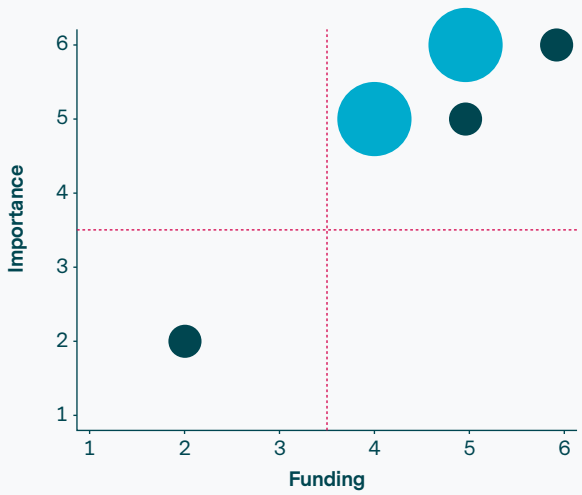


Development of vaccines with alternative delivery routes (e.g. oral or nasal)

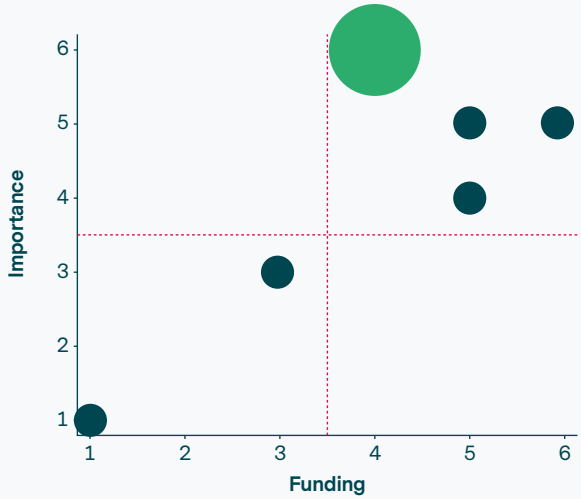


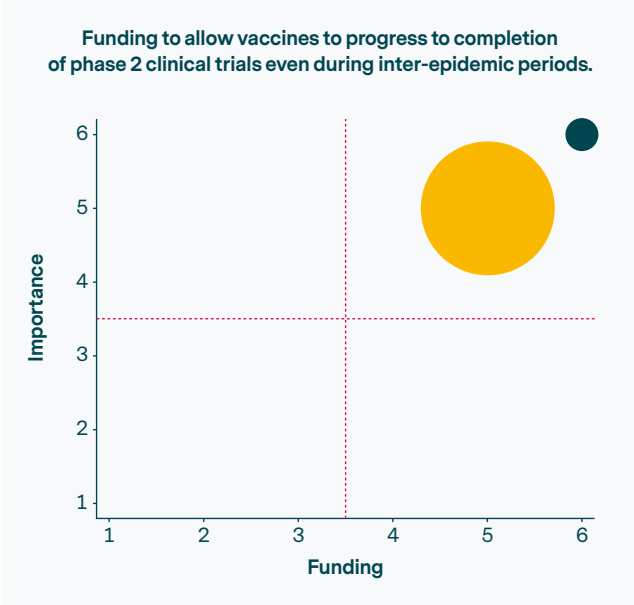
Funding for GMP production facilities (including in LMICs)

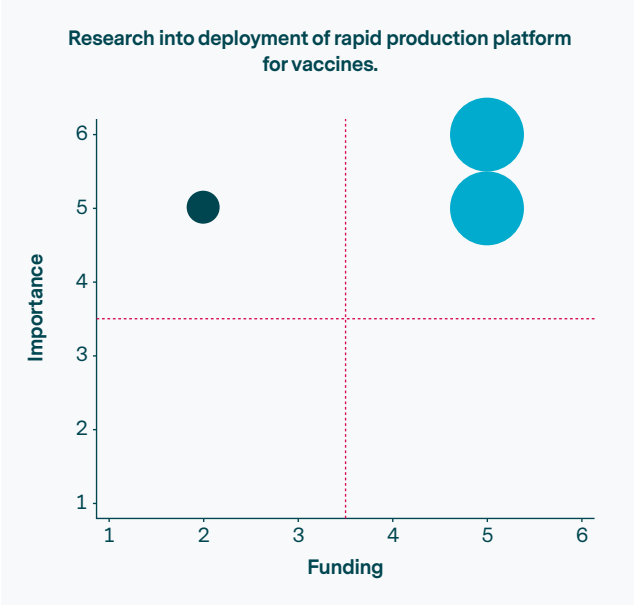
Standardised diagnostic tests for priority diseases.

