UK vaccines network

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Conference report

UK vaccines network: Mapping priority pathogens of epidemic potential and vaccine pipeline developments

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ABSTRACT

During the 2013–2016 Ebola outbreak in West Africa an expert panel was established on the instructions of the UK Prime Minister to identify priority pathogens for outbreak diseases that had the potential to cause future epidemics. A total of 13 priority pathogens were identified, which led to the prioritisation of spending in emerging diseases vaccine research and development from the UK. This meeting report summarises the process used to develop the UK pathogen priority list, compares it to lists generated by other organisations (World Health Organisation, National Institutes of Allergy and Infectious Diseases) and summarises clinical progress towards the development of vaccines against priority diseases. There is clear technical progress towards the development of vaccines. However, the availability of these vaccines will be dependent on sustained funding for clinical trials and the preparation of clinically acceptable manufactured material during inter-epidemic periods.

1. Introduction

The re-emergence of Zika virus since 2007 and the 2013–2016 Ebola outbreak in West Africa highlighted the risks that epidemic infectious diseases still pose. The outbreaks stimulated a re-examination of priorities in research and development of vaccines to these diseases at national and international levels. The UK Vaccines Research and Development Network (UKVN) was set up under the instructions of the British Prime Minister in 2015 and an expert working group (WG1) was convened to map the priority pathogens capable of causing future epidemics. A subsequent meeting of the group occurred in 2017 and progress and revised priority pathogens were considered. This report summarises the findings of both meetings and reviews the international emerging disease vaccine research and development landscape.

Abbreviations: CEPI, Coalition for Epidemic Preparedness Innovations; CHIKV, Chikungunya virus; CCHF, Crimean-Congo Haemorrhagic Fever; MERS, Middle East Respiratory Syndrome; MVA, Modified vaccinia virus Ankara; NCBI, National Centre for Biotechnology Information; NIAID, US National Institute of Allergy and Infectious Diseases; SARS, Severe Acute Respiratory Syndrome; UKVN, UK Vaccine Research and Development Network; VSV, Vesicular Stomatitis Virus; WHO, World Health Organisation.

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The 2013–2016 Ebola outbreak marked a paradigm shift in the attitude of governments and international organisations to high impact epidemic infectious diseases. Prior to this, disease epidemics had been dealt with on a largely reactive basis, with co-ordinated development of disease control strategies, vaccines and antiviral drugs occurring only in response to large scale outbreaks. Although good academic research on the trends in emergence and basic biology of outbreak diseases was often available, it almost invariably stalled at the level of demonstrating that immunogens were effective in small scale trials in animal models [1–3]. The Ebola virus outbreak has followed the pattern of intensification of research effort following major outbreaks previously seen with other diseases (such as SARS and MERS coronaviruses). For example, a search of NCBI PubMed for 'Ebola vaccine' reveals 240 original scientific reports (excluding review articles) in the 37 year period 1976–2013 compared to 612 reports in a 3.5 year period between 2014 and July 2018. However, there is some hope that there will be co-ordinated clinical research for epidemic diseases following this outbreak and, critically, technology transfer to pilot methods suitable for large scale vaccine manufacture before large outbreaks of other pathogens arise.

