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Process mapping of vaccines: Understanding the limitations in current response to emerging epidemic threats

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ABSTRACT

Vaccination remains the most successful and effective mechanism of pathogen control. However, their development and deployment in epidemic settings have been limited, and the 2015 Ebola outbreak in West Africa identified several bottlenecks linked to a lack of investment in pathogen research, infrastructure or regulation. Shortly after this outbreak, the UK Government established the UK Vaccine Network to ensure the UK is better prepared to respond to pathogens outbreaks of epidemic potential. As part of their work, the network commissioned the creation of a Vaccine Development Tool (http://www.vaccinedevelopment.org.uk/) to serve as a guide to the key stages in vaccine development. The tool also set out to capture the key, rate-limiting bottlenecks in the development of vaccines against emerging infectious disease such that corrective action could be taken, be it through research, funding, infrastructure and policy, both in the UK and internationally. The main research bottlenecks were related to understanding pathogen biology, identification of appropriate animal models and investment in the manufacturing sciences, especially into process development. Infrastructure gaps in GMP manufacturing and fill-finish were also identified and limitations in GMO regulation and regulatory and ethical approvals, especially for outbreak pathogens required new policy initiatives. The UK Vaccine Network has since begun work to correct for these limitations with a series of funding calls and development programmes. This paper seeks to summarise the Vaccine Development Tool and its key findings.

1. Introduction

Timely response to epidemics requires the development, manufacture and distribution of vaccine. Activities by the UK Vaccine Network (UKVN) and the WHO have seen the identification of several pathogens that have epidemic potential [1]. However, the development of effective vaccines against these pathogens requires improved coordination between policy makers, funders, researchers, vaccine manufacturers, and regulators, if we are to develop and deploy vaccines to mitigate the spread of epi- or pandemics [2].

Set in the context of the Ebola outbreak that began in 2014, multiple stakeholders were mobilised to respond to the humanitarian crisis of this escalating outbreak. Although there was no licenced Ebola vaccine available, approximately fifteen different vaccines were in preclinical development, including DNA vaccines, virus-like particles and viral vector [3]. Levine et al. [4] described how these candidates had largely been developed as part of the bioterrorism preparedness programme, BioShield, in the United States. Due to the relatively low geographic prevalence of infection there was a limited market and thus a poor case for industry to develop a vaccine for commercial purposes. However, concerns over the potential use of Ebolavirus as a bioterrorism agent resulted in a number of stockpiled sources that had undergone testing in animal models [4].

As the Ebola epidemic worsened, the availability of small vaccine stockpiles, taken together with the threat of further spread, catalysed stakeholder engagement to test the vaccine in humans to determine safety for potential deployment. Researchers, industrialists, regulators, and funders worked together to expedite the process of carrying out first-in-man trials of the Ebola vaccine[1]. Several

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[1] Unprecedented international consortium assembled to accelerate collaborative multi-site trials of candidate Ebola vaccine, Wellcome Trust, 28th August 2014 (https://wellcome.ac.uk/press-release/unprecedented-international-consortium-assembled-accelerate-collaborative-multi-site). Last accessed August 2018.

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vaccines were deployed as part of the international response [5] although this outbreak also served to highlight the necessity of effective public health systems and infrastructure, and community engagement in order to mitigate disease spread through cultural or social practices [6]. In the case of Ebola, it was fortuitous that several candidate vaccines were already in development and immense global efforts made the vaccine available. However, this also conspicuously highlighted that nations around the world need to be better prepared for outbreaks of all infectious diseases, particularly those with the potential for high levels of morbidity and mortality, and that other measures to control infection spread should also be implemented [7].