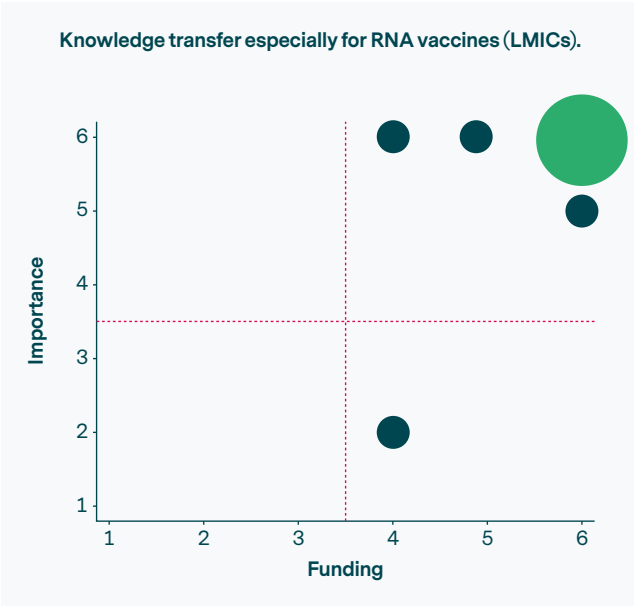


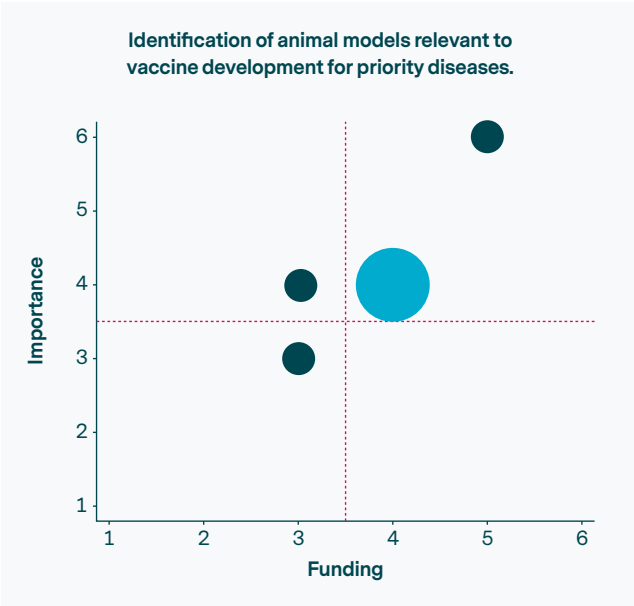
Vaccines that are stable at 40 oC.

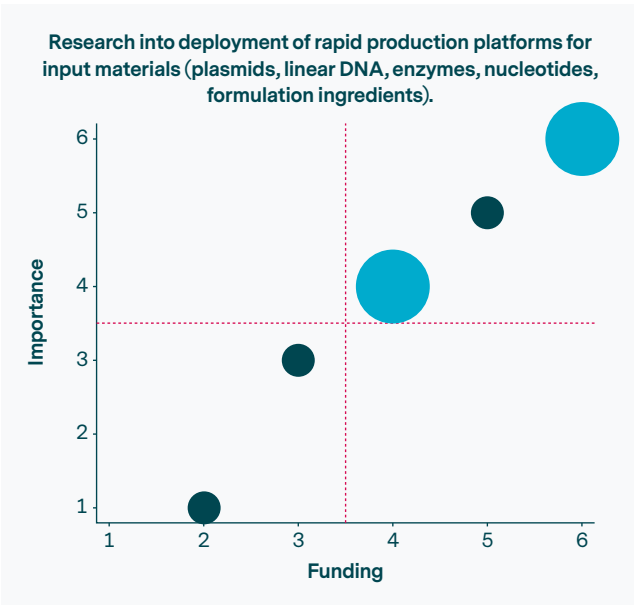












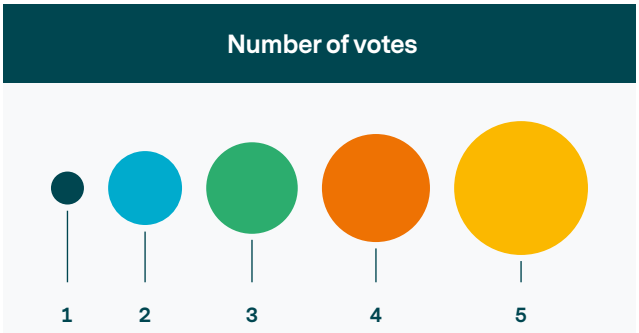


Figure A1.3. Bubbleplots showing range of opinion for technical gaps where the panel reached a consensus. Each spot represents the score of one panel member, where two or more panel members gave exactly the same score the area of the spot has been adjusted as indicated by the key to the bottom right. Wording used for each technical gap is above the corresponding graph. Continued on page 68.

