wellcome

Effective Vaccine Ecosystem

August 2020

GLOBAL HEALTH

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Contents

Acronyms

AMC	Advance Market Commitment
AMR	Antimicrobial Resistance
APC	Advanced Purchase Commitment
AVAREF	African Vaccine Regulatory Forum
BARDA	Biomedical Advanced Research and Development Authority
BMGF	Bill & Melinda Gates Foundation
BSL	Biosafety Level
CDC	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
CHIM	Controlled Human Infection Model
CMO	Contract Manufacturing Organisation
COGM	Cost of Goods Manufactured
COGS	Cost of Goods Sold
COVID	Corona Virus Disease
CTD	Common Technical Dossier
DALY	Disability-Adjusted Life Years
DCVMN	Developing Country Vaccine Manufacturing Network
EAG	Expert Advisors Group
EID	Emerging Infectious Disease with epidemic potential
EMA	European Medicines Association
ETEC	Enterotoxigenic Escherichia coli
EUAL	Emergency Use Assessment and Listing
FDA	Food and Drug Administration
GBD	Global Burden of Disease
GMP	Good Manufacturing Practice
GNI	Gross National Income
GSK	GlaxoSmithKline plc
HIC	High Income Country
HIS	Human Infection Studies
HPV	Human Papillomavirus
ICH	International Council on Harmonisation
IFFIm	International Finance Facility for Immunization
IHME	Institute for Health Metrics and Evaluation
IP	Intellectual Property
IVI	International Vaccines Institute
JE	Japanese Encephalitis
LIC	Low Income Country
LMIC	Low- and Middle-Income Countries
MCV	Measles Containing Vaccine
MERS	Middle East Respiratory Syndrome
MIC	Middle Income Country
MMGH	MM Global Health Consulting
MRC	Medical Research Council
mRNA	Messenger Ribonucleic Acid
MSD	Merck, Sharp & Dohme
ND	Neglected Disease
NIAID	National Institute of Allergy and Infectious Diseases
NRA	National Regulatory Authorities
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulation Harmonization
PDP	Product Development Partnership
PQ	Prequalification
RNA	Ribonucleic Acid
ROI	Return on Investment
RSV	Respiratory syncytial virus
SII	Serum Institute of India
SRA	Stringent Regulatory Authority
TB	Tuberculosis
TCV	Typhoid conjugate vaccine
TPP	Target Product Profile
UN	United Nations
USD	United States Dollar
VIPS	Vaccine Innovation Prioritization Strategy
WEF	World Economic Forum
WHO	World Health Organization
WP	Work Package

Executive Summary

The global vaccine ecosystem does not optimally realise vaccines' potential to deliver health improvements. With this research effort, Wellcome aims to identify solutions that will improve the vaccine ecosystem, focusing on challenges faced between a vaccine candidate's transition into Phase 2 clinical development and first country introductions. In alignment with Wellcome's mission and strategy, this research focused on emerging infectious diseases (EID), diseases affecting low-income countries (LIC) and those with the potential to impact antimicrobial resistance (AMR). Starting from an analysis of the vaccine ecosystem, the research mapped vaccine developers' decision-making and the challenges faced in their development work. This analysis informed the prioritisation of challenges that have a sizeable impact on developers and public health, and for which solutions could improve the functioning of the vaccine ecosystem.

Characterisation of the vaccine ecosystem

Vaccine developers operate in a complex ecosystem in which the majority of development programmes for EID, relevant for AMR or focused primarily on LIC, face technical and regulatory challenges and are not attracting sufficient attention from policymakers, funders or developers. As a result, relatively few developers are engaged, few development programmes are active for these diseases and few innovative solutions are pursued.

A review of the vaccine development programmes that had reached at least Phase 2 clinical development in the period 2009-2019 revealed two factors associated with the number of engaged developers: (a) projected size of the financial opportunity – with preference for diseases whose global burden or the risk of severe disease is higher; (b) risk of development – with preference for existing technology where established knowledge makes the risk smaller.

Developer decision-making

Understanding when, why and how vaccine developers make decisions is critical to identifying the most appropriate levers to alter either the inputs or the outputs of those decisions, or both. Decisions are triggered by many internal and external events and influenced by factors whose importance evolves over time, as vaccine development programmes unfold. The same factors have variable influence depending on the type of developer, from academic institutions to multi-national companies with a portfolio of licensed vaccines.

This research explored, and was validated via an expert survey, which factors and sub-factors have the most influence on developer decisions and how these factors change over time and by the type of developer. In the pre-pivotal phase, unmet medical need and technical feasibility are the most important factors. Technical feasibility continued to be an influential factor in the subsequent pivotal trial phase. Within technical feasibility, clinical development and licensure feasibility aspects emerged as the sub-factors developers most closely scrutinise. As development programmes progress towards early commercialisation and first country introductions, value creation potential assumes the greatest influence on vaccine developers' decisions; revenue potential and the total required investment, in particular, are the factors most likely to be considered. Licensure feasibility is also of great importance at the time the first licensure is pursued, and the licensing strategy is finalised. Overall, value creation was the most influential factor, followed by technical feasibility, unmet medical need and strategic fit. Details on each phase of development is available in Chapter 2 of this report.

Figure 1: The most important factors during each phase of development

Survey respondents were asked to weight the importance of each sub-factor within the category by allocating 100 points per category.

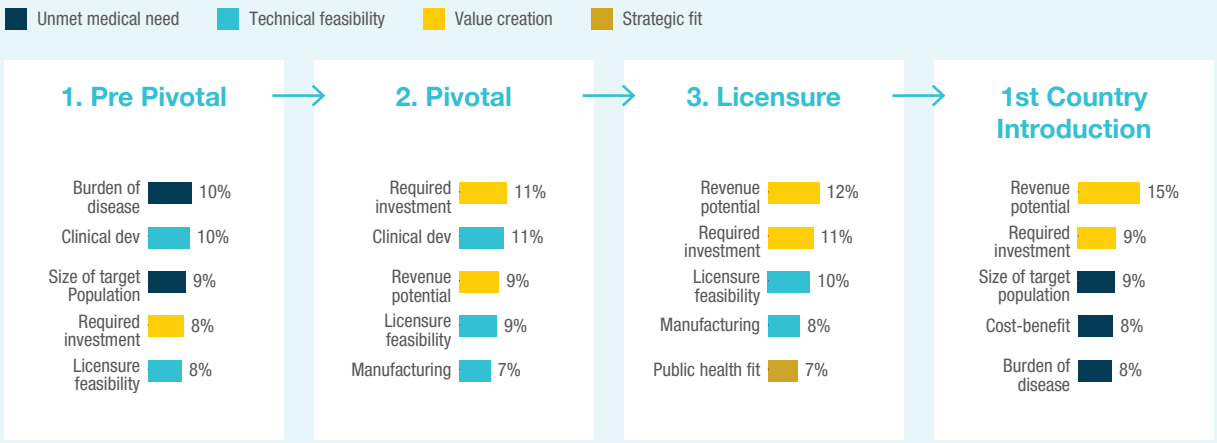


Figure 1 displays the most important factors during each phase of development.

Other factors can and do play an influential role on decisions depending on the specific disease, vaccine development programme characteristics and type of developers. Those above, however, are almost always considered when decisions are taken.

Priority challenges and current efforts to address them

A multitude of challenges cause developers to stop progressing candidates from Phase 2 clinical development through licensure and to first country introductions. This research identified 54 challenges within the following key categories: regulatory, clinical, manufacturing, market and policy, financial outcomes. These challenges vary in terms of their hypothetical impact in cost, time and public health relevance. From the standpoint of the vaccine developer, decisions are influenced by the estimated time and cost of overcoming the challenges and by the strategic fit of specific vaccine candidates in their portfolio. As a consequence, some challenges are more important to developers than others; the research prioritised 16 challenges based on time, cost and public health measures (Figure 2).

Figure 2: Sixteen priority challenges

Regulatory

- Lack of correlates
- Lack of support for alternative clinical pathways
- Few capable NRAs
- Limited regulatory harmonisation

Manufacturing

- Production processes not shareable
- Long manufacturing lead time
- Lack of technology transfer partners

Market & Policy

- Insufficient public budgets
- Lack of data for assessing impact
- Lack of use of appropriate economic models

Financial outcomes

- Opportunity costs outweigh vaccine's economic rationale
- Pricing pressure discourages innovation
- Lack of partners to commercialise vaccine
- Insufficient funds for late-stage development
- Manufacturing investments to be done at risk
- Available incentives not sufficiently attractive

Regulatory challenges

With the transition into Phase 2 clinical development, the focus of regulatory activities turns towards proving the efficacy and safety of the vaccine as necessary for licensure. Among the several challenges encountered in this phase, the **lack of recognised surrogates or correlates of efficacy** and **lack of support from regulators for alternative clinical pathways** are especially impactful. As a result of these challenges, clinical trials to achieve licensure may become prohibitively large and expensive, disincentivising developers from continuing. Ultimately it is up to the developer and regulator to agree on a path forward for each vaccine, but several initiatives, such as the Human Vaccines Project, are engaged in scientific discovery and new ways to conduct data analysis to advance the identification of surrogates and improve clinical trial efficiency. Expanding these efforts with participation, input and guidance from experienced regulators might produce significant medium-term breakthroughs in development speed and efficiency.