The United Kingdom (UK) has a strong international reputation for scientific research and innovation, and a long history in vaccinology. Along with other countries, the UK Government mobilised resources to manage the Ebola outbreak, as well as played a role in testing Ebola vaccines in the UK, and West Africa. Alongside these efforts, the UK Chief Medical Officer for the Department of Health and Social Care (DHSC), Dame Sally Davies, raised the question to government and related stakeholders – *what could the UK do to be better prepared for future outbreaks of infectious diseases?* A partnership was instigated across the DHSC, the UK Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), who then worked together to establish a 'UK Vaccine Network' (UKVN, www.gov.uk/government/groups/uk-vaccines-network) bringing together a small number of specialists from industry, academia and relevant funding bodies to make targeted investments in specific vaccines and vaccine technology for infectious diseases with the potential to cause an epidemic.

At its inaugural meeting in July 2014 the UKVN discussed potential priority areas for investment. Members agreed that four Working Groups (WGs) with the following foci:

WG1: To **prioritise 10–12 pathogens most likely to cause an epidemic** or pandemic in the short to medium term.

WG2: To rationalise **where and when vaccine development resources should be prioritised** when intervention is possible.

WG3: To understand the challenges in vaccine development and the key rate limiting steps for any given vaccine in development.

WG4: To **address manufacturing capacity** for vaccines.

This paper describes the activities undertaken by Working Group 3 on Vaccine Development. The group created a visual process mapping tool to better understand the potentially rate-limiting bottlenecks associated in moving a vaccine candidate from discovery through to development and early Phase clinical trials; then into clinical manufacture and Phase 3 trials. The primary purpose of the tool was to act as a visual aid for early discovery and development scientists, highlighting the major steps required to fully develop any experimental vaccine. The secondary, and crucial purpose of the tool, was to identify any generic bottlenecks that may slow down development. Identifying such strategic limitations may identify corrective actions, that may in turn help to overcome potential delays or setbacks when expediting vaccine development during epidemics. Actions could be taken by policy makers to correct for limitations in regulation, funders to identify limits in scientific knowledge that could be corrected with appropriate investment, and for government and trans-national organisations to consider local and global response. Though the genesis of this tool was considered in the context of epidemic preparedness, the tool itself is sufficiently far-reaching that it can be utilized by the wider vaccine community. Considering the global nature of vaccines, it is important to understand the interdependencies that exist between discovery, development and manufacture. This tool gives scientists vision of the considerations that will need to be made along the development process. In taking a much more holistic approach to vaccine development it is hoped that this can support other international such as the Global Vaccine Action Plan [8], which relies on the continued supply of vaccines to meet immunization targets. Thus, the tool serves multiple users and purposes, and we report on its main findings in this paper.

2. Methods

2.1. Mapping the processes

After initial literature consultations, a basic schematic overview of the major steps was created, which then fell into four main areas: (i) pre-clinical discovery; (ii) pre-clinical development; (iii) manufacturing; and (iv) clinical trials. Several subgroups were convened to discuss these areas; membership was drawn from the UKVN, a core group of specialists that made up WG3 and further expertise consulted according to need. Process schematics were made, and members undertook interactive discussions to add in, remove, and reorganise steps. The UKVN Secretariat led on organising a series of iterative workshops that repeated this process several times; each time a skills gap analysis was carried out to ensure appropriate expertise was representing different disease/vaccine interests, and from across the vaccine sector from academic and industry discovery, development, regulation, manufacturing and clinical trials. The repeated process of interactive mapping, refinement of core documents, and presentation of progress back to the subgroups stimulated dialogue on the map as a whole. This was a concerted effort to break down silos between disciplines and sectors, and address how choices made in early discovery may affect the later development pathway.

2.2. Making the tool

Once the iterative, interactive working subgroups had met to agree the final nodes and bottlenecks on the map, the final figures were transcribed into PowerPoint. These images were then used as the basis for interactive webpages, which were constructed by the MRC Regulatory Support Centre (MRC RSC, https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/). The MRC RSC offered designs for the main menu, layout and colour scheme and once agreed with the Secretariat, all graphics for the tool were drawn using Adobe Illustrator then saved in a web-friendly format. The website was built in Dreamweaver using HTML5 coding. Efforts were made to make the site responsive to different devices, and while this was possible for the text it was not possible to do so for the maps due to the complexity of the subject. The final version can be seen at www.vaccinedevelopment.org.uk.