Topic	Technical Gap	Arguments
3	Knowledge transfer especially for RNA vaccines (LMICs).	"There is currently little or no funding for technology transfer. Without this, development of LMIC based manufacturing sites would be pointless." "RNA vaccines have been a huge success story during the Covid pandemic, however there is very little freedom to operate because the latest technology advances are held within a small number of pharmaceutical companies. We have been working with BMGF to access the technology for LMIC animal health applications, without success so far. Establishing research programmes to develop affordable human and animal RNA vaccine technology for global access would have significant impact." "RNA is a flexible platform technology which in principle is less complicated than other biotech. There is not much funding I'm aware of explicitly for this topic." "Lower priority funding. CEPI, industry and other international agencies are already funding this work" "In my opinion, knowledge transfer in vaccine development esp. RNA vaccines is important, however, not well funded. Malaysian researchers have lots of experience esp. in the development and commercialisation of veterinary vaccines. These veterinary vaccines are either the inactivated, sub-unit and virus-vectored. None has ventured into RNA vaccines even for veterinary use. Let alone RNA vaccines for human. As mentioned earlier, although funding from international agencies are available, fundamental research in developing RNA vaccines have not taken off yet in the country, therefore, funding in this area is still very very low." "The response to this query is the same as the one above-mentioned. mRNA vaccines technical strategies are recently being experienced. Grant organisations are not yet convinced and may be afraid due to biological side effects on the human genome." "Establishing research programmes to develop affordable human and animal RNA vaccine technology for global access would have significant impact." "There should be some caution, as stated previously, that mRNA is not viewed as a 'silver bullet'. It will not be useful for all diseases." "RNA is a flexible platform technology which in principle is less complicated than other biotech. Hence it should have high importance."
9	Funding to allow vaccines to progress to completion of phase 2 clinical trials even during inter-epidemic periods.	"The WHO Blueprint lists diseases with both epidemic potential and which are not adequately funded. Hence, it is surprising to see this result." "a priority BUT the candidate has to have solid NHP-challenge efficacy data behind it." "It is important to undertake phase 2 clinical trials for any new potential vaccine candidate." "In Malaysia, we have not produced any vaccines yet to go to the stage of phase 2 clinical trials. Currently, the request for funding of such work is nil or minimal, the funding in this aspect is also low. However, if in future, there are vaccines available for phase 2 clinical trials, it will be well funded."
12	Research into deployment of rapid production platforms for vaccines.	"Assuming this means new technologies, such as disposable fermenters, then this is a priority " "Establishing infrastructure to deploy vaccines at scale is critical. These infrastructures can be established and deployed to control endemic and neglected diseases in LMIC, so they are fully operational in an epidemic or pandemic." "Rapid production platform is the key for any vaccine during epidemic/pandemic, in order to use widely." "Removing all bottlenecks to vaccine manufacturing, deployment and administration has been demonstrated to be critical for the Covid-19 pandemic." "already funded"

Table A1.4. Arguments considered by the panel when reaching a consensus.

13	Research into deployment of rapid production platforms for input materials (plasmids, linear DNA, enzymes, cleotides, formulation ingredients).	"Is this actually research or logistics? In the current pandemic shortages of materials are rate limiting" "Establishing infrastructure to deploy vaccines at scale is critical. These infrastructures can be established and deployed to control endemic and neglected diseases in LMIC, so they are fully operational in an epidemic or pandemic." "Removing all bottlenecks to vaccine manufacturing, deployment and administration has been demonstrated to be critical for the Covid-19 pandemic."
15	Identification of animal models relevant to vaccine development for priority diseases.	"I think there is insufficient funding in this area as firstly, human vaccine research in Malaysia is not well established and so is identification of animal models for vaccine development. Furthermore, researchers would use animal models established by other researchers. Another setback is the lack of Animal BSL-3/ 4 facilities in the country to carry out studies on infectious diseases." "Again, likely to be disease specific. There is certainly little funding for development of models for new zoonoses but plenty for several more established diseases." "Very similar answer to question 11, for example, the investment in the development of a Rift valley fever vaccine for livestock by the UKVN has advanced the development of a human vaccine." "Very High Priority. Without effective in vivo models we cannot identify potential efficacious vaccines."
20	Vaccines for livestock and wildlife for zoonotic diseases.	"I don't have access to accurate figures but global investment in human vaccines dwarfs investment in animal vaccines. The ideal situation would be parallel development of vaccines for humans and livestock/ wildlife where the infection also causes significant disease in animals or animals represent an important source of human infection. Knowledge of vaccine efficacy in a natural host can also accelerate vaccine development for the same or closely related pathogens in humans." "high priority to understand disease burden of zoonotics in animals to understand risk and threat." "Future funding is susceptible to ODA cuts" "Could be useful, particularly for vector-borne viral diseases." "Vaccines for livestock and wildlife for zoonotic diseases are important, however, taking such examples as the highly pathogenic Avian Influenza and Nipah virus infections in Malaysia, vaccination of poultry and pigs is not practiced in the country, as the governments' policy towards zoonotic diseases is `test and cull'. Researchers are therefore discouraged from research into vaccine development for livestock and wildlife. Although international funding are highly available, due to the policy in Malaysia, researchers are not keen to develop vaccines for zoonotic diseases in livestock, thus resulting in this area being not well funded." "This is difficult since most funders are veterinary or human only and rarely both. To make matters worse, domestic livestock are clearly ranked higher than wildlife, although the latter are often the disease reservoir. If we carved out wildlife as a separate section I would support more funding for this."
24	Standardised diagnostic tests for priority diseases.	"As far a we know, there has been very little funding for international serological standards. These are critical if we are to compare vaccine strategies. NIBSC is a World leader in this but needs funds." "Standardised diagnostic tests for priority diseases are conducted by government (Ministry of Health) or MOH approved private laboratories, as only results from these laboratories are valid. These test are usually WHO or OIE approved tests. Research into development of new tests are still conducted by researchers but these are usually for academic purposes, unless researchers seek to get the developed test for international testing and validation. Malaysian government encourages commercialisation of new tests or products and this type of research is well funded." "This should not be seen as a stand alone priority, the development of diagnostic tests including assessing cross protection afforded by vaccination against circulating variants and strains should be linked to vaccine development, including DIVA tests." "Higher priority. Reliable accessible diagnostics tools are essential to support in field vaccine efficacy studies. Again, compared to vaccine development this is a relatively low cost activity but extremely valuable." "Again the ODA funding cut may cause funding issues." "NA but, depends on strategies of funds arising by diagnostic laboratories / or relevant the factories and also by technical and financial partners. WHO, OIE, FAO could be solicited by their Members States."