Advances in regulatory science, typically made by experienced vaccine regulators, are not always matched or applied by regulators with less experience. This results in a situation where **too few national regulatory authorities (NRAs) are able to efficiently and flexibly regulate the primary licensure of a novel vaccine**. An additional complication is the **lack of harmonisation on the requirements for quality, efficacy, labelling, packaging and safety of biologicals and diagnostics** across NRAs. The dearth of regulators able to oversee an efficient and effective regulatory strategy and guide developers through the regulatory process, constrains developers, in particular those with less experienced and knowledgeable regulatory staff. This greatly influences the geographies where development of novel vaccines occurs. Primary licensure of a vaccine with global demand is just the starting point – licensing in nearly 200 countries whose requirements may carry bespoke components adds costs for developers and extends the time to access of vaccines in many countries. The World Health Organization (WHO) and several experienced regulators have partnered with less-experienced regulators for capacity building, and there are some frameworks for improving harmonisation, mutual recognition or employing centralised procedures such as the European Medicines Agency (EMA). However, pursued in the typical fashion, these efforts

will likely take decades to yield substantial results. Nearer-term solutions, particularly regarding harmonisation and mutual recognition, are possible and would substantially improve access to licensed vaccines in additional countries.

Manufacturing challenges

The ability to establish commercial-scale vaccine manufacturing efficiently and expediently is influenced strongly by developers' **lack of possibility to share production processes and/or facilities** and by the **long lead-time for establishing manufacturing capacity**. In most cases, investments to build a dedicated manufacturing facility or production suite at the scale needed to satisfy projected demand are made prior to Phase 3 clinical development. These investments can take up to five years to complete and have little to no utility if the final clinical phase is not successful. These challenges have traditionally been driven by the unique nature of the manufacturing process for each vaccine and, consequently, the need for a custom-built manufacturing facility. Platform vaccines (e.g. viral vectors, messenger Ribonucleic Acid (mRNA)) could potentially change this paradigm for at least a portion of vaccines by enabling commonalities in manufacturing processes and facilities. Absent this paradigm shift, common manufacturing facilities have been funded in a few instances by governments to proactively address the need for developer investments and advanced planning. These solutions have been relatively recently established, have not yet proven their utility and are unlikely to deliver game-changing solutions at least in the short-term. Shifting to platform manufacturing techniques and multi-purpose manufacturing facility designs are innovative solutions that may see results over the coming decade. Investments in early science that would improve manufacturing or process design for future vaccines could spur impact in this area.

Developers unable or unwilling to establish manufacturing capacity for vaccine candidates are often faced with the **lack of partners available and capable of receiving a technology transfer**. Finding partners is often very difficult. Although early to mid-stage vaccine development is conducted by a large number of organisations, far fewer are capable of manufacturing a licensed vaccine, in particular any using more innovative technologies. The inability of smaller developers to identify potential partners generally leads to abandonment of some promising vaccine candidates. Initiatives to expand the number of manufacturers through targeted technology transfer coupled with technical assistance have been successful for influenza, polio and cholera vaccines. Each of those initiatives was disease-specific, but the concept could be expanded to a broader effort for vaccines where global supply, not market uncertainty, slows access. Existing organisations, such as the International Vaccines Institute (IVI) and manufacturers' associations, could engage in a broader platform of technology transfer and partnering.

Market and policy challenges

The demand for vaccines is most often driven by public health needs that may encounter **insufficient public budgets for purchase and implementation of immunisation programmes**. Immunisation budgets reflect both the general state of a country's public finances (ability to pay) and decision makers' political will to invest in immunisation (willingness to pay). Uncertainty about country willingness to fund immunisation is the source of considerable risk on the part of developers who sell vaccines. Public health bodies such as WHO make recommendations regarding which vaccines should be introduced by countries, influencing country decisions and budget allocations. Initiatives such as the Sabin Institute Sustainable Immunisation Financing programme assists countries in public budgeting for immunisation. Developers often advocate directly with countries for specific vaccines. Ultimately, however, countries' public health finances will dictate whether they choose to initiate and maintain vaccination programmes. There remains a gap in using data-informed and evidence-based advocacy for increasing and sustaining public health budget allocations for vaccination programmes.

Partially driving the uncertainty of demand is the **uncertainty of policy recommendations and lack of data for assessing potential impact of**

vaccination in target populations and **the lack of appropriate models for economic valuation globally or in certain countries**. Without a solid evidence base to demonstrate disease burden and potential impact of vaccination, or a commonly accepted method for valuing the economic benefits of immunisation, advocacy for greater public spending on vaccination programmes is more difficult. Measuring global disease burden is a daunting task, but several initiatives funded by supranational organisations have made, and are making, progress. There has been relatively less effort in translating those data into models of potential economic benefit to countries and gaining a broad agreement on the principles for doing so. Neither developers nor individual countries are appropriate leaders of this effort. As the world's normative institution for health, WHO is the logical entity to undertake this effort but lacks capacity to do so alone. By collaborating with external experts, progress could be seen in relatively short time in this important area.

Financial outcome challenges

The financial dimension is the source of some of the most fundamental challenges. Financial realities of both developers and purchasers of vaccines force considerations of whether the **opportunity cost outweighs the vaccine's economic rationale**. Developers' internal prioritisation focuses resources toward more profitable products (e.g. oncology treatments or chronic condition medications) at the expense of vaccines. **Pricing pressure may discourage innovation for improvements** to existing vaccines. Smaller developers or academic institutions in particular may face **limited availability of aligned partners to commercialise vaccines**. The absence of sufficient financial incentives and rewards for vaccine developers is an oft-cited challenge for the category of vaccines in-scope for this analysis and has been recognised by initiatives and stakeholders such as Wellcome Trust and the Bill and Melinda Gates Foundation (BMGF), which all provide push funding.

The long time-horizon of vaccine development and investments creates a particular challenge of having **insufficient access to funds for late-stage development** – the most expensive development stage – because of the high-risk and long-time lag prior to return from any investment. The nature of vaccine manufacturing and the **need to make expensive manufacturing investments prior to clinical success or demand certainty** exacerbates the funding gaps. Because **available incentives (e.g. pull mechanisms) are insufficiently attractive for developers**, technically possible vaccines are not being developed due to economic constraints. Governments and foundations have financially supported many disease-specific initiatives through both funding and incentives, and several governments are now addressing manufacturing investment needs. Despite these efforts, securing private capital lags behind, particularly in some of the countries where emerging vaccine developers are located, owing to an overall knowledge gap among private investors and to the insufficient development of the private financing market.

The predominance of the priority challenges linking to market and policy and financial outcome challenges, is in part, a natural consequence of examining vaccines in Phase 2 development or beyond. At this development stage, many of the fundamental scientific and technical questions have been resolved or accepted and the focus of activity (and challenges) turns towards market economics where there is relative uncertainty of demand for vaccines. Vaccine demand is usually not characterised by incremental change but by large-step changes made either by nature (in the case of an outbreak) or national policy (in the case of a vaccination programme initiation).

Table 1: Cost, time, public health implications of each priority challenge

Challenge	Cost	Time	Public health
Lack of recognised surrogates or correlates of efficacy	●	●	◐
Lack of support for alternative clinical pathways	●	○	◐
Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*	◐	◐	●
Lack of harmonisation on requirements across NRAs*	●	◐	●
Lack of possibility to share production process and/or facilities*	●	◐	●
Long-lead time for establishing manufacturing capacity*	●	◐	●
Lack of partners available/capable of receiving technology transfer*	◐	◐	●
Insufficient public budgets for purchase and implementation of immunisation programmes	○	●	●
Lack of data for assessing potential impact of vaccination in particular in specific target populations	◐	●	○
Lack of use of appropriate models for economic valuation globally or in certain countries*	○	○	●
Opportunity costs outweigh the vaccine's economic rationale	●	○	◐
Pricing pressure may discourage innovation for improvements*	●	○	●
Limited availability of aligned partners to commercialise vaccine*	○	◐	●
Insufficient access to funds for late-stage development*	○	●	●
Need to make expensive manufacturing investments prior to clinical success or demand certainty*	●	○	●
Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	●	○	●

Table 1 displays how solving each challenge would have implications on cost, time and public health impact. A full-circle ● indicates a large cost or time requirement, or bigger public health impact relative to a half-circle ◐ and an empty-circle ○ which indicate a smaller cost or time requirement, or a smaller public health impact. Achieving substantial improvements in the overall vaccine ecosystem will require targeting these priority challenges. Universal challenges (those that are associated with each in-scope disease) are denoted with an asterisk (*).

The potential to drive forward solutions

Various efforts are underway to address each of the 16 priority challenges, but all have proven, to varying degrees, insufficient to resolve them. The global immunisation community has been largely focused on designing solutions that could bring individual vaccines through late-stage development and first country introductions. Although this approach has yielded discrete successes, a more focused, synergistic and horizontal set of solutions is required to provide systemic, long-term benefits to the vaccine ecosystem.