Although there remain questions regarding the long term sustainability of commercial vaccines for emerging (and potentially emerging) epidemic diseases, some of the factors that previously limited vaccine development beyond a small laboratory scale are now being addressed. The possibility of conducting phase II/III clinical trials during an outbreak, at least as part of a ring vaccination strategy, has been demonstrated [4–7]. This has highlighted that prototype vaccine trials need to be better integrated into emergency response protocols during an outbreak [8,9]. The caveat to this is that such trials need to be very carefully managed and communities affected must be actively engaged to prevent misunderstandings about what researchers are doing [10,11]. Also, performing research during an outbreak presents extra challenges compared to similar research conducted on endemic diseases. Partnerships between researchers and local health authorities need to be quickly and effectively established; local regulatory and ethical approval must be granted for any vaccination trial; ideally local physicians should be recruited to deliver the vaccine and monitor patients; sometimes these factors are additionally complicated by a lack of local infrastructure (power, water, internet access) hampering storage and administration of large batches of vaccine [8,12,13]. A fundamental problem for funding trials for vaccines to emerging epidemic diseases with outbreak potential is that such vaccines are not commercially attractive prior to an outbreak, or during inter-epidemic periods. Given the costs and extended timeframes of developing, licensing and manufacturing a new vaccine it is understandable that the commercial priority lies with endemic diseases in wealthy countries where there is a predictable market for the vaccine every year [14]. Emerging and outbreak diseases are sporadic by definition and although outbreaks can be large there can be long periods between outbreaks and therefore there is no guaranteed market for the vaccine product. In this context, the willingness of governments and inter-governmental organisations such as WHO to support commercial scale vaccine development and to invest in establishing a bank of experimental vaccines is key to preparedness for future outbreaks. It is important that the international community develops a strategic approach to avoid duplication and ensure all gaps are covered. Obviously the United States Government and other agencies have their own unique additional objectives to address vaccines for bioterror agents. Overall, WHO and the Coalition for Epidemic Preparedness Innovations (CEPI) are in a good position to promote a cooperative approach to emerging disease vaccine development.

2. Process used to generate the UKVN priority list

As with all publicly funded initiatives limited resources demand prioritization of pathogens targeted for vaccine development. In the case of the UKVN, prioritization was based on expert review of available information on diseases that represent a known or potential threat for an epidemic disease cross referenced with the state of vaccine availability for those diseases. Specific criteria for inclusion on the list included: case fatality rate (CFR) and disability burden of disease, regularity of outbreaks, evidence for geographical spread, zoonotic impact and ease of transmission from animal hosts to humans where the disease was zoonotic, potential for human-to-human transmission, availability of diagnostic platforms and existing investment and development stage of current vaccines, and finally whether there was evidence that the infection/disease could be treated effectively through another intervention.

The review panel included individuals with expertise in epidemiology and vaccine development, as well as infectious disease experts in human and animal health, and representatives of major UK funding bodies (MRC, BBSRC, Wellcome Trust, Department of Health and Social Care). The panel specifically focussed on diseases with the potential to cause high impact epidemics in humans. Animal diseases were only included in the consideration when they had substantial zoonotic potential (for example, Rift Valley Fever). Influenza A virus was excluded on the grounds that there were, and remain, separate funding routes for the development of vaccines for emerging pandemic Influenza A subtypes. A long list of epidemic diseases for which no suitable vaccine was available was devised, and subsequently reduced to a list of 14 priority pathogens by the scientific experts on the panel by a voting system (Fig. 1). Based on its late stage of commercial vaccine development Dengue virus vaccine research was subsequently deprioritised. A total of £101 million (US$131 million), from the £120 M UKVN allocation, was spent on funding specific projects addressing the initial priority list and the original list was again reviewed after two years to identify any gaps or revisions necessary.

3. Comparison of priority lists between organisations.

In addition to the UKVN, other organisations around the world have undertaken similar outbreak pathogen prioritisation processes. WHO generated a list of 8 priority pathogen groups in 2015, which it reviewed in 2017 and 2018 [15]. The criteria for assessing prioritisation used by WHO was based on 8 criteria (Human transmission; Medical countermeasures; Severity or case fatality rate; The human/animal interface; The public health context of the affected area; Potential societal impacts; and Evolutionary potential). This WHO blueprint has been the basis for the selection of priority diseases for vaccine development by the numerous funding agencies, including CEPI. The US National Institute of Allergy and Infectious Diseases (NIAID) also prioritises pathogens based on transmission, mortality and requirement for public health preparedness. Although it does not specifically take into account availability of vaccines, the NIAID priority A list does include many of the pathogens that are outbreak type diseases [16]. As might be expected given the similar focus of these organisations on the promotion of human health, there is considerable overlap between these lists (Fig. 2). The bunyaviruses Rift Valley Fever and Crimean Congo Haemorrhagic Fever, filoviruses Ebola and Marburg, and the paramyxovirus Nipah, arenavirus Lassa fever, and coronavirus Middle East Respiratory Syndrome, appear on all the priority lists. Only WHO also includes Hendra and Severe Acute Respiratory Syndrome Coronavirus. UKVN includes Chikungunya and Q fever, and NIAID includes smallpox, anthrax, botulism