There was evidence that having two rounds of consideration resulted in a change of panel opinions.

The Delphi method is an iterative process where the panel re-scores topics on the same criteria after consideration of arguments where no previous consensus has been reached. Only 4 topics reached consensus after the first round of scoring (topics 1, 7, 8 and 11 from table A1.3). For the remaining topics where consensus was finally reached there was a change in the pattern of opinion between the first and second rounds of scoring (Figure A1.4). Since not all members of the panel took part in every round of scoring and the scoring process was anonymous it is possible that different scores in different rounds do not represent a change of opinion in the same people. However, the consistent number of participants between rounds seems to argue against this interpretation of the change in scores.

Limitations

Although care was taken to ensure a wide range of appropriate expertise in the panel it should be noted that as with any Delphi process this analysis represents the opinions of a panel of experts. The outcome of the study could easily be affected by the makeup of the panel. All panel members were contacted individually ahead of the first survey and all agreed to take part. However, the series of surveys took place over the summer months (first survey released on 22nd July, final survey returned on 16th September) which is a time when many people are unavailable due to holidays. Even with these limitations the threshold of 50% of the panel responding to each survey was met. To avoid potential problems with lack of expertise in specific area this 50% limit was applied to topics where panel members indicated they did not know enough to score a topic. There were two topics which fell into this category, topic 17 'Improved delivery of mRNA vaccines' and topic 22 'research into correlates of immunity for priority diseases' which had 5 and 6 responses in the final survey respectively. Of these it is likely that topic 22 would have reached consensus if there had been one more response. Panel members were asked to declare whether they had received funding from previous rounds of UKVN on the final survey 2/7 respondents had and the areas of research funded did not overlap. Therefore, since a single individual would not be enough to bias the consensus scoring used in the study towards their own research this limitation was deemed an acceptable risk.

Acknowledgements

The survey team would like to thank all panel members for participation in the process. We recognise that the process involved a substantial investment of time as some of the surveys were very lengthy due to the number of topics considered.

Number of votes

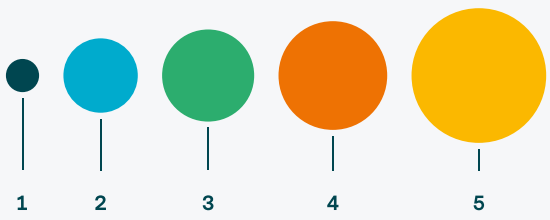
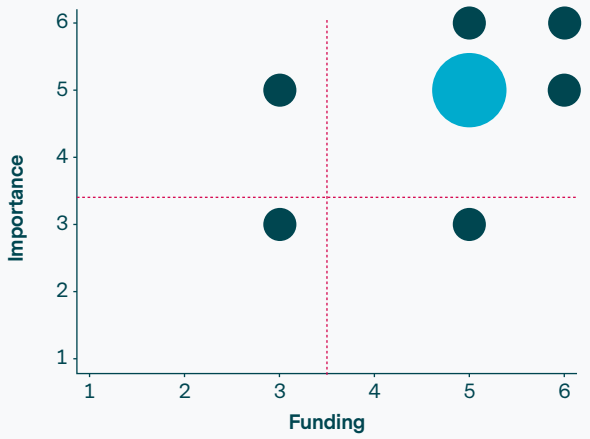


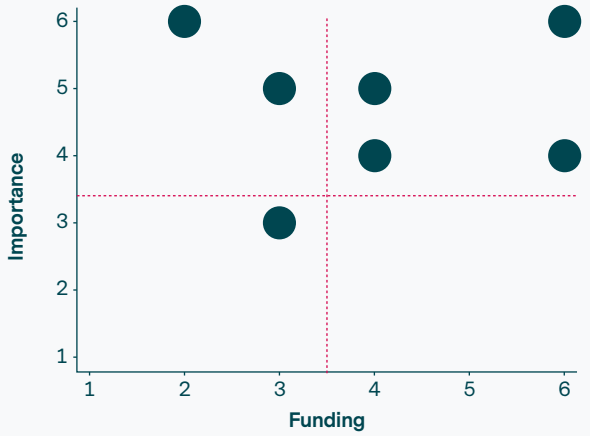
Figure A1.4. Examples of topics where there was a clear change in the pattern of scoring between the first and second rounds. Paired bubbleplots are presented with the plot on the left representing the original panel opinion and the panel on the left representing the panel opinion for the same topic after consideration of arguments from the rest of the expert panel. Areas of spots were adjusted when more than one panel member gave identical scores (as indicated in the key at the bottom right). Continued on page 72.

First round of scoring

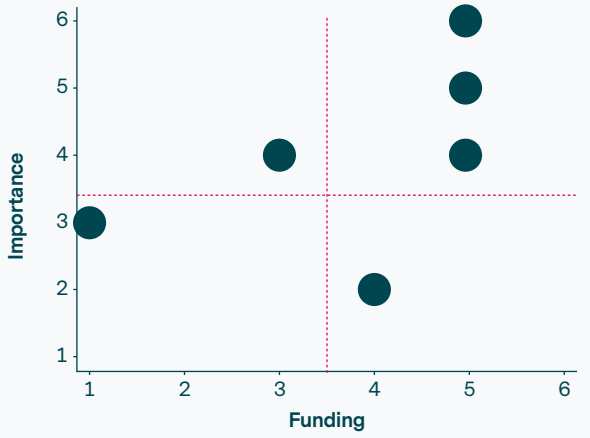
Knowledge transfer especially for RNA vaccines (LMICs).