Effective solutions should focus on bringing efficiencies to development including regulatory, clinical and manufacturing impediments – activities that could fundamentally result in a more predictable, less time-consuming and less costly development and licensure pathway for a variety of desired vaccines. Advances in regulatory science and manufacturing technology are occurring, but at a slow pace. They could be accelerated with a more concentrated effort to improve basic scientific understanding that engages the developers and regulators who are the main interlocutors for these challenges.

Solutions for the challenges related to economics and access are more complex in that they involve fundamental questions of political economy, markets and valuations of human life.

To address the priority challenges that have the highest impact on the vaccine ecosystem, Wellcome could focus on the areas emerging as having the potential to generate the highest and longest-lasting impact, in view of their systemic and cross-cutting nature (Figure 3). Specific tactics to support each strategy are provided in Chapter 5 of this report.

With the goal to improve flexibility and/or reduce costs of meeting regulatory requirements to enable licensure and initial use, maximum impact on reducing cost and risk is possible through strategies focused on regulatory challenges by increasing scientific understanding and **modernising the approach to demonstrating efficacy and safety of vaccines for licensure.** Improving access to vaccines and lowering costs for both developers and purchasers can be aided through **enhancing regulatory harmonisation** and **promoting regulatory centralisation** among countries.

Improving flexibility and/or reduction of costs of manufacturing the vaccine to the right standard and volume can be achieved by **enhancing manufacturing innovations** that can bring time or cost efficiencies to manufacturing and **expanding the manufacturing base to** allow for more entities able to complete, directly or with partner support, late-stage vaccine development.

Positively impacting the predictability of the market and the likelihood of the policy support for use can be achieved with a set of wide-ranging solutions, starting from the foundation of **promotion of evidence-based decision making** by policymakers. Other solutions focus on countries as the ultimate financers of vaccines including specific targeted work to increase access by **increasing country fiscal space for immunisation (ability to pay)** and **increasing awareness of the full value of vaccination (willingness to pay).** Finally, a multi-stakeholder strategy to **increase demand predictability** could directly affect developer economics and risks.

Figure 3: A potential strategy for Wellcome to implement

Impactfully address the sustainability of the vaccine ecosystem to ensure that promising vaccine candidates progress into use

Improve feasibility and/or reduce costs of meeting regulatory requirements to enable licensure and initial use

- Modernise approach to demonstrating efficacy and safety of vaccines for licensure
- Enhance regulatory harmonisation
- Promote regulatory centralisation

Improve feasibility and/or reduce costs of testing under current clinical trial requirements

- Implement strategies before transition into Phase 2

Improve feasibility and/or reduce costs of manufacturing the vaccine to the right standard and volume

- Enhance manufacturing innovations
- Expand the manufacturing base

Positively impact the predictability of the market and the likelihood of policy support for use

- Promote evidence-based decision making
- Increase country fiscal space for immunisation/ ability to pay
- Increase awareness of the full value of vaccination/willingness to pay
- Increase demand predictability

Improve feasibility of recouping all costs, while still resulting in a vaccine deemed worthwhile by those funding procurement and delivery

- Promote the value of innovation
- Drive creation of new funding models
- Increase availability of partners for vaccine commercialisation

4 axes of action

Convene | Advocate | Fund | Incentivise

Lastly, improving the flexibility to recoup all costs while still resulting in vaccines deemed worthwhile by those funding procurement and delivery could benefit from solutions that aim at **promoting the value of innovation** to ensure that new technologies are adequately valued and funded. **Driving creation of new funding models** remains an area ripe for actions aimed at positively impact the economics of vaccine developers and **increasing the availability of partners for vaccine commercialisation** allows a more robust and competitive market to develop that does not sacrifice promising innovation.

Learnings resulting from the emerging changes being implemented across all categories of challenges as a result of the efforts for the development of SARS-CoV-2 vaccines should be examined and leveraged. While some early lessons can be gleaned now, the final outcomes of ongoing vaccine development and deployment should be observed prior to drawing any conclusions. Some lessons and advances arising from the development of a vaccine to address a global pandemic may not apply to diseases of lesser consequence and should be kept in perspective.

Conclusion

Vaccines are recognised as one of the most cost-effective public health interventions. However, a large number of scientifically possible candidates are not progressing beyond Phase 2 clinical development because of systemic constraints that prevent or retard their development. Those challenges are not insurmountable, but successfully addressing them will demand focused attention on their root causes and radical change in perspective and priorities. Fashioning a more efficient, effective and equitable vaccine ecosystem will require focusing on systemic solutions that go beyond functional, disease/product and organisational boundaries and interests. This will require interrogating established and entrenched wisdoms.

This research presents a number of strategies and detailed tactics that can provide the foundation for a broad and systemic reform agenda for the global vaccine ecosystem. Leveraging the sense of urgency instilled by the SARS-CoV-2 pandemic, this reformation could have the potential of addressing long-standing challenges that have hampered the vaccine ecosystem for decades.

Project background

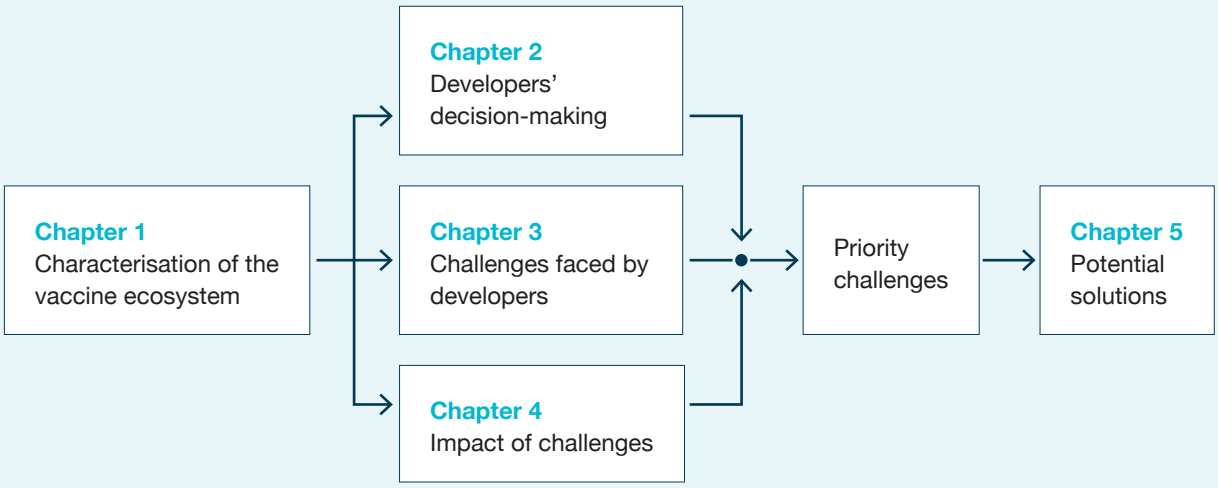
The Wellcome Trust wants to ensure that the vaccine ecosystem is effective in supporting the development of new vaccines and the improvement of existing ones. The focus of this project is on vaccines that prevent disease epidemics, for diseases that predominantly affect low-income settings and those that may help prevent diseases linked to antimicrobial resistance (AMR).

By analysing available evidence, consulting subject matter experts and gathering insights, this project identified areas where focused interventions may improve the vaccine development ecosystem. The project undertaken by MMGH Consulting (MMGH) was structured in four work packages (WPs): characterisation of the vaccine ecosystem, analysis of vaccine developer decision-making, prioritisation of universal challenges and identification of solutions.

This research investigated the following questions:

1. How do developers make decisions to continue or discontinue vaccine development?
    - When are decisions made and what triggers the need for a decision?
    - Which are the most influential factors?
    - How do the factors change over time?
    - How are the factors different by type of developer?
2. What are the most relevant challenges that create barriers (i.e. gaps, blockages and hurdles) to the late-stage development, licensure and initial use of vaccine candidates?
    - What are the root causes of those challenges?
    - Which type of developer is most affected by each challenge?
    - Which vaccines or vaccine archetypes are affected by each challenge; which challenges effect all vaccines and are universal?
    - What is the cost/value in time and/or money of each identified challenge?
    - How do the challenges effect influential factors in continuing or discontinuing development of vaccines of interest?
    - Which challenges/factors are most relevant in slowing/ending development of vaccines of interest?
3. Which are the priority challenges that, if addressed, could significantly improve the ecosystem for development of vaccines of interest?
4. What are the currently ongoing solutions to these prioritised challenges?
5. Which prioritised challenges require additional solutions?

Figure 4: Structure of research report



Research approach

MMGH employed a mixed-methods research approach that allowed full use of both qualitative and quantitative insights to gain a deeper understanding of the overall vaccine ecosystem, of critical stakeholders' motivations and constraints and of recommendations for interventions.

The analysis was done in four work packages (WP) that included a characterisation of the vaccine ecosystem and initial identification of challenges (WP1/Chapter 1), an exploration of developer decision-making (WP2/Chapter 2), a validation and prioritisation of challenges (WP3/Chapter 3 and 4) and, finally, identification of potential solutions (WP4/Chapter 5) (Figure 4).