3. Results

The process mapping workshops culminated in production of a website, with standalone pages for maps that distinguished the following major subdivisions: (1) Target Product Profile (TPP); (2) Pre-clinical Discovery; (3) Pre-clinical Development; (4) Clinical Development; and (5) Regulatory Affairs and Ethical Approvals (Fig. 1). Due to the mandate and remit of the tool to be used by the UKVN for the development of vaccines for outbreaks, WG3 agreed that the tool did not need to address steps for market access and authorisation, as outbreak vaccines would not normally undergo this process – instead being deployed in small populations according to need once necessary evidence on safety and immunogenicity had been achieved.

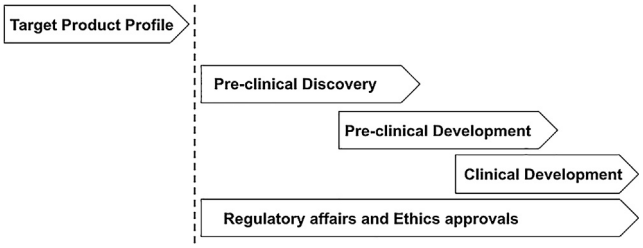

Fig. 1. Overview of the tool with Target Product Profile as the entry point. Giving consideration into what is actually required by the target population is best captured by the target product profile and should be used as a reference document during the development process.

3.1. Target product Profile

The Target Product Profile (TPP) is a descriptive document that sets out clear parameters for the characteristics of the desired end product, its intended use, and market. It is the designated entry point into the process map. This came about through repetitive discussions that prevailed on the importance of the TPP at all stages in development; in simple terms, to know what it is you are making, and for whom. WG3 agreed that the significance of the TPP and the relevance to even the earliest exploratory basic science work, should not be underestimated, therefore prominently placing the TPP, aimed to engage early discovery scientists to consider what the end product is, and how the choices made during pre-clinical discovery and development influence them. The consensus opinion within the working group was that the TPP should be seen as a strategic planning document that should be utilised as a benchmark as data emerges. During normal development, this is a tool for novel vaccine creation. However, in an outbreak situation, the TPP acts as an essential checklist under accelerated timescales. It is worth noting that that the importance of TPPs is widely shared and recent work by the WHO and CEPI includes creating standard TPPs for priority pathogens.

3.2. Bottlenecks

Iterative workshops hosted ongoing discussion on what was involved in each step, and where might rate limiting steps slow down development. There was agreement that almost anything could be described as a bottleneck in that each step is necessary, and by the nature of discovery research and development, such endeavours take time. However, in order to scrutinize the bottlenecks that could potentially be ameliorated by corrective action or investments by governments, research funders and policy makers, WG3 agreed that the tool should only identify steps where corrective action could be taken that could potentially accelerate vaccine development. The main bottlenecks and the corrective action required are summarised in Table 1. An additional important consideration, was that the identification of these bottleneck 'nodes' should be sufficiently generic so as to be applied to a range of vaccine types, and pathogens – thus WG3 refined the key steps to common denominators that were shared across approaches. Overall, many of the bottlenecks focused around gaps in funding for scientific knowledge, training, and infrastructure. An additional item was harmonisation of regulation, especially with regards to the release of genetically modified organisms (GMOs). The bottlenecks can readily be seen on the process map by clicking 'show bottlenecks' on each map page; below we describe the main bottlenecks highlighted at each stage.

3.2.1. Pre-clinical discovery

Within pre-clinical discovery, understanding pathogen biology and developing the appropriate animal challenge models are seen as significant limiting factors, especially with emerging infectious disease. The ability to screen, test, and verify potential new antigens is of critical importance. Increased research funding into standardised methodologies for *in vitro* and *in vivo* testing and work into human-livestock host immunology would be critical to increase capacity.

As lead candidates are identified, ensuring that the work has the appropriate freedom to operate becomes increasingly important. A review of the Intellectual Property landscape including searches on the antigen, cell line, and biological methods employed to create them are required and time to completion could be as little as three months, but increases with complexity. Conducting a freedom to operate review is an important step towards commercialisation. Yet, in an outbreak scenario, special regulations such as compulsory licensure and step-in rights may allow this issue to be side-stepped, but would require further clarification in policy.