Standardised diagnostic tests for priority diseases.

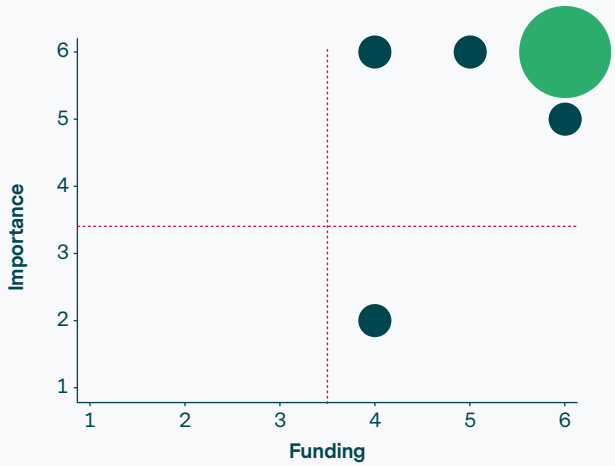


Vaccines for livestock and wildlife for zoonotic diseases.

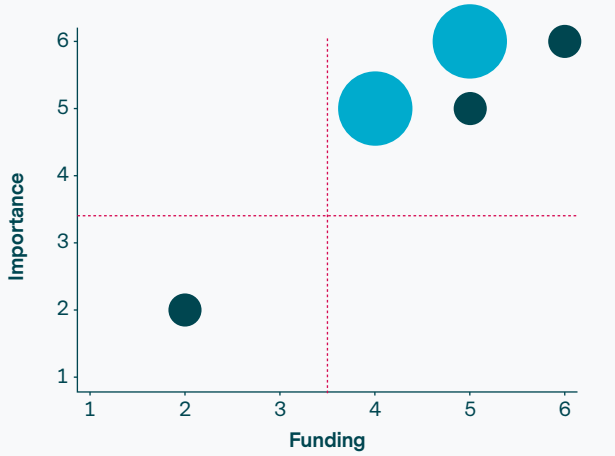


Second round of scoring

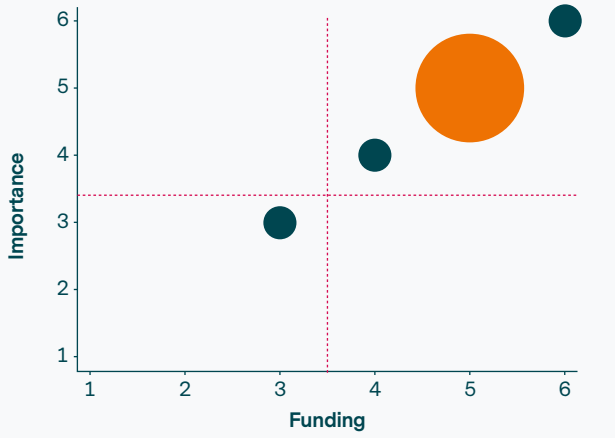
Knowledge transfer especially for RNA vaccines (LMICs).



Standardised diagnostic tests for priority diseases.



Vaccines for livestock and wildlife for zoonotic diseases.



APPENDIX 2: MARKET-BASED INTERVENTIONS TO SUPPORT DEMAND FOR NEW VACCINES

Advance Market Commitments

The Gavi-Merck AMC for late-stage development of the rVSV-ZEBOV vaccine for Ebola described in the main body of the report shows how AMCs can support epidemic disease vaccine development and deployment – but this is just one type of model. There is a spectrum of potential AMC designs that could be used to support vaccine development, depending on product specification and crucially, on the dimensions of the envisaged market. Table 5 summarises some of the main options and the extent to which they might be applicable to epidemic disease vaccine development. The design of incentive structures under each model is complicated and depends on the development stage of the vaccine. Paradoxically, economic evidence suggests that more complex incentive structures may be required for near-to-use products than those at earlier stages of development.[83]

Portfolio approaches

A basic principle of AMCs and APCs is that they pre-specify a single product profile for an individual disease. Risks and benefits are linked to that product alone and cannot be offset against other products. A portfolio-based approach, on the other hand, would fund a series of programs at various stages of development, theoretically reducing the overall risk of investment – either for a single disease, or across diseases. The UK Vaccine Task Force (VTF) used a portfolio approach to secure doses of a range of candidates in development from an early stage in 2020 and has been regarded as a successful example of risk pooling – benefiting from the unusually successful development record for COVID-19 vaccine candidates by comparison with recent experience with other diseases.[81] However, using data on current preclinical candidates for nine epidemic diseases from the WHO Blueprint list, it has been estimated that annual expected returns from a 'mega-fund' to support epidemic disease vaccine development along similar lines would be around -60%.[xi] For an epidemic disease vaccine portfolio to break even financially, the implication is that either (i) focus on a narrower set of candidates may be needed, or (ii) the value of developed vaccines would have to be orders of magnitude greater than is suggested by current assumptions about market size, probability of success in development, and the probability of an outbreak actually occurring.[109]

Prizes as incentives to vaccine development

Turning to evidence from other scientific fields, prizes have been used to incentivise leading-edge research where market size is uncertain and can be structured to remove exclusivity rights so that lower prices can be secured. They have been used in both the US and Europe to incentivise development of point-of-care tests.[110] In the early-to-mid 2000s, DARPA funded a series of 'Grand Challenges' in the early to mid-2000s to promote development of autonomous vehicles for defence use with prizes ranging from $1-2m in size.[111] Similarly, Medical Innovation Prize Funds – proposed in a series of congressional bills in the United States in 2011-12 but never adopted, would have financed development of new therapeutics for HIV based on allocation of a set percentage of GDP in any given year.[109] Prizes have also been proposed as a means of incentivising development of novel antimicrobials where, because of the threat of antimicrobial resistance, there may be a positive incentive to reduce final sales volumes.