The first step of the research focused on the definition and description of the vaccine ecosystem (i.e. the description of the in-scope diseases and vaccines, trends emerging from the development of these vaccines, and the preliminary definition of vaccine archetypes). Next, the decision-making processes and influences on vaccine developers were mapped, providing important context to both the challenges and potential solutions. The full characterisation of challenges included the definition of their root causes, the description of what would be required for developers to surmount the challenge and the degree of universality of the challenge. Challenges were quantified on the basis of the financial and time impact for the developer if they were to persist in development and overcome the challenge as well as the public health impact. Challenges were then narrowed down to 16 prioritised challenges. The priority challenges were validated by evaluating their relationship with the most impactful factors in developer decision-making (as identified in an online survey of developers), case studies and expert advisor input. Finally, current attempts at solving the 16 priority challenges and the organisations engaged in solving them were described and an evaluation was conducted to determine the level of unmet need of each challenge. Additional information on methodology follows in the next section, and detailed methodology for each element of the research is available in the Annex.

Methodology overview

A systematic literature review was conducted to identify and initially characterise vaccines and vaccine candidates of relevance to this project and to identify preliminary challenges. Quantitative data points for each vaccine in scope were collected and analysed, encompassing development times and costs, and any technical failures (e.g. clinical trial endpoints not being met). An Expert Advisors Group (EAG) provided feedback and validation of the preliminary findings.

Decisions faced by various types of developers were gleaned from the literature review. Events that trigger development decisions, factors influencing decisions and how those factors change during the course of development were collected from a survey primarily targeting current and former vaccine developers and analysed. In addition, the range of decision outcomes and how the influences change with different types of

developers were also analysed with input from the EAG. This survey was conducted in March - April 2020.

These findings were then translated into four fictional case studies encompassing four preliminary vaccine archetypes. The case studies explored how four types of developers would confront decisions regarding one of these vaccine archetypes. The case studies were simulated with the EAG to contribute to the hypothesised challenges and archetypes and the selection of priority challenges.

Challenges facing vaccine developers were organised into five categories based on the research areas indicated by Wellcome and further subdivided by topic. For each challenge, root causes were identified and costs in money and time to developers of addressing these challenges were estimated. In addition, challenges were enumerated across vaccines and within a refined set of archetypes. Based on that information, a subset of priority challenges was selected.

Finally, ongoing activities aimed at addressing the priority challenges were identified. For each one, the level of success was assessed to highlight areas of unmet need. This final step of the analysis was complemented with the addition of potential additional interventions, including disruptive ones, to serve as a base for prioritisation of potential target solutions.

Expert guidance

Throughout the analysis, an EAG advised Wellcome and MMGH on the project content. The EAG represented a diverse range of expertise and affiliations, and all have experience in leadership or decision-making with an organisation funding or undertaking vaccine development. EAG members were:

David Bloom	Professor of Economics and Demography in the Department of Global Health and Population at the Harvard T.H. Chan School of Public Health
Tim Cooke	Chief Executive Officer, NovaDigm Therapeutics
Mahima Datla	Managing Director, Biological E Limited
Priscilla Ferraz-Soares	Deputy Director of Management and Market, Bio-Manguinhos/ Fiocruz
Frederick Kristensen	Deputy CEO, Coalition for Epidemic Preparedness Innovations (CEPI)
Helen Mao	Co-founder and senior vice president, CanSino Bio
Allan Saul	Former Director of the GlaxoSmithKline (GSK) Vaccines Institute for Global Health
Greg Widmyer	Director, Integrated Delivery, Bill & Melinda Gates Foundation (BMGF)

Limitations

This report is subject to a number of limitations inherent to this type of research. Limitations differed slightly across the four work packages, with some common elements:

- Systematic literature reviews (WP 1 and 2): Reliance on peer-reviewed literature carries the risk of introducing multiple sorts bias [1] (well documented in the literature itself) and grey literature may be of varying quality [2], especially if it lacks external review.
- Quantitative analysis (WP 1, 2, 3): The quantitative analysis is subject to a number of limitations. Primary data in this field has a number of known limitations including: (a) the data of interest is generally considered confidential and most often not shared by developers; (b) it is not likely to be consistently and sufficiently robust (accurate, timely, complete); (c) a de novo collection of data typically requires very long duration to be completed; (d) not all the relevant insights are quantitative in nature (particularly those related to developers' decision-making process). Data on development failures are often unpublished (publication bias); when published, the data may be incomplete (owing to sample or observation bias or merely the imperative to hold what may be proprietary information in confidence) and, finally, for available data, the level of detail required for the analyses to be significant may reduce sample size to levels that are not amenable to in-depth quantitative analyses.
- Online survey (WP2): The survey created for this research was not a validated tool and may be subject to unknown biases. Additionally, the survey population was not a random sample and conclusions are subject to response bias. In general, online survey respondents are less likely to remain engaged if the survey lasts more than 10 minutes, and this survey required an estimated 30 minutes to complete. Finally, the survey was administered in March - April 2020, and it subject to the external effects of the COVID-19 pandemic affecting the number of responses, the type of respondents and the content of their responses.
- Expert judgement (WP 1, 2, 3, 4): Both the EAG (described above) as well as the MMGH team (see Annex for profiles) are composed of individuals with years of experience in the field of vaccine research, development and deployment. The shared and unique experiences of these experts are subject to various biases, most notably confirmation bias.
- Case studies (WP 3) and Wellcome staff workshops (WP 4): MMGH constructed and presented to the EAG case studies representing challenges confronted by specific types of developers for particular vaccines. The EAG was asked to role-play vaccine developers in order to shed light on developer decision-making. In the context of this report, this qualitative research element was important to further explicate survey findings and to shed additional light on the nuances of developer decision-making. Nonetheless, it is inherently artificial and, as a study tool, should be considered primarily as a validation device rather than stand-alone research. Similarly, the internal workshops conducted with Wellcome staff cannot be considered research per se, though they were useful for informing the content of the solutions section of this report.

Chapter 1: Characterisation of the vaccine ecosystem

Vaccine developers operate in a complex ecosystem in which the majority of development programmes for EID, relevant for AMR and focused primarily on low-income countries face significant challenges and are not attracting sufficient attention.

Developers tend to prioritise diseases where the market opportunity is bigger – because of a higher global burden or of the risk of severe disease outcomes – and markets where the risk of development is smaller because vaccines can leverage existing technology.

To provide a factual foundation for the research, an analysis of the vaccine development ecosystem focused on the period 2009-2019. It enabled a selection of vaccines and diseases consistent with the scope of the research and provided valuable insights on the ecosystem dynamics. The resulting description of the ecosystem provides a framework for better understanding development challenges and potential solutions.

A systematic scan of all vaccine development at Phase 2 or later during the period 2009-2019 identified 61 vaccines in development. Focusing on diseases and potential vaccines for epidemic diseases, relevant for LIC or important for combatting AMR, 33 vaccines were identified as in-scope for the analysis. These vaccines provide the most representative set of data and examples relevant for the research and should be thought of as proxies for other diseases and vaccine candidates with similar characteristics. In contrast, vaccines for diseases that are not relevant for LIC, that have a primary market in high-income countries (HIC) or that are primarily targeted at biodefense were excluded. The distinction between vaccines in- and out-of-scope was sometimes blurred, and inclusion decisions were then made based on expert judgement. Whether a specific vaccine is in-scope does not indicate a lack of importance nor is it expected to change the directional or specific conclusions of the analysis.

The diseases and corresponding vaccines considered in- and out-of-scope for the analysis are presented in Table 2.

Table 2: Diseases and candidate vaccines in and out of scope for analysis

In-scope diseases/vaccines	Out-of-scope diseases/vaccines
Chikungunya	Anthrax
Cholera	Candidiasis
Clostridium difficile	Crimean-Congo haemorrhagic fever
Dengue	Cytomegalovirus
Ebola	Enterovirus A71
Enterotoxigenic Escherichia coli (E. coli) (ETEC)	Epstein-Barr Virus
Group A streptococcus (Group A strep)	Haemophilus influenza type b (Hib)
Group B streptococcus (Group B strep)	Hantaviruses
Hookworm	Hepatitis A/B/C
Human Papillomavirus (HPV)	Hepatitis E
Japanese encephalitis (JE)	Herpes Simplex type 2
Lassa fever	Human immunodeficiency virus (HIV)
Leishmaniasis	Human metapneumovirus (hMPV)
Malaria	Lyme borreliosis
Measles	Non-typeable Haemophilus influenzae
Meningococcal meningitis (monovalent C and multivalent)	Norovirus
Middle East Respiratory Syndrome (MERS)	Pandemic influenza
Nipah	Polio
Nontyphoidal Salmonella	Respiratory syncytial virus (RSV)
Plague	Ross River virus
Pseudomonas aeruginosa	Seasonal influenza

In-scope diseases/vaccines	Out-of-scope diseases/vaccines
Rabies	Smallpox
Rift Valley fever	Syphilis
Rotavirus	Tick-borne encephalitis
Salmonella paratyphi	Tularaemia
Salmonella typhi (typhoid)	Varicella
Schistosomiasis	Venezuelan equine encephalitis
Shigella	West Nile virus
Staphylococcus aureus (S. aureus)	Western equine encephalitis
Streptococcus. pneumoniae (S. pneumoniae)	Yellow fever
Tuberculosis (TB)	Zoster
Whole cell Pertussis	
Zika	

While the in-scope diseases form the basis of the analysis, a working hypothesis was developed that these diseases may cluster into “archetypes” or groups of diseases and vaccines that share a large majority of challenges and thus could benefit from similar solution sets. An initial hypothesis for the diseases and vaccines identified four archetypes: emerging infectious diseases with epidemic potential (EID); diseases with a relevance to anti-microbial resistance (AMR) risk, neglected diseases (ND) and improved vaccines – i.e. those whose development targets the enhancement of an existing product. For more detail on archetypes please see Chapter 4.