Table 1
Summary of the vaccine development tool bottlenecks. These bottlenecks identify generic rate-limiting stages in vaccine development that could be alleviated through further research spending, changes in policy of investment into infrastructure.

Stage in development	Short description	Type of bottleneck
Pre-clinical discovery	• Pathogen biology including - Human-host immunology - Pathogen Challenge model • Freedom to operate	• Research • Policy
Pre-clinical development	• Process development including, - Critical process parameters - Critical quality attributes - Adjuvants and formulation • Animal model choice • Scale-up and clinical manufacture - GMP bulk - GMP fill-finish	• Research • Research • Infrastructure
Clinical development	• GMO regulation • Trial sites and NRA approval • Regulatory and ethical approval	• Policy

3.2.2. Pre-clinical development

Pre-clinical development is a complex, multi-step, and time-consuming process (Fig. 2). It requires that vaccine candidates undergo strain development and confirmation of antigen presentation, verified by animal studies. This is followed by process development to ensure that a scalable, robust, and GMP compliant manufacturing process is created. Material generated at the end of pre-clinical development can be used for animal toxicology studies and forms the basis of a clinical trial application.

The first bottleneck encountered is in strain development. Some development work can occur using a research cell bank, however research cell banks are generally not to GMP standards therefore delays at later stages can be avoided by ensuring banks are GMP compliant. This will often require re-cloning into traceable cell lines that are GMP certified and free of any adventitious agent.

Major bottlenecks are around Process Development to create a scalable, GMP compliant, manufacturing process and the determination of the critical process parameters. At this stage manufacturers must address if the vaccine can in fact be manufactured in a scalable process. There is no generic manufacturing process for vaccines, thus almost all processes are designed from the bottom up, which adds costs and delays to any future intervention plan. Platform manufacturing technologies are a method to overcome this issue by streamlining manufacturing with generic operations into which your selected antigen(s) can be introduced. Viral vectors are one such platform technology that was effectively

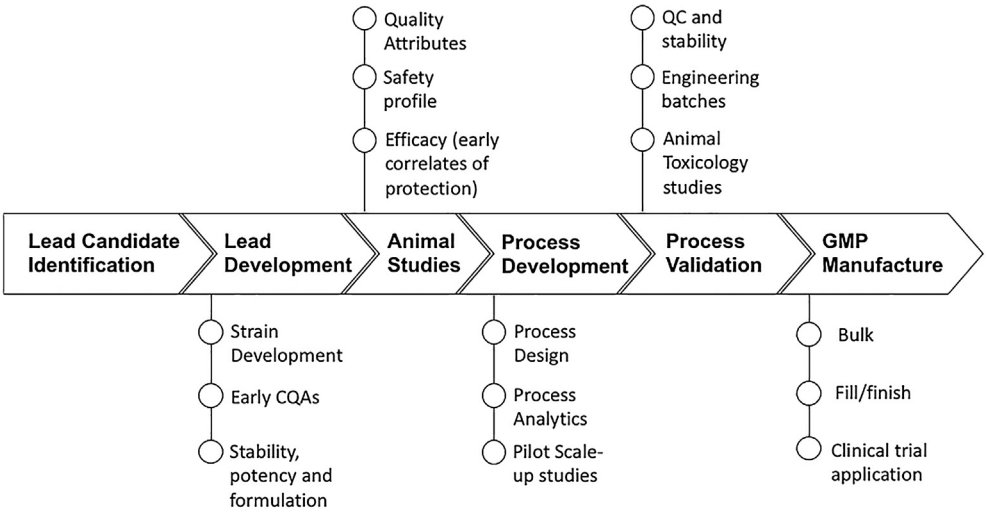

Fig. 2. Pre-clinical simplified development map. This map summarises the main bottlenecks in pre-clinical development following lead candidate identification. The target product profile is re-evaluated during this process to ensure it correctly reflects manufacturing data, and developers are encouraged to liaise with regulatory bodies and ensure early input at any relevant stage.