However, there is no track-record of using prizes as an incentive to late-stage vaccine development, possibly because the size of prize pool required to offset costs and risks is too great. There are concerns too about the disincentive to long-term, incremental development processes posed by one-off innovation rewards.[112] Finally, de-linkage through prizes does not overcome barriers to manufacturing and access to new products when much of the market for epidemic disease vaccines would be in LMICs with limited ability to pay, and clear mechanisms would be needed to ensure that intellectual property rights were not then held by developing companies with little scope for broader use.[113]

APPENDIX 3: AN OVERVIEW OF BARRIERS TO VACCINE DELIVERY IN LMICS

Context is key in determining the effectiveness of vaccination delivery, but we can identify some broad principles that apply universally in terms of demand- and supply-side barriers to vaccine uptake.[114]

xi. In reality, this is likely an overestimation of the return on investment for IDEP vaccine development in this portfolio. The authors of this analysis make a number of assumptions, including the use of single-dose regimens; and that the probability of successful passage from preclinical to phase 2 development is as high as 32% (among others) that are unlikely to apply in practice.

AMC	Design and principles	Limitations for application to epidemic diseases
Basic model (Gavi AMC for pilot Pneumococcal Conjugate Vaccines (PCV))	· Prospective estimation of likely market size for new vaccine product · High income country partners guarantee market by paying fixed price for new vaccine product, reducing cost-per-dose for LMIC recipients if product development succeeds. In the case of the pneumococcal AMC, $1.5bn was committed upfront by bilateral and philanthropic donors to fund development, with a tail price of $3.50 per dose.[88] · Requires agreed target product profile (TPP) to set out technical criteria for new vaccine, and inform price estimation	· Assumes durable high income partner interest in financing AMC, which may not exist outside the context of epidemic response, nor for epidemic diseases to which their populations are unlikely to be vulnerable · Requires degree of competition between manufacturers to increase probability of success · Prior estimation of price requires in-house expertise and knowledge of costs of goods, manufacturing and the potential market which may not be available for epidemic diseases (especially if a poorly characterised or novel pathogen) · No provision for technology transfer to LMICs to ensure the long-term production viability of any new products under the PCV AMC.[88]
COVAX AMC (COVID-19)[82]	· Two-pronged design in which HICs pay for vaccines received, whereas LMICs receive vaccines partly or wholly-funded through COVAX AMC, allocated on the basis of population size · Scale of funds contributed through HICs and donor streams would enable investment in late-stage R&D for new, promising products · Combined purchasing power would theoretically enable COVAX to drive down prices for new products	· As above, and in addition: · Relative share of contributions predicated on existence of a truly global market, which is highly unlikely to exist for any epidemic disease · Assumes the incentive for HICs to contribute outweighs the incentive to directly purchase from manufacturers – which has not proven to be the case in reality.
Benefit-based AMC[82] (No real-world examples – theoretical model)	· Health Technology Assessments and value-based pricing are used to guarantee overall market revenue, based around a target product profile (e.g. generated by WHO). · Participating countries make a revenue-based commitment to purchase vaccines at prices determined by ability to pay. Size/pricing of orders may also be adjusted according to scale of country contributions to push funding, to ensure that taxpayers do not pay twice. · Third party guarantor(s) e.g. the World Bank, or a regional development bank provide assurance to industry that payments would be met in the event that individual actors are unable or unwilling to pay.	· As for the basic model, but in addition: · Estimation (in advance) of the prospective value of a vaccine is often highly uncertain and likely to be even more so for epidemic diseases that may not be well characterised. · Model assumes participation from a sufficient range of countries (of varying income levels) and social investors to supply funding at a level appropriate to vaccine development needs – which may not apply for epidemic diseases where the HIC market is very small. In reality, sizeable MIC markets would be needed to make this model work.

Table 5. Forms of AMC design – both real-world and theoretical – and an assessment of potential limitations when applied to vaccine development for epidemic diseases.

Determinants of population demand for vaccination

From a demand perspective, although the context of an epidemic may change individual- and community-level willingness to take up a new product, vaccine hesitancy remains a potent barrier and can be influenced by personal attitudes but also wider societal norms and structural factors. Globally, research suggests strong willingness to take up COVID-19 vaccines among populations in many LMICs for example,[115] but this picture is by no means universal,[116] and we know from vaccine deployment in previous outbreaks that community concerns, especially regarding products that are perceived as new and relatively untested, can undermine engagement even during an active epidemic.[117]

Determinants of vaccine supply

From a delivery perspective, many factors can influence facility readiness to administer vaccinations, including availability of viable vaccine supply (in turn dependent on a functioning cold chain down to facility level, access to reliable storage facilities, access to supporting consumables needed to administer vaccine products, and robust supply chains to ensure timely delivery of doses and consumables in appropriate quantities to the site of administration); health workforce availability and capability at facility all the way up to national level; the availability and robustness of information and monitoring systems to track vaccine vials, monitor delivery, identify eligible populations and those who have actually received doses; robust waste disposal systems; and of course the range of macro-level functions including adequate funding, governance and accountability to ensure the effective operation of any health service.[114] Centrally, few LMICs have the capacity and capability to procure vaccines at scale independently; UNICEF has for many years played a key role in supporting pooled procurement of vaccines for expanded program on immunization (EPI) programmes in somewhere between 80-100 LMICs annually so that they can be purchased affordably.