Quantitative analysis of ecosystem

A quantitative analysis revealed that the majority of vaccines targeting neglected diseases and diseases related to AMR were characterised by the presence of few developers and by a small number of late-stage clinical trials. Conversely, “improved’ vaccines” were characterised by a higher number of developers and a higher number of late-stage clinical trials. A few vaccines that could be considered in the EID and AMR archetype differed from this general rule and clustered with TB and malaria in an intermediate space where there were several developers but slow progress into late-stage clinical development (Figure 5). For details on the methods and sources, refer to the Annex.

Further analysis to determine which disease characteristics are associated with the presence of a larger number of developers for a particular vaccine showed some relationship with the vaccine’s potential market value and with the level of development risk.

Figure 5: Relative status of vaccine development for in-scope vaccines (as of 2019)

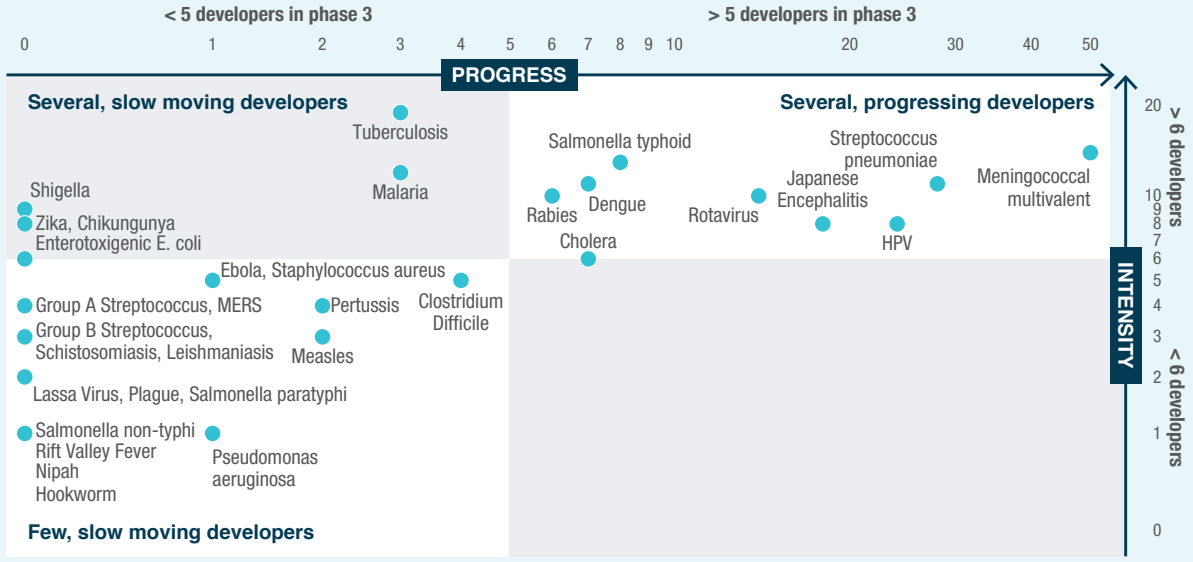


Figure 6: Relationship between market value and the number of developers

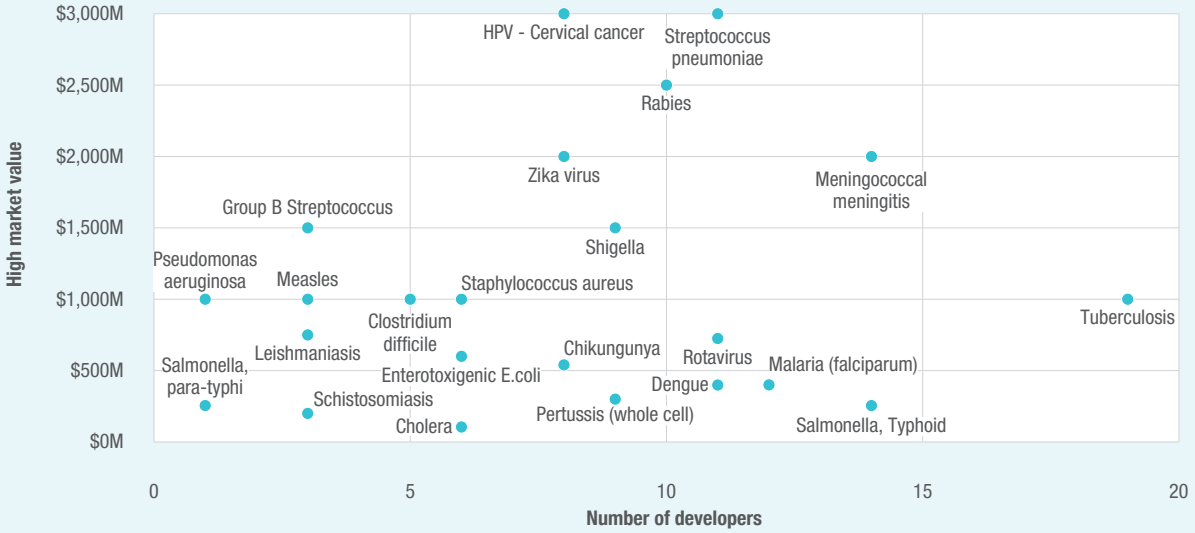
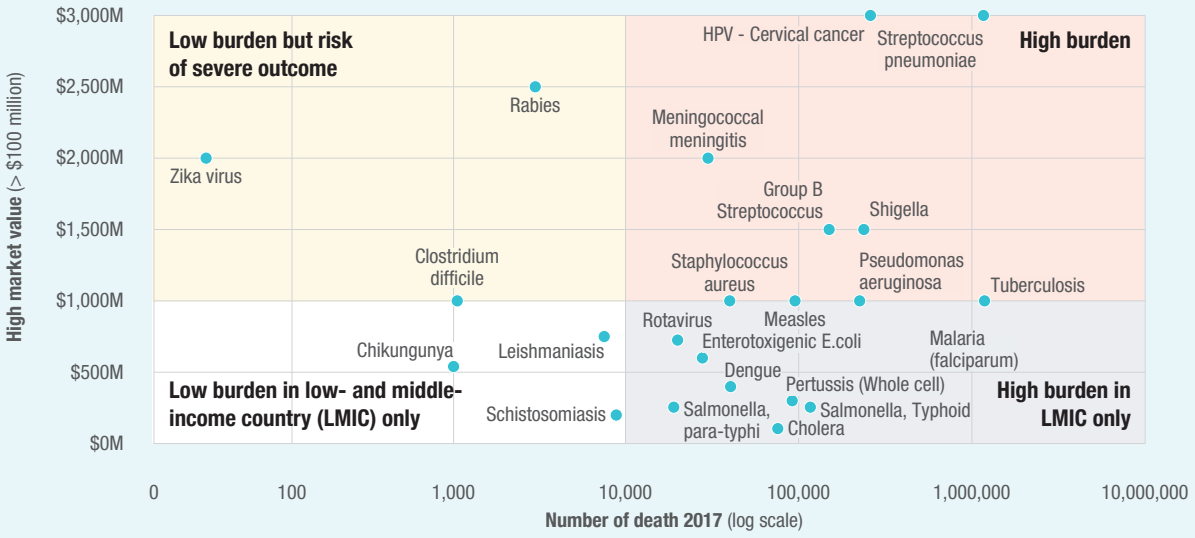


Figure 7: Clustering of vaccines by burden of disease and income level

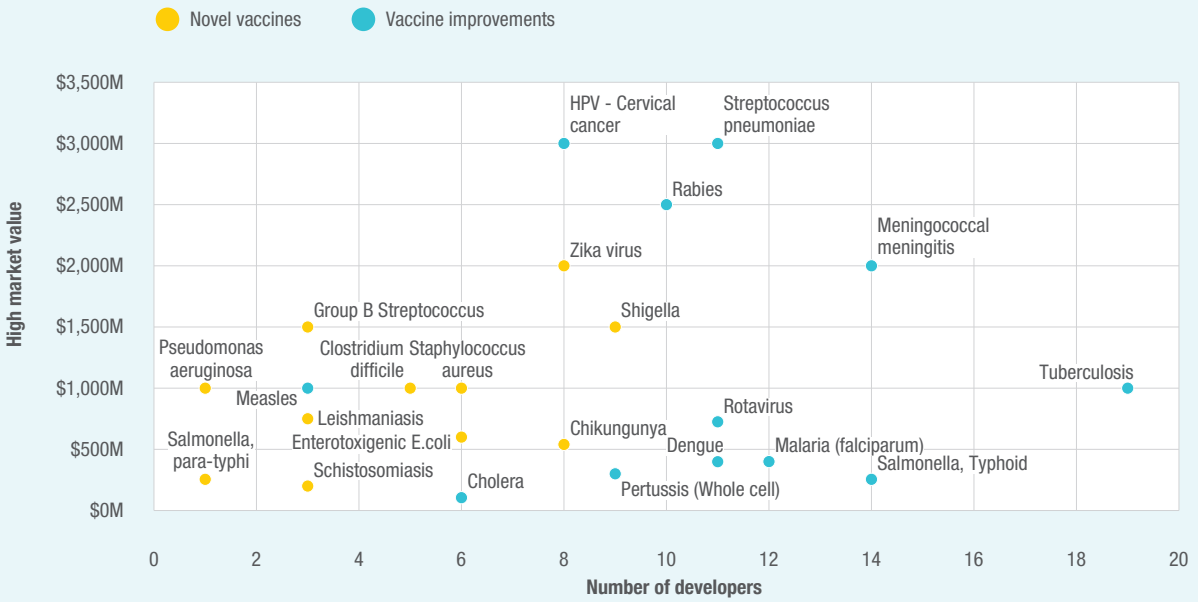


For 24 of the 33 in-scope diseases and associated vaccines with estimated market values over 100 million USD per year, the relationship between market value and the number of developers showed a weak correlation (r=0.31) between the two variables indicating a moderate preference from developers for markets with a higher value (Figure 6).