employed during the Ebola outbreak [9,10]. Looking more broadly, recombinant sub-unit vaccine technologies are another platform technology that could be used in other epidemics and has been successfully demonstrated in context of influenza vaccines [11]. Other advances in nucleic acid based vaccines, such as DNA and RNA, offer a future, though as yet unrealised potential, for generic manufacturing and release testing of vaccines. The determination of the range of physical, chemical, biological, or microbiological properties that ensure the quality of the desired product, is described as 'Critical Quality Attributes' (CQA) and requires well-defined analytics which in the long term can reduce Quality Control (QC) costs. Finding suitable analytics that can resolve complex antigen structure, increase understanding of degradation pathways and formulation needs is a continuing bottleneck. Funders must ensure that process development, manufacturing, and analytics are not overlooked in future research calls.

Further bottlenecks are encountered during animal *in vivo* studies; characterising immunogenicity and reactogenecity in relevant animal models is imperative for taking forward vaccine candidates into Phase 1. With this model there are further potential bottlenecks associated with Home Office approvals, and Containment Level 3 and 4 facilities depending on the pathogen of study, and supply of animals.

GMP manufacturing is an infrastructure bottleneck that requires funders and policy makers to examine the pressures upon the current manufacturing model. Almost all vaccine manufacturers operate at capacity and are dedicated to production of a single product. 'Step-in' rights in an emergency scenario will disrupt supply of an essential vaccine, but also cause delay. Recruiting a CMO to the task may help to alleviate the situation, but essential training and know-how is required. Furthermore, some sites may only be suitable for certain vaccines classes, which can range from protein sub-unit vaccines to live viral and bacterial vaccines. Based on vaccine class, facilities may not have the appropriate containment level for bulk manufacture of the drug substance, or the fill-finish for drug product. Indeed, many facilities do not have fill-finish operations co-located and fill-finish is also a bottleneck in clinical development due to the limited number of appropriate sites and the volume of vials required for Phase 2 and 3 trials.

The UK Government, with the UKVN providing evidence and advice, has identified manufacturing infrastructure as a significant bottleneck, and it has sought to invest into a new Vaccine Development and Manufacturing Centre (https://www.gov.uk/government/news/medicine-and-vaccine-manufacturing-centres-apply-for-funding). Other organisations, such as CEPI [12], have also issued calls for proposals into new platform manufacturing technologies (cepi.net). The situation exists under the status quo that we may have a vaccine that can be utilised to fight a future epidemic, but not have the manufacturing capacity to enable production and distribution. These latest calls seek to reverse current limitations.

3.2.3. Clinical development

Many of the priority pathogens are prone to sporadic outbreaks, and due to potential lethality, it will not be possible to conduct full Phase 3 trials, and even Phase 2 studies may prove challenging in a human population due to the unpredictable nature of these outbreaks. Nonetheless, the sequential clinical trial steps that would comprise the 'normal' steps in development of a vaccine being taken forward for licensure have been incorporated into the tool. Clinical trials require great investment and resource to execute, and the lengthy nature of the process could itself be described as a bottleneck; for the purposes of the tool however, we highlight fives steps within clinical development. Current GMO regulations do not distinguish vaccines based on viral vectors, or live, replication incompetent vectors based on bacteria and viruses. Current regulation stipulates that use of GMO vaccines is done so under 'contained use' or 'deliberate release' protocols to prevent release into the environment. Consequently, this may involve obtaining separate approvals, modifications to the trial site, modified procedures for sterilising, administering and disposing, separate storage facilities and special training of staff to handle GMOs. Overall, this whole area would benefit a revision of regulations and derogating the use of common vaccine vectors in separate regulations from the currently applicable GMO guidance would have a substantial beneficial impact in speeding up approvals.