Access

Community level access to vaccination is the bridging factor between demand and supply that influences the extent to which coverage is ultimately achieved. This includes factors such as the simple presence of health facilities locally that can deliver vaccines, the ability (both physically and financially) for people to reach service providers, and factors such as national regulations concerning eligibility. A key consideration for COVID-19 vaccines, for example, has been the need for adult vaccine delivery pathways, for which only around 10% of countries in the WHO Africa and South East Asian regions had any prior experience before the pandemic – all from hepatitis B and influenza vaccine deployment.[59] But we also know that health services do not necessarily provide the optimal context for vaccine delivery, depending on the population. Although they have tended to be the preferred route of delivery for childhood (EPI) vaccines because of relative ease of linking to antenatal and post-natal care, school-based delivery for older children and teenagers depends for success on legal requirements for attendance by age that vary between countries.[118]

Governance and situational awareness

To these general barriers, we should add those specific to early detection and prompt action in the event of an outbreak – particularly the need for robust surveillance systems – and here the record both globally and at country level leaves much to be desired. Partly this is because emerging pathogens are inherently difficult to spot. The Global Influenza Surveillance and Response System (GISRS), originally established in 1952, provides a model for global collaboration for early detection, but it focuses on an established, albeit seasonally variable, pathogen.[119] For COVID-19, the Independent Panel for Pandemic Preparedness and Response has documented key delays following the emergence of first cases that contributed to delays in mobilisation of the global response. At country level, the largest number of outbreaks reported to the WHO originate from countries in Africa for which delays to detection are the longest.[120] Strengthening of both global and local systems for early detection is a key focus of the Panel's current work, and of the G7's recent '100 days' report.[121]

Robust national governance mechanisms are essential for effective deployment of available vaccines. Regulatory capability is one key aspect of this (and is addressed in more detail in the main report), but a second, key function lies in identifying the most appropriate segments of the population to vaccinate from a risk-benefit perspective to help ensure the cost-effectiveness of vaccination programmes. In the UK, this function has been performed by the Joint Committee on Vaccines and Immunisation (JCVI), but the capacity and funding security of the equivalent bodies – national immunization technical advisory groups (NITAGs) – in LMICs is highly variable, as is the extent to which they are integrated with wider decision-making processes regarding vaccine procurement and deployment.[122,123] These governance shortfalls, as well as the requirement for speed in deployment, help explain the use of stockpiles for some epidemic diseases, managed through global governance mechanisms (see chapter 7).

Vaccination delivery in special settings

While the challenges to equitable delivery described above are common to many LMICs, there are also barriers that are common to many of the contexts in which epidemic disease outbreaks are most likely to occur. We know, for example, that a majority of the children worldwide who have not received core EPI schedule vaccinations live in settings in humanitarian crisis especially those affected by armed conflict.[124] Here, the challenges to vaccination uptake are profound: acute and chronic insecurity reduces population demand for vaccination (for many reasons including, simply, the prioritisation of other basic needs over preventive health services), but delivery is also disrupted by damage to health facilities, supply- and cold-chain disruption, and health workforce attrition among other factors. There are examples of successful campaigns even in the face of armed conflict (including the DRC case study in Box 3, and polio vaccine deployment in non-government controlled areas of Syria in 2013), but these contexts present quite specific challenges for delivery and success depends on engagement with a wide variety of actors.[125] From a technological perspective, the imperative to develop oral/needle-free vaccines, and products with improved temperature stability to simplify delivery in unstable settings is also strong – and could be considered for UKVN's next funding round.