Market value was found to be higher for vaccines against diseases with a high global burden of deaths compared to diseases where the burden, even if large, was concentrated in low- and middle-income country (LMIC) settings. Low-burden diseases that carry the risk of severe outcomes also tended to have high market value similarly to higher burden global diseases (Figure 7).

Lastly, given that most in-scope vaccines have relatively low market values, the level of development risk – as defined by a technology that has been proven (and approved by a regulator) and by the existence of an established market – emerged as a critical influencing factor. Having low development risk through both a proven technology and an established market appeared to attract more developers, regardless of market value (Figure 8).

Figure 8: Clustering of vaccines by degree of development risk



Chapter 2: Developer decision-making

Decisions concerning vaccine development programmes are triggered by many internal and external events and influenced by various factors whose importance evolves over time. The factors have different influence depending on the type of developer.

Events triggering vaccine development decisions

Understanding the timing and factors that influence developers' decisions on whether to continue vaccine development provides insights into the timepoints and reasons behind their decisions to delay or stop development. Based on this knowledge, the challenges that are more frequently associated with these decisions can be identified and prioritised.

Throughout the phases of vaccine development between transition into Phase 2 and introduction in the first countries, decisions can be triggered by a variety of events resulting from forces and events internal or external to the vaccine developer.

Internal events

Ongoing/planned

Results from clinical trials are the most typical and important events triggering project reviews and decisions. Scheduled reviews such as annual or bi-annual scientific- or business-focused project and portfolio reviews are also particularly relevant in the case of large manufacturers where projects have spill-over effects on other projects in the portfolio, resulting in comprehensive portfolio reviews.

Ad-hoc events

Corporate events such as leadership changes can result in the need for new decisions or reconsideration of existing ones. The selection of partners, including Clinical Research Organisations (CROs), Contract Manufacturing Organisations (CMOs) and financing partners can also require decisions. Internally or externally initiated business development opportunities (e.g. the acquisition of a product in development, a merger with another developer, a technology transfer) can also force a decision on development. Finally, unplanned events during a clinical trial (e.g. significant recruitment delays) may require immediate intervention and development decisions.

External events

Push events stemming from shifts in the environment or pull events intended to influence vaccine development are also important decision triggers.

Pushes

Disease outbreaks are one of the most impactful events that can trigger vaccine development decisions. Similarly, pressure from stakeholders and/or the media may push vaccine developers to act in response to a specific event (e.g. an emerging safety concern, supply shortages). New opportunities for financing vaccine development can also push developers into decisions.

Mergers, acquisitions or changes with competitors' vaccines development pipelines may cause a re-evaluation of a development programme and new decisions. Scientific advances can also open an unexpected "window of opportunity" that require new decisions. Lastly, changes in regulatory policies that increase or reduce friction in the system can trigger the need for new decisions.

Pulls

The availability of new financial incentives (e.g. Advance Market Commitments, priority review vouchers) normally triggers a re-evaluation of current development programmes. Non-financial pull factors can include a recommendation for vaccine use by WHO or prioritisation in the Gavi Vaccine Investment Strategy.

Factors influencing vaccine development decisions

The factors, criteria and data that influence vaccine developer decisions at different points in the development cycle can be looked at in many ways. One way is to look at the progression in vaccine development via the periodically repeated question, “Are we ready to move to the next phase?”. This approach sees the development process as primarily linear and posits that minimum criteria for progression can be defined across the different phases.

An alternative way is to extend the perspective beyond the question whether the project is ready to move to the next phase but also whether the project should move to the next phase. This second approach was used as a baseline for the survey conducted during March/April 2020 and the resulting analysis of the factors influencing developer decisions. Survey respondents were asked to weight the importance of each sub-factor within the category by allocating 100 points per category. Across the different phases of clinical development from Phase 2 to early commercialisation, the four categories ranked as follow: value creation, technical feasibility, unmet medical need and strategic fit.

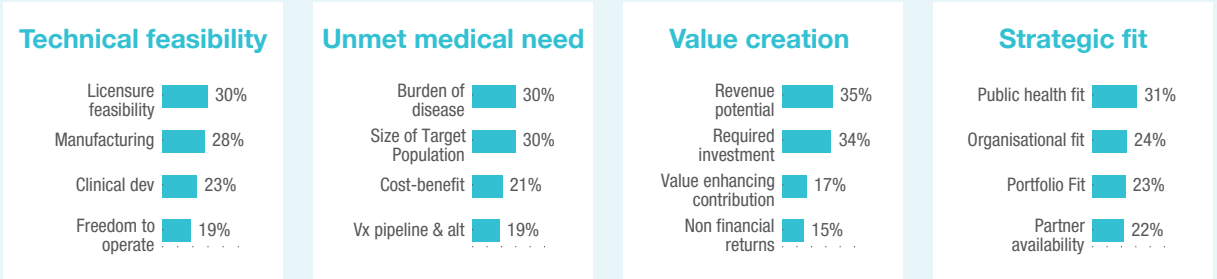
Figure 9 describes the relative importance of each sub-factor within each category. The size of the box refers to the level of influence of each area.

Technical feasibility

The technical feasibility of vaccine development is most influenced by:

- Licensure feasibility – The requirements of the reference regulatory authority is perceived as the most important factor (more than 95% of survey responders rated this factor as very important or important) followed by the selection and sequencing of countries where the vaccine will be licensed in the first years (80% of survey responders rated this factor as very important or important).
- Manufacturing process characteristics – Almost all manufacturing-related factors have significant influence on vaccine development progression. Scalability of the manufacturing process was identified as the most critical factor (more than 90% of survey responders rated this factor as very important or

Figure 9: Relative importance of each sub-factor within each category



important). Quality control requirements, as covered in the broader area of CMC (chemistry, manufacturing and controls) represent a large component of the manufacturing area and, as such, is a very important factor (more than 85% of survey responders rated this factor as very important or important). The complexity of the manufacturing as a result of the technology involved, the required size of the manufacturing facility, and the vaccine design also bear a significant influence on developers' decisions (80% of survey responders rated this factor as very important or important).

- Clinical development feasibility – The development probability of success was identified as the most influential factor (more than 90% of survey responders rated this factor as very important or important) followed by the emerging safety profile of the vaccine as assessed from clinical trials (more than 90% of survey responders rated this factor as very important or important). Thirdly, the expected size and difficulty of the pivotal trial/s play an important role (more than 85% of survey responders rated this factor as very important or important). This last factor is a direct consequence of the disease epidemiology, the target geographies, the design of the clinical trials and the position of the reference regulatory authority.
- Freedom to operate – The ability to access all intellectual property (IP) required for development, whether through ownership or licensing arrangements is important. Having an overall freedom to operate [3][1] significantly influences decisions, in particular in the early phases of vaccine development (more than 85% of survey responders rated those factors as very important or important).

Unmet medical need

The most significant factors related to unmet medical need that influence vaccine development decisions are:

- Size of the target population – used as a measure of the magnitude of the problem. The size of the target population as defined by epidemiological parameters was identified as the key reference point for vaccine development decisions (90% of survey responders rated this factor as very important or important).
- Burden of disease – used as a measure of the relevance of the medical need in the population. Mortality and morbidity emerged as the most relevant indicators (more than 85% of survey responders rated those factors as very important or important) influencing vaccine developers' decisions. Periodicity and frequency of a disease is also considered a relevant influencing factor while Disability-Adjusted Life Years (DALY) and probability of outbreak occurrence are seen as the least important.
- Cost-benefit – used to value different interventions addressing unmet medical needs. The perceived importance of the disease by policy makers – not the actual evaluation of benefits to costs – emerged as the most important factor (more than 80% of survey responders rated this factor as very important or important). This is a reflection of the fact that policy makers' decisions are generally based on a broader set of factors not limited to pure quantitative assessment. Strong evidence of cost-effectiveness is also seen as influencing vaccine development decisions (more than 75% of survey responders rated this factor as very important or important).
- Vaccine pipeline and alternative treatments – used as a proxy for how much of the medical need is truly unmet. The existence of a rich

1. Freedom to operate is intended as "the ability of a Company to develop, make, and market products without legal liabilities to third parties (e.g. other patent holders)"

pipeline of vaccines provides the most important indicator (65% of survey responders rated this factor as very important or important) and also measures the perceived level of direct competition. Existence of other health interventions – both preventive and therapeutic – are also seen as relevant influencing factors, albeit with a lower influence.