Obtaining Regulatory Approval may be especially difficult in the context of an international trial, where local rules may differ from country to country, or the National Regulatory Authority (NRA) itself may have insufficient experience and seek expert opinions, which can further delay the process. Engagement with the NRA at an early stage is essential, as seeking opinion on the proposed trial design can capture any 'in country' requirements. The

availability of trial sites may also impede progress; particularly if sites are not approved to work with GMO vaccines, or there are other limitations such as lack of infrastructure, skilled personnel, and capacity. Working with credible and experienced partners will help to minimise delay and several clinical trial networks already exists to facilitate clinical development, some of which are pathogen specific that can further minimise this bottleneck.

To overcome these bottlenecks, finding clinical trial sites and experienced NRAs that can act as credible authorities is essential, and early discussions need to occur in tandem to development and production to avoid delays.

3.2.4. Regulatory affairs

The process mapping tool emphasises the importance of ethical and regulatory considerations throughout the entire process, as the iterative workshops continually highlighted the importance of early engagement so the appropriate advice and input shape the R&D. The tool provides an overview and signposting to other organisations and information sources, as many outbreak vaccines may never go through market authorisation due to there being no commercial incentive for the manufacturers. Nevertheless, there will be several stages where necessary approvals must be obtained in order to proceed with developing and testing a candidate. For regular marketing authorization in the EU, vaccine developers must provide a full development dataset of pre-clinical and clinical trial results to evidence Clinical Safety and Efficacy, as well as evaluation of a positive benefit-risk ratio. The mapping tool highlights that:

- To discuss the TPP the UK Medicines and Healthcare products Regulatory Agency (MHRA) can be approached at any time.
- Animal work is regulated under the Animals (Scientific Procedures) Act 1986 (ASPA). A UK Government Home Office licensure must be provided at an institutional, personal and project level.
- The use of GMO vaccines is regulated by separate legislation, and approval must be given by the Health and Safety Executive (HSE).
- To carry out experimental medicine studies of immune responses in humans the Health Research Authority (HRA) provides ethical approvals through the Research Ethics Service (RES) for projects in the NHS (led from England).
- Clinical Trial Authorisation (CTA) is made through a formal application to the MHRA. Trialists must provide information on the mode of action, nature of the target, animal model studies and an IMP dossier with preclinical toxicology data, and any human mechanistic/proof of concept studies.

Though these regulations are specific for the UK, many other countries require a similar level of scrutiny.

In the case of life-threatening infections, it is conceivable that many of the priority vaccines under development will ultimately never undergo the standard clinical trials process and be used in an outbreak situation under EUAL [13]. In these circumstances, it is imperative to test novel vaccine candidates in well characterised animal models. Previously applied to defence vaccines due to the limitations of clinical testing, the FDA Animal rule [14] may provide a pathway to test novel vaccine candidates. In outbreak settings, as was the case with Ebola, it is possible to undertake an emergency use protocol and expedite authorisation to ensure a promising vaccine candidate can be deployed for human use, if it is justified as major interest for public health and/or therapeutic innovation.

3.3. Case studies

Once a generic framework that could be applied to vaccine R&D broadly was established, the working group undertook a series of meetings applying the process map to three case studies of different vaccine candidates under development for three of the UKVN's priority pathogens: MERS Viral Vector vaccine, Zika protein subunit/VLP vaccine (Fig. 3), and the Prokarium Vaxonella® Plague vaccine (Fig. 4). The case studies can be accessed through the main landing page of the process map[2].

MERS was selected as there are several candidates in later stages of development, including the viral vectored vaccine candidate ChAdOx1 MERS. The viral vector approach overcomes a number of bottlenecks to speed up development, mainly impacting on the preclinical development stages to overcome delays that would be associated with masterseed bank production, pre-formulation work/*in vitro* and *in vivo*, and lead identification. Antigen identification bottlenecks are also overcome, through straightforward selection of the spike protein (the major external antigen of coronaviruses) which elicits neutralising antibodies to the receptor binding domain [15]. The bottlenecks that remains relevant from the generic tool are: basic understanding of human/livestock host immunology; using an appropriate animal challenge model (camels would be suitable, but few places have facilities for such a large model); and the three main bottlenecks in clinical development of obtaining ethical and regulatory approval, working with vaccines classified as GMOs, as the viral vector platform has been altered genetically from its original form, and the availability of overseas trial sites.