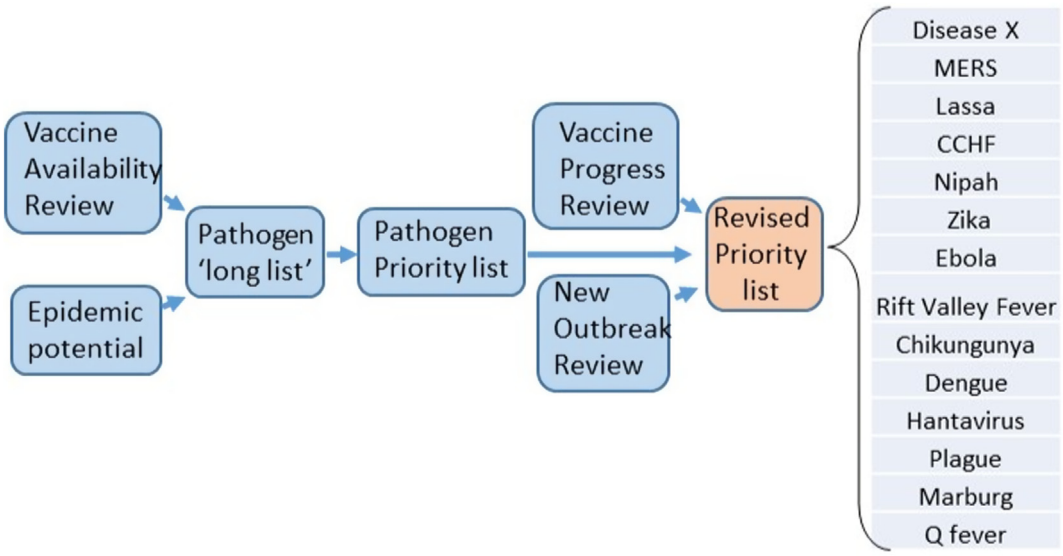

Fig. 1. Process used to generate and revise the UKVN priority list for outbreak diseases. The initial review was based on expert review of epidemic potential, vaccine availability and current therapies. This was revised after two years to take into account vaccine progress, new information and new outbreaks. The current priority list is shown on the right hand side of the figure. MERS- Middle East Respiratory Syndrome, CCHF- Crimean Congo Haemorrhagic Fever.

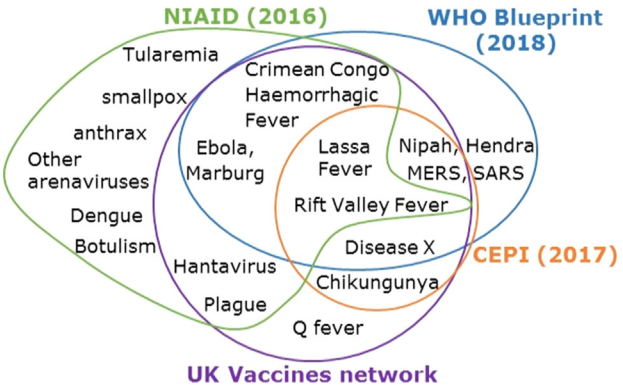

Fig. 2. Priority pathogens compiled from WHO Blueprint (blue), Coalition for Epidemic Preparedness Innovations (Orange), UK Vaccine Research and Development Network (purple), National Institute of Allergy and Infectious Disease Priority A list.