Although all factors can be assessed individually, the influence of the unmet medical needs generally results from a consolidated view that takes into account all factors and their mutual relationship.

Value creation potential

Most developers of late-stage vaccines are influenced by elements of value creation potential including:

- Revenue potential – or the expected cash inflow generated from the commercialisation of the vaccine. Time to licensure emerged as the most influential factor (70% of survey responders rated this factor as very important or important). The likelihood of a recommendation for vaccine use at global level increased the revenue certainty (67% of survey responders rated this factor as very important or important). Finally, willingness and ability to pay at country level has the potential to move the decision forward within the development programme (67% of survey responders rated this factor as very important or important).
- Required investment – or the expected cash outflow for development. As a reflection of their magnitude, investments for clinical development and manufacturing setup are the factors most influential on vaccine developers' decisions (respectively more than 90% and more than 85% of survey responders rated these factors as very important or important).
- Value enhancing contribution – The availability of internal funds is considered the most important factor influencing decisions (70% of survey responders rated this factor as very important or important). The opportunity for accessing grant funding can also influence vaccine developers' decisions by reducing the developers' financial needs (more than 55% of survey responders rated this factor as very important or important).
- Non-financial returns – Societal and reputational impact both have significant influence on decisions depending on individual companies' positions and strategies (80% of survey responders rated this factor as very important or important).

Strategic fit

Strategic fit in the developer and broader public health space also influences decisions, including:

- Public health fit – the existence of strong support from key global health stakeholders has a large influence on decisions (more than 85% of survey responders rated this factor as very important or important). Similar influence is attributed to the existence of a clear WHO position (more than 75% of survey responders rated this factor as very important or important). The presence of strong, disease-specific opinion leaders and advocates can also influence decisions by supporting clinical trials and influencing policy decisions at all levels (67% of survey responders rated this factor as very important or important).
- Organisational fit – factors that align with the developers' strategy and priorities. The existence of a strong internal champion has a strong influence on decisions and their outcomes (70% of survey responders rated this factor as very important or important). Similarly, alignment of the development programme with the priorities of important stakeholder groups influential in the board of the developer was also deemed important (67% of survey responders rated this factor as very important or important).

- Portfolio fit – product-specific factors also influence vaccine development decisions. The existence of a vaccine "platform" potential can influence the outcome of vaccine development decisions (80% of survey responders rated this factor as very important or important) (e.g. more than one vaccine using similar technical approaches or targeting similar customers where there are synergies).
- Partner availability – a number of partners are used to perform vaccine development activities. Among these the availability of a financial partner interested in sharing the financial burden of the development was indicated as the factor playing the most important role in vaccine development decisions (67% of all survey responders rated this factor as very important or important). Respondents representing companies with no licensed vaccines assigned a rating of very important or important to the availability of partners for: financing (62%), technology (50%) and manufacturing (42%); as opposed to respondents from companies with licensed vaccines whose comparative ratings were financing (36%), technology (36%) and manufacturing (27%).

Evolving importance of factors over time

Although the focus of this analysis is on influencing factors after Phase 2 clinical development, it is important to acknowledge that several decisions are taken before Phase 2. The decision-making process begins broadly and gets more detailed as it progresses, resulting in reconsideration of prior decisions or the need to repeat certain activities. It is not possible to have clarity on everything at the start: early decisions are based on highly uncertain data, with the understanding that new information will bring greater certainty. Data improvement is a process that never stops but gets more granular with time, thus providing more clarity on the potential benefits and risks to the developer.

In anomalous cases with an over-riding public health need or motivation to advance development quickly, decisions can be compressed and take place in parallel, thus diverging significantly from the typical process (e.g. COVID-19). This process divergence is paired with a necessary divergence from the relative importance and influence of factors influencing those decisions. Although certain external and technical factors (e.g. establishing a minimum safety profile) must still progress in a structured pattern, the importance and reliance on other internal factors (e.g. potential for value creation) may not be considered in the same way.

In this evolving environment, the standard sequence of vaccine development phases (2, 2a, 2b, 3) is becoming less delineated. Therefore, in this analysis a less strictly delimited sequence has been adopted and structured in the following four phases:

- pre-pivotal trials, including all the decisions taken through Phase 2;
- pivotal trials, covering the decisions taken at the transition and during Phase 3 clinical development;
- licensure, including all decisions taken after the completion of the pivotal trials leading into achievement of the first marketing authorisation;
- first country introduction, covering all decisions taken in preparation for the first country introductions.

The relative importance of the four areas of influencing factors changes considerably across the life cycle of vaccine development.

Figures 10 – 13 describe the changing influence over time, with size of the block, indicating the relative importance.

Figure 10: Factors influencing the decision-making process in the pre-pivotal phase[2]

Pre-Pivotal Trials – In the pre-pivotal trials, technical feasibility and unmet medical need are the most influential factors on vaccine developers' decisions. The focus on technical feasibility is primarily centred on the assessment of a viable clinical development pathway that will allow a reasonable chance of success in a time frame and with an investment consistent with the size of the business opportunity.

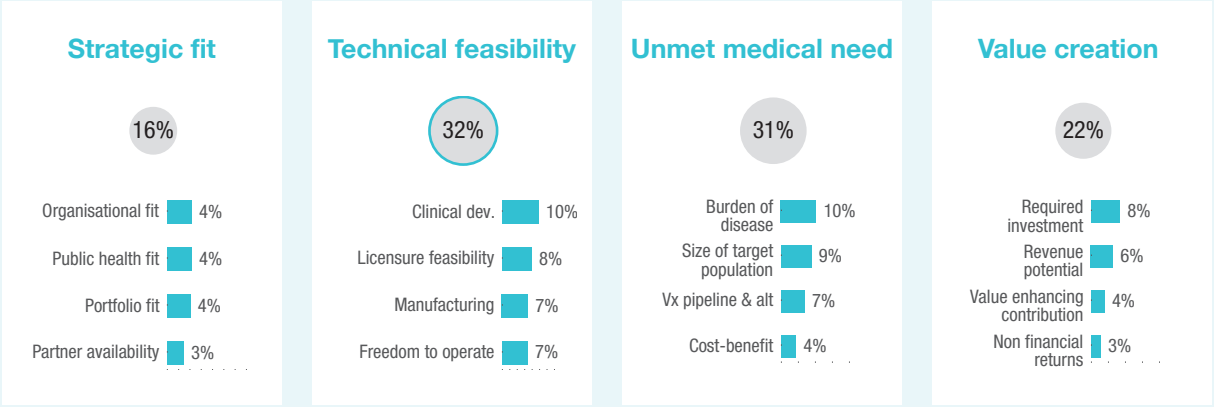
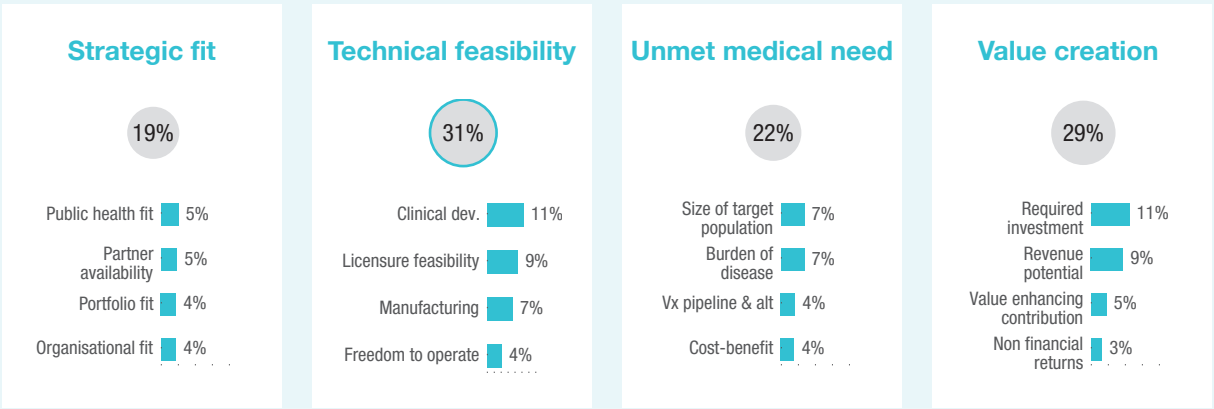


Figure 11: Factors influencing the decision-making process in the pivotal phase

Pivotal Trials – During this phase, factors with the strongest influence on the decisions remain substantially unchanged but their weights shift moving from unmet needs towards value creation potential. The most influential factors in this phase of clinical development are the feasibility of the clinical development and the viability of the regulatory pathway. Phase 3 trial design and location will largely have been determined but the selection of a trial location will be intimately linked to the ability to secure a capable principal investigator and sufficient infrastructure. The regulatory pathway during this phase will focus on timing the readiness of the manufacturing process with the proper execution of the clinical trials, as agreed with the reference agency and likely micro-negotiations with the agency on the manufacturing readiness aspects.