More bottlenecks were identified when applying the Vaccine Development Process Map to a novel Zika vaccine. At the time of the UKVN formation, Zika was little heard of, and had only modest investment as a potential emerging virus in UK research funding portfolios. As the work of the UKVN progressed, the Zika outbreak unfolded, and funders in the UK and internationally were mobilised to increase investments. The UKVN immediately added Zika to the priority pathogen list, and contributed to a number of funding streams to support vaccine R&D. Applying the process mapping tool to such an emerging pathogen, allowed the visualisation of the significant number of unknowns and challenges when dealing with a little-known emerging disease without platform approaches (Fig. 3). In the earliest pre-clinical discovery stage, pathogen biology and host immunology were both rate limiting, particularly in identifying regions of the virus that could be used as a possible antigen. *In vitro* studies and deploying an *in vivo* challenge model were also rate limiting as the generation of reagents and the appropriate assays need to be established. Without a robust set of assays and generation of some antigen in the early discovery phase, the bottleneck would be overcome however identification of the surrogate/correlate of protection in the appropriate challenge models will be important. It should be noted that many vaccines have launched without the establishment of correlates of protection and will depend on the licensure sought and the severity of the disease and its outbreak.

In pre-clinical development, due to the novelty of the vaccine, process development, assays, adjuvantisation and formulations were identified as bottlenecks. Time could be saved if a platform technology was used for this vaccine, circumventing many steps in process development and formulation. In clinical development, deploying a human challenge model to study the response to a vaccine studies were considered rate-limiting, and it must be noted that in the case of emergency or experimental licensure, a strategy might be to establish some animal challenge data and seek to establish safety data in a Phase 1 trial before expansion into a Phase 2a/b trial. However, demonstrating efficacy can only be one in endemic or outbreak situations and will require early

[2] http://www.vaccinedevelopment.org.uk/outreak-casestudies.html.

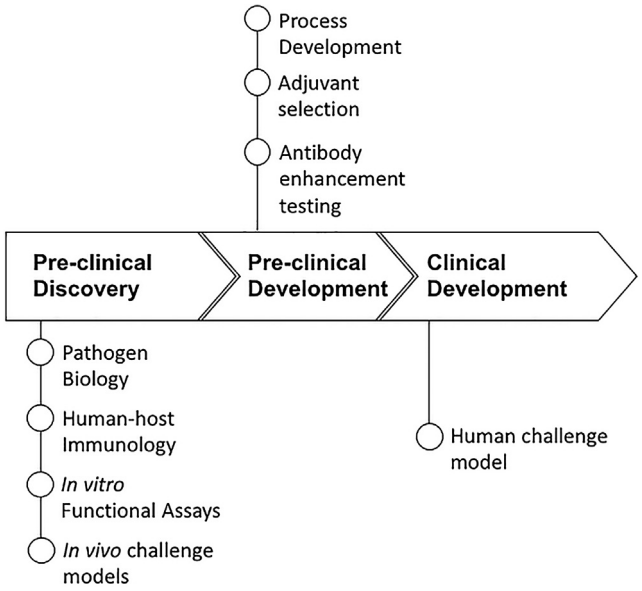

Fig. 3. Zika case study summary. As a relatively neglected pathogen until recently, much of the bottlenecks identified are in the pre-clinical discovery phase, which requires antigen identification and development of assays and challenge models. The need for a new vaccine also incurs bottlenecks in the pre-clinical development phase and in clinical development.