and some new world arenaviruses (Lujo, Junin, Machupo, Guanarito and Chapare viruses) in its priority A list. Hantavirus and plague are shared between the NIAID and UKVN lists only, and the emergence of an as yet unknown disease (Disease X) is specifically accounted for in the WHO Blueprint, CEPI and UKVN lists. These differences reflect both the different priorities of the organisations compiling the lists and the uncertain nature of prioritising diseases that are not currently, or are only intermittently, a problem in different parts of the world. Very often the differences between lists is the result of small variations in the perceived risk of diseases by members of the review panel. In part, this is a consequence of the fact that surveillance data for many outbreak diseases is limited and the most important drivers contributing to outbreaks are poorly characterised. For example, the UKVN prioritised Hantavirus, plague, Chikungunya and Q fever were all on the WHO long list, while Hendra and SARS were on the UKVN long list but not the final list. Future prioritisation exercises would be facilitated by better surveillance information for all priority diseases. This would include serosurveillance data in 'at risk' populations, where they can be identified, to assess whether changes in immunity at a population level can be linked to the risk of an outbreak.

4. Progress towards disease control

Since the onset of the West African Ebola virus outbreak in 2013 there has been some notable progress towards the control of some of the diseases on the priority lists, particularly Ebola virus. In 2015, there was no approved vaccine for Ebola virus and arguably this lack of an effective vaccine for use in emergency situations was one of the factors that contributed to the size and duration of that outbreak. While effective vaccines were produced and tested during the outbreak [4–6,17], which may prove important in future control, they were available too late to make a significant impact on disease control in 2013–2016 [18]. It is notable that the Democratic Republic of Congo, which has had repeated Ebola virus outbreaks since 1976, had outbreaks in both 2014 (before vaccines were available) and 2018, after vaccines had been tested in West Africa. During the 2014 outbreak in Djera there were 66 cases and 49 deaths. During the 2018 outbreak in neighbouring Bikoro, Iboko, Wangata and Ntondo by June 14 there were 66 cases but only 28 deaths (14 from confirmed Ebola cases). By the same date, 2730 people in the country had been vaccinated with the rVSV-ZEBOV vaccine using a ring vaccination strategy [19]. Additionally, for the current the current outbreak in the east of DRC over 170 000 people have been vaccinated. As always, it is particularly challenging to assess the impact of vaccination for a disease in an outbreak situation, in particular to quantify the cases that do not occur due to vaccination rather than the number of observed cases. Unlike an endemic disease, where there is a baseline disease incidence, an emerging epidemic disease is by its nature relatively unpredictable in the number of cases that will occur without intervention. During a ring vaccination trial in Guinea, 10 cases of Ebola occurred where vaccination was delayed in contrast to no cases, after 10 days, in vaccinated individuals where vaccination provision was immediate, thus providing evidence the vaccine may save lives [5]. In addition to the rVSV-ZEBOV vaccine, several other promising EBOV vaccines have undergone clinical or pre-clinical development since 2015 (Table 1).

For the other pathogens on the UKVN priority list the progress towards clinical development of vaccines has been mixed. There is now a licensed tetravalent Dengue vaccine manufactured by Sanofi Pasteur, which is a recombinant virus based on the yellow

Table 1
Vaccines reported as tested clinically against UKVN priority diseases.* where peer reviewed results are available the reference has been included, otherwise the ClinicalTrials.gov identifier has been listed. rV = Recombinant virus vaccine, iV = Inactivated virus vaccine, iB = inactivated Bacterial vaccine, VLP = Virus like particle vaccine, Sub = Subunit vaccine, N = Nanoparticle, IgG = Therapeutic antibody, DNA = DNA vaccine, VSV = Vesicular stomatitis virus, Ad5, Ad26 = replication defective Human Adenovirus type 5 and type 26 respectively, ChAd1 = Chimpanzee Adenovirus type 1, ChAd3 = Chimpanzee Adenovirus type 3, MVA = Modified Vaccinia virus Ankara, CHIKV = Chikungunya virus, CCHF = Crimean-Congo Haemorrhagic Fever virus, RVFV = Rift Valley Fever Virus, SARS = Severe Acute Respiratory Syndrome, MERS = Middle East Respiratory Syndrome.