APPENDIX 4: MAPPING STAKEHOLDERS AND THEIR FUNCTIONS IN GLOBAL EPIDEMIC DISEASE VACCINE DEVELOPMENT AND DEPLOYMENT

Stakeholder (or group)	Funding	Remit	Constraints	Indicative level of support for vaccine development and roll-out
Technical bodies: oversight and coordination				
WHO	Member state governments (through assessed and voluntary contributions); private sources (e.g. BMGF)	In general: convening capability, technical advice, norm-setting, identification of priorities for vaccine development research In relation to R&D specifically: hosting the Blueprint In relation to response: part of the 4 founding members of the ICG (and host to the secretariat function)	Answerable to member state governments and, to this extent, constrained in terms of the action they may take to support preparedness and response	Up to $500,000 through the Contingency Fund for Emergencies to support immediate deployment of stockpiled vaccines in the event of an outbreak
ICG	Direct funding to ICG is restricted to support for the WHO's secretariat function; funding for stockpiles varies according to the vaccine	Rapid deliberation on country-level requests for access to stockpiled vaccination in the event of an epidemic of a relevant pathogen; agreement to release of stockpiled vaccines if pre-defined criteria are met; some scope for financial support to immediate response	WHO are answerable to member state governments and, to this extent, constrained in terms of the action they may take to support preparedness and response	Up to $500,000 through the Contingency Fund for Emergencies to support immediate deployment of stockpiled vaccines in the event of an outbreak
Donors and/or funders				
Bilateral donors	Taxpayers	Predominantly supra-level financial support to third parties e.g. CEPI, Gavi	Typically do not possess in-house technical capacity or expertise to be able to 'pick winners' in the R&D process (act primarily as third-party donors)	Variable according to the donor, but UK is a significant player (e.g. in pledging £250m to CEPI's work on COVID-19 vaccine development)
Private/ philanthropic funders (e.g. BMGF, Wellcome Trust	Private sources (BMGF); charitable endowment (Wellcome)	BMGF: research, discovery, preclinical development all the way through to manufacturing and delivery (including work on dosing strategies and delivery platforms) Wellcome: vaccine R&D; support to global initiatives (central role in developing the blueprint for CEPI)	In practical terms few. Wellcome's dedicated vaccine spend declined slightly in 2020 compared to 2019. BMGF is by some way the major private/ philanthropic actor in this space.	BMGF: $220m for vaccine development in 2020 Wellcome: £15m dedicated to vaccine development research in 2020 (under priority stream)
International financing institutions (IFFIm)	Government donors; international financial markets (through issued bonds)	Supra-level financial support to third parties e.g. Gavi	IFFIm is dependent on long-term pledges from donors, which are used to generate additional finance via market-issued bonds. This model has been used only for funding endemic disease vaccines to date.	IFFIm: difficult to determine on per annum basis, but $837m disbursed to Gavi for vaccine investment cases since 2006, of which $276m was f or vaccine R&D

Table 6. Mapping of key stakeholders in epidemic disease vaccine R&D, their functions and an estimation of the financial volume of support provided by them. This list is indicative rather than comprehensive.

Technical bodies: push				
CEPI	Government donors; private/ philanthropic sources	Core remit covers (i) research, discovery and pre-clinical development, (ii) early-stage development of new products, and (iii) regulatory matters and licensure As part of the pandemic response, has expanded to support phase 2b/3 development and large-scale manufacturing for new products	No specific focus on downstream development and market pull	$3.5bn request for replenishment round to cover the period 2022-26
PATH	Mixed: private foundations provided around 50% in 2020; a little over 20% from the US government. Large donation from BMGF in 2017 to support vaccine development and deployment	Works across the spectrum from preclinical research on novel vaccine candidates through clinical trials to approaches for new vaccine introduction and deployment (predominantly with a focus on technologies)	None identified.	Vaccine-specific spend not readily discernible, but $87.5m allocated to global health programmes overall in 2020
Technical bodies: pull				
Gavi	Government donors, private/ philanthropic organisations, innovative financing. Direct contributions account for 23% of funding; innovative finance (through IFFIm) the remaining 77%.	Range of market shaping activities, but for epidemic diseases specifically, AMC funding for Ebola vaccination, as support to the global vaccine stockpile, through a dedicated mechanism initiated in 2014 and renewed in 2020. Wider health system strengthening activities implemented to support vaccine deployment in Gavi-eligible countries (which include some but not all of those vulnerable to epidemic disease outbreaks).	Primary focus on vaccines for endemic diseases. Gavi's Vaccine Investment Strategy for 2021-25 includes support for vaccine deployment for pandemic influenza as a disease of epidemic potential, but not for other epidemic diseases.	Donor pledges totalling $7.5bn to support Gavi's activities in the period 2016-20123 $383m on health system strengthening to support immunisation delivery in 2020
UNICEF	Government donors, private/ philanthropic organisations	Supporting procurement and in-country deployment. Procurement function principally for EPI vaccine delivery, but also integral to ICG's model for epidemic vaccine stockpiles, and UNICEF is a core member of COVAX.	As a UN institution, answerable to member state governments.	$1.4bn in procurement spending on vaccines (predominantly EPI) in 2020; $104m on cold chain equipment
International pharma-ceutical firms	Funding through profits from sales of products across portfolios (vaccines form only a small part for the larger firms)	Variable according to the firm, but predominantly focused on high-income country markets. Prominent role in supporting late-stage development of newer platforms that have come to the fore as part of the COVID-19 response.	Sustainability of prospective markets for vaccines for epidemic diseases.	Variable by firm.
New South pharma-ceutical firms	Funding through profits from sales of products across portfolios	Variable according to the firm, but generally catering to LMIC markets through mass-production of vaccines under license.	Sustainability of prospective markets for vaccines for epidemic diseases. As CDMOs, many firms in this group are constrained by the willingness of international pharmaceutical firms to share know-how and technology with them, and by IP constraints.	Variable by firm.

APPENDIX 5: LIST OF INTERVIEWEES

Dr Simone Blayer, **PATH**

Sophie Bracken, **FCDO**

Nel Druce, **FCDO**

Professor David Heymann, **London School of Hygiene and Tropical Medicine**

Dr Bruce Innis, **PATH**

Axel Lambert de Rouvroit, **Gavi**

Jo Mulligan, **FCDO**

Professor Peter Piot, **London School of Hygiene and Tropical Medicine**

Cathy Roth, **FCDO**

Rachel Silverman, **Center for Global Development**

Rajinder Kumar Suri, CEO, **Developing Countries Vaccine Manufacturers' Network** (**DCVMN**)

Patrick Tippoo, **African Vaccines Manufacturing Initiative** (**AVMI**)

Saul Walker, **FCDO**

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