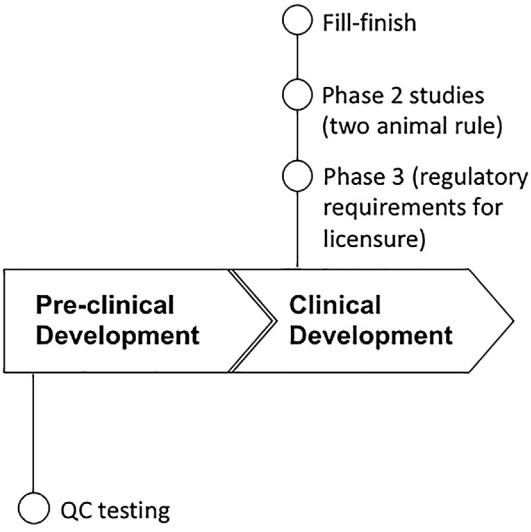

Fig. 4. Plague case study summary. The total number of bottlenecks is reduced due to the use of a live bacterial vector system being exploited as a platform technology. Plague antigens are already known and well characterised, thus, many of the bottlenecks shift to clinical development and testing of the vaccine candidate.

engagement of the NRA, and locating suitable overseas trial sites has the potential to be rate-limiting.

A plague vaccine potentially has dual application: the development path could be in collaboration with government agencies in producing an anti-bioterror vaccine but could be expanded and developed as a vaccine against endemic disease in regions such as Madagascar. This dual nature affects the way we think about the TPP and development path. As with the MERS case study the Plague Vaccine exploited a platform technology – Prokarium's Vaxonella platform – thus many bottlenecks, particularly in preclinical development, were circumvented (Fig. 4). The main bottlenecks are in the clinical phase and animal rule regulations necessary to follow for licensure and are particular to this pathogen and vaccine approach, and included: Quality control; Phase II regulatory requirements for two animal models; Fill Finish; and in Phase II safety studies, meeting requirements for licensure regulations.

The case studies have demonstrated how useful the process map can be in vaccine development, and how using platform technologies enables many development steps to be circumvented and thus overcome rate-limiting steps, which could be vital in an outbreak situation where speed of development must be minimised where possible.

3.4. Prioritisation guide

As an additional feature, the tool also presents some of the work completed by WG2, which was undertaken to better understand the feasibility and challenges of developing vaccines for the major UKVN prioritised pathogens. The UKVN members agreed that to develop a new vaccine might not always be the most appropriate response in an outbreak setting, particularly if a candidate vaccine is early stage and presents significant R&D or manufacturing challenges. Thus, it may be more appropriate to deploy other healthcare interventions to manage the disease, such a therapeutic antibodies or containment procedures.

The prioritisation guide addresses the 'Technical Feasibility' of creating a vaccine together with 'Public Health Value' based on pathogen severity and alternatives to vaccination. A final consideration was the time scale and cost of development, with the single criterion to address the available vaccine candidate(s), considering the stage in development of any existing candidates. This included manufacturing considerations, and whether any vaccine may already be stockpiled.

Each criteria has a red, amber or green status, and taken together will enable decision-making on the suitability of pursuing vaccine R&D in an outbreak setting.

4. Conclusion

This tool represents a first step towards understanding the limiting factors in vaccine development and epidemic preparedness. However, there are still several key outstanding challenges it does not fully capture. The first is sustained funding for this problem, which is partly address through the creation of the Coalition for Epidemic Preparedness Innovation (CEPI, www.cepi.net), however improved co-ordination is still required between industry, academia, government and international organizations, such as the WHO. This will be a key priority for policy makers in the future. Infrastructure and manufacturing capacity needs to be accurately assessed, especially fill-finish capacity for the different vaccine types/classes. Additionally, continued research is required to better understand the correlates of protection, appropriate animal models and, of course, the discovery of new antigens that can protect against these emerging pathogens.

An extraordinary array of technologies are under development that have the potential to change our ability to respond to emerging infectious diseases. Amongst these, viral vector and subunit vaccines are at the forefront, however future innovations with nucleic acid based vaccines are on the horizon. Currently, there are no DNA or RNA vaccines licensed for human use. Yet should this milestone be reached, many of the bottlenecks described currently will be eliminated. In the meantime, funders, governments and policy makers must all focus to overcome the existing bottlenecks identified and employ better co-ordination to overcome future epidemic threats.

Declaration of interest

The author declares that there is no conflict of interest.

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