Pathogen	Vaccine	Type	Backbone	Trial level	Manufacturer	References/Clinical trials reference*
Ebola virus	rVSVΔG-ZEBOV-GP	rV	VSV	II/III*	Merck	[4,5,50]
	Ad26.ZEBOV, MVA-BN-Filo	rV	Ad26, MVA	III	Janssen Vaccines & Prevention	NCT02543567
	Ad5-EBOV	rV	Ad5	II	CanSino Biologics Inc	[7]
	ChAd3-EBO-Z,	rV	ChAd3,	II	NIAID/GSK	[4,36]
	EBOV-GP	N		I	NovaVax	NCT02370589
Marburg Virus	MVA-BN-Filo	rV	MVA	III	Janssen Vaccines & Prevention	NCT02543567
Hantavirus	HTNV/PUUV	DNA	plasmid	I/II	US Army	NCT02116205, NCT01502345
	Hantavax	iV	ROK 84/105 strain	III	Green Cross Corporation, ROK	[24]
	HFRS	iV	HTNV + Seoul Virus	IV	Zhejiang Weixin Bio-Pharmaceutical Co., Ltd., China	[25,26]
Chikungunya	MV-CHIK	rV	Measles virus	II	Themis Bioscience	[37], NCT03101111
	CHIKV VLP	VLP	CHIKV	II	PaxVax Inc	NCT03483961
	VRC-CHKVLP059-00-VP	VLP	CHIKV	I	NIAID	[38]
	ChAdOx1 Chik	rV	ChAd1	I	University of Oxford	NCT03590392
Plague	rF1V vaccine	Sub	–	II	DynPort Vaccine Company LLC	NCT00332956
	Plague vaccine	Sub	–	II	Lanzhou Institute of Biological Products Co., Ltd, China	NCT02596308
Rift Valley Fever	MP-12	V	RVFV	II	US Army	NCT00415051, [28]
	TSI-GSD 200	iV	RVFV	II	US Army	NCT00584194
Zika	VRC-ZKADNA090-00-VP, VRC-ZKADNA085-00-VP	DNA	plasmid	I	NIAID	NCT02996461, NCT02840487, [39]
	VLA1601	iV	Zika	I	Valneva Austria GmbH	NCT03425149
	ZPIV	iV	Zika	I	US Army	[35]
	MV-ZIKA	rV	Measles virus	I	Themis Bioscience GmbH	NCT02996890
MERS	SAB-301	IgG	–	I	SAB Biotherapeutics	[41]
	MVA-MERS-S	rV	MVA	I	University of Hamburg	NCT03615911
	ChAdOx1 MERS	rV	ChAd1	I	University of Oxford	NCT03399578,
Q fever	NDBR 105	iB	–	I	US Army	NCT00584454
CCHF	KIRIM-KONGO-VAX	iV	CCHF	I	Tubitak	NCT03020771

fever 17D attenuated vaccine backbone [20,21]. Due to concerns over antibody dependent enhancement of disease, this vaccine is only recommended for particular age groups in endemic areas who have been pre-screened for antibody responses indicating prior Dengue exposure [22]. A second attenuated tetravalent Dengue vaccine is under development by Takeda and has shown promising results in a phase 2 clinical trial [23]. There are now two licensed inactivated hantavirus vaccines which are available in South Korea (Hantavax), and China (HFRS vaccine) [24–26], but these vaccines are not available elsewhere. Inactivated plague vaccines have been manufactured since the 1890s [27] however there are currently no vaccines of this type being marketed. In terms of new vaccines against plague, there are two candidates that have reached phase 2 clinical trials (Table 1) both are subunit vaccines based on recombinant F1 and V plague antigens. Phase 2 trials have also been completed for vaccines against Chikungunya and Rift Valley Fever virus, although the Chikungunya vaccines are likely to reach the market faster since their development is being driven by commercial organisations. The RVFV vaccines were tested by the US Army and therefore may not be immediately available for the general population [28]. It is interesting to note that new RVFV vaccines are being developed for animal vaccination but to date there have been no trials of these vaccines in humans [29–31]. Vaccines for other pathogens on the UKVN list are less well developed, immunogens for ZIKV, SARS, and CCHF have all reached phase I clinical trials. In the case of ZIKV there is also a good chance that these will be taken forward for more advanced clinical testing. Encouraging preclinical vaccine data exists for CCHFV [32] and in the 1970s the Bulgarian Ministry of Health produced a vaccine based on an inactivated CCHFV but no reliable human efficacy data exists. More recently a Turkish formalin inactivated vaccine has been reported to have been tested clinically in humans (Table 1). There is a Q fever vaccine that is available in Australia manufactured by Seqirus that is reported to be effective [33,34], however the vaccine is not currently licensed in other countries. For Lassa and Nipah no vaccine for use in humans has progressed beyond pre-clinical testing. However, CEPI has recently funded five large vaccine programmes for Lassa which are likely to lead to early clinical trials. One of the key observations emerging from consideration of existing and new vaccines is that differences between countries in the licencing process and the level of prior efficacy data required substantially affects the time new vaccines take to reach the market.

In terms of vaccine technologies, a range of different approaches have proven effective. Inactivated virus vaccines have been shown to be effective for a range of priority pathogens [24,25,35] and arguably have the lowest level of technology development required. The drawbacks are the safety issues related to growing and preparing hundreds of litres of highly pathogenic virus, the potential for incomplete inactivation, and the requirement for multiple doses of vaccine to achieve immune protection. Recombinant virus vaccines, where the genome of one virus is modified to express antigen(s) from another pathogen have also been very successful, with VSV, MVA, human and chimp adenoviruses, and measles all effective for the delivery of foreign antigens to stimulate strong immune responses [5,7,36,37]. The use of measles vectored vaccines has the additional advantage that it may provide some additional protection against an endemic human disease (measles). Subunit and VLP vaccines for plague and Chikungunya have also been tested in clinical trials [38]. There is also some evidence that nucleic acid (DNA, mRNA) based vaccines can be immunogenic in humans for some diseases [39,40]. Although not

strictly vaccines, the development of therapeutic antibodies that can be used post exposure during an outbreak, such as those developed against MERS coronavirus, may be particularly useful for outbreak type diseases provided that they are effective in the field [41].

5. Outstanding challenges

Significant challenges remain for the control of epidemic diseases, despite more clearly defined priorities in terms of pathogen selection. In particular, early identification and reaction to an outbreak is critical [18], there is a need to provide sustained investment in surveillance for disease outbreaks. Maps that predict outbreak risk may help to guide resource allocation with respect to infrastructure development and surveillance. The need for surveillance is further complicated by the requirement to monitor 'Disease X' [15], the previously unknown pathogen that can have major impacts on health during an outbreak. Recent advances in sequencing technologies have led to the identification of many previously unknown viruses [42–44]. This is likely to increase even further with efforts to sequence DNA and RNA from other eukaryotes including wildlife. While most of these new viruses do not pose a threat to human health, identifying those that do in a timely manner is one of the major challenges of modern surveillance. This underlines the importance of international collaboration including with low income/endemic disease countries. Another challenge is that of implementing the Nagoya Protocol with respect to the use of samples from low and middle income countries. Previously, countries could control the physical export of samples to ensure that there was agreement on how samples could be used. With the advent of portable sequencing devices that can be used in the field [45–49] and gene synthesis technologies it is now possible to design and produce a new vaccine starting with only sequence data, without physical transfer of material.

Currently there are relatively few diseases caused by bacteria that appear on the priority list. This is largely related to the effectiveness of antibiotic treatments. However, the threat of emergence of a previously unknown disease must be balanced against that of emergence of antimicrobial resistance in known bacterial pathogens.

Technical challenges around unwanted adverse effects of vaccines such as those associated with dengue vaccines [21] and the development of vaccines useful in resource poor settings are real, but are likely to eventually be overcome. Other challenges are in addressing negative attitudes that result in vaccine hesitancy in populations that would benefit from routine vaccination for outbreak type diseases to protect the wider community. The question of how and whether wildlife populations should be vaccinated if there is a zoonotic disease also needs to be addressed. Also, vaccinating livestock against diseases that first infect livestock and then humans may be a highly effective way to prevent new human disease outbreaks, and the time and costs required to achieve licensure of livestock vaccines are considerably lower than for human vaccines. Vaccination of sheep, cattle and goats against RVFV, pigs against Nipah, sheep against CCHFV and camels against MERS could prevent human infections, but in the last two examples the disease does not cause significant economic losses and vaccination of livestock would be more difficult to introduce. Indeed, if the primary reason for livestock vaccination was to benefit human public health, uptake by farmers would be low unless the benefits to the community were clear and there was no commercial cost to the farmer from vaccination.

The commercial and political challenges associated with epidemic diseases are significant. Since outbreaks are sporadic, investment tends to wane between outbreaks for the establishment of emerging diseases vaccine research and development, especially progressing prototype vaccines to proof of clinical efficacy. This includes funding preclinical trials in nonhuman primates. The new WHO and CEPI initiatives may overcome this problem but it is important that this momentum towards the development of effective vaccines is maintained even in the absence of a recent outbreak. A second political challenge was highlighted in West Africa and in the more recent outbreak in DRC, it is vital that local communities are actively engaged in the vaccine testing process to avoid disinformation [10,11]. Furthermore, it is crucial that local government and healthcare agencies are fully integrated into any disease outbreak response.

6. The funding landscape

Since 2016 the arrival of CEPI has provided strong financial support for the development of MERS, Nipah and Lassa vaccines towards Phase 2 studies. With donor commitments of >US$700 million to date, CEPI still lacks the financial force of the Wellcome Trust or the Gates Foundation (both of which are CEPI donors). The US government, through civil and military programmes is the largest sponsor for vaccines on the priority list. Other significant state contributors include the UK and Norway. China and India have emerged as vaccine players, but government funding mechanisms are not transparent at this time. Corporate vaccine funding remains important, with global R&D spend estimated at up to US$7 billion (on a purchasing power parity basis), but only for commercially viable vaccines. As already discussed this is a particular issue for vaccines against epidemic diseases. Vaccine development from lab bench to registration can cost over US$1 billion, with large-scale manufacturing plants costing another US$1 billion. Without guaranteed sales, there is no incentive for a company to invest in vaccine development. Only in the case of biosecurity vaccines, such as anthrax or smallpox has the US government funded both manufacture and purchase of vaccine stockpiles. There is a question over whether the international public sector can guarantee purchase and manufacture of priority list vaccines. The use of platform technologies to develop both commercial and emerging pathogen vaccines would obviate the need to build separate large-scale manufacturing plants in order to produce a stockpile of the emerging pathogen vaccine. Of note is the growth of Indian vaccine manufacture – now making more doses each year than the top four vaccine manufacturers – this is backed by supply to the Indian public sector market and growing sales to the international public sector (for example UNICEF).

7. Conclusions

Although future outbreaks may result from as yet unknown or poorly understood pathogens there is no excuse for governments not to prepare for known threats. 'Disease X' represents the hardest scenario to prepare for, however previous emerging disease outbreaks have been associated with pathogens that have already been described, or pathogens closely related to them so the exploration of platform vaccine technologies for known priority pathogens is logical. Progressing vaccine development for known threats to a field-ready state may also provide a springboard for the development of vaccines against new, related, diseases. Clearly, the time taken to develop even such modified vaccines requires that other epidemiological approaches are used as the primary focus of disease control. However, it is vital that these approaches are integrated with the testing of new vaccines. To this end, it is imperative to undertake phase I and II safety and immunogenicity studies and produce vaccine stockpiles during inter-epidemic periods so that vaccines are available for rapid deployment to compliment established outbreak control efforts and permit the collection of valuable clinical efficacy data.

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