2. Methodological disclaimer: In order to measure the relative importance of each factor influencing decisions, the scores provided by the responders have been weighted based on the weight of the different thematic areas (technical feasibility; unmet medical need; value creation potential; and strategic fit) as determined by survey respondents. While a logical link exists between the score of the single factors and the score of the thematic area, the request to consider such a link while scoring was not made explicit in the survey and has been implemented on review of the results by the MMGH team.

Figure 12: Factors influencing the decision-making process in the licensure phase

Licensure – With the successful completion of the pivotal trial the focus of vaccine developers' decisions switches towards value creation potential. The revenue potential becomes the most influential factor followed by some remaining considerations on the investment required to complete clinical development, achieve licensure in all targeted geographies and prepare for the launches. In addition to the financial perspective, considerations about the regulatory steps required and key decisions about the utilisation of the installed manufacturing capacity also carry weight at this stage.

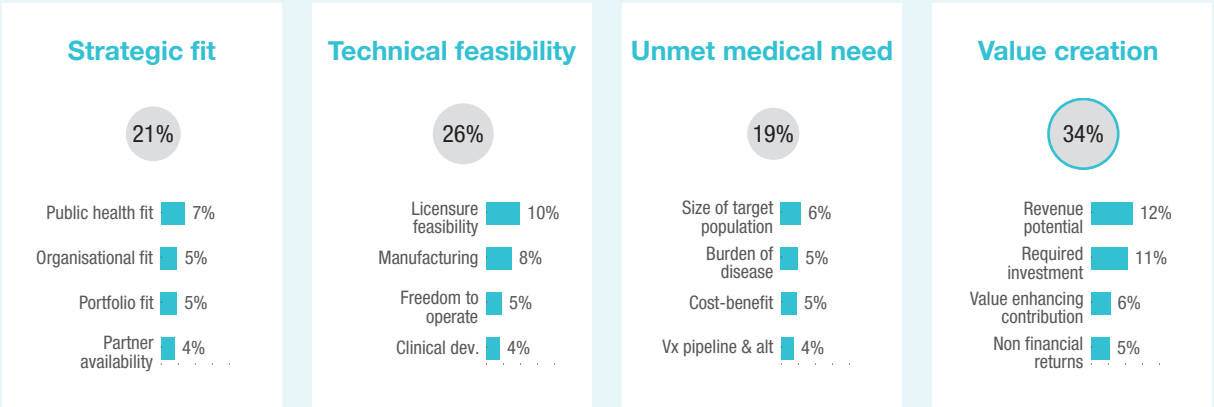
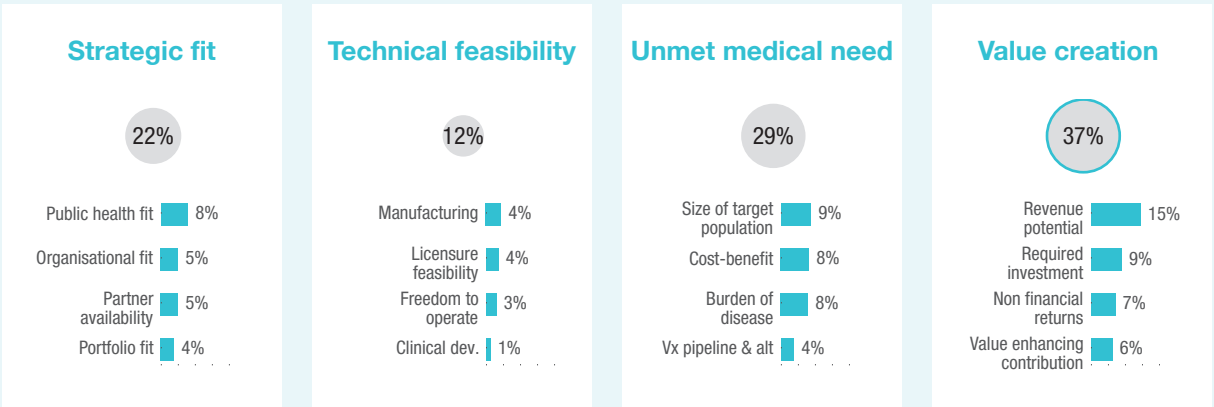


Figure 13: Factors influencing the decision-making process in the first country introduction phase

First country introductions – During first country introductions a number of critical decisions are still to be taken by vaccine developers. Value creation potential and unmet medical need are the most influential areas at this stage. Vaccine developers are primarily focusing on the revenue potential of the vaccine as result of the target populations that can be reached in view of the indications and of the policy recommendations that have been made, or are under discussion at global, regional and country level. Clarity on the burden of disease measures has an influence on these decisions



Different developers' priorities

The relative importance of influencing factors varies depending on the type of organisation making the decisions and the range of viable outcomes available.

Large, established manufacturers

Throughout the transition to pivotal trials, large manufacturers' decisions are driven by technical feasibility concerns and have the ability to stop development of an individual vaccine more readily because these manufacturers are less dependent on a single product's development. One of the most common reasons for stopping development/ disinvesting is the opportunity cost, where other development opportunities (internal competition) would derive a greater or quicker return on investment (ROI), thus strategic fit and opportunity cost are significant influencing factors in large organisations. Finally, the opportunity for value creation will play a strong role throughout developers' decision-making, driven by the strong need to contribute to the overall financial performance of the organisation for long-term viability and continuous innovation in future vaccines.

Mid-sized private companies

Technical feasibility is an important consideration for mid-size private companies. These companies will likely give special consideration to the portfolio fit of new vaccines, building upon existing expertise to increase the likelihood of successful development. Building a strategic portfolio and executing on development projects that are a good strategic fit are critical to companies with fewer resources. Finally, value potential is essential to mid-sized companies. Although these companies may not seek out the high-risk and high-reward development of novel vaccines, they must focus on vaccines with a favourable business case.

Mid-sized parastatal developers

Mid-sized parastatal (national) developers are either owned by, or closely aligned with, a government. They can also have several vaccines licensed but typically their portfolio is focused just on vaccines of national and regional relevance. These developers are typically first focused on the unmet medical need in the population of their country. The strategic fit with national needs is critical and often the over-riding factor in decision making.

Mid/small biotech organisations

Smaller organisations of this kind, typically without any licensed vaccines, are often willing to take greater risks when considering the factors of technical feasibility and may continue development more tenaciously, often not stopping development but rather adjusting plans. The potential to create value, whether through continued development or through an "exit" by licensing or acquisition, is a driving force and, unlike large vaccine developers, value may be designed to be realised prior to vaccine licensure.

Academia/government developer

Academic and government-associated developers are primarily housed in universities or government research agencies. These organisations are influenced by unmet medical need and research projects that will have a strategic fit in the organisation's research agenda and priorities. These developers are often entirely dependent on external funding to progress development to the point when they can sell the rights of the vaccine and may make decisions solely dependent on whether they receive continued funding.

Product Development Partnerships

Product Development Partnerships (PDP) can operate similarly to academic/government developers in that they tend to focus on specific disease targets or specific missions. They can be very different in terms of size of their portfolios. PDPs are therefore highly influenced by decisions related to unmet medical need and strategic fit. Furthermore, a PDP that is focused on a single disease will naturally be influenced by managing a portfolio of candidates for the same disease hence seeking to answer the question of which of the vaccine candidates could advance in development, rather than whether they should advance in development. The independence that a PDP has to make decisions with financial implications will depend on the relationship with its funder(s), where some PDP funders will view the influencing factors as primarily technical, others might view them in a more balanced way and incorporate cost-benefit factors.

Range of potential outcomes

The range of outcomes resulting from decisions may include project adjustments rather than strict go/no-go outcomes [4] can be influenced by factors outside of the individual vaccine candidate's progression through development. For example, in more advanced stages of development of a portfolio of candidates, there may be a need to select a limited number of candidates for advancement, leaving many halted [5]. Without the forced down-selection, those halted candidates might have continued development on their individual merits.

For each decision point, a range of potential outcomes is possible, including:

- **Continue as planned** is a rare outcome because of the complexity of interactions throughout the development process. While one element of the development programme may go forward as planned, other aspects (e.g. process development) might be adjusted.
- **Adjust investment size, target and goal** is bi-directional, with decisions to accelerate or slow development both possible. Unexpected clinical outcomes or technical issues are frequent causes of adjusted plans. A desire to decrease or delay investment is often intimately linked to the need to adjust plans and course of action.
- **Delay/defer** is a common outcome for all types of developers and is linked to multiple factors that can upend development planning, ranging from internal technical or business constraints to external factors.
- **Decide to partner** as a potential outcome, is a very important decision, and can take many forms. This can be a common and sometimes pre-planned outcome particularly for very small developers who do not have the capacity to proceed with development in the absence of clinical and industrial partnerships.
- **Disinvest/sell** may materialise if a developer is no longer interested in a programme that still retains some market potential. Under those circumstances, the developer may sell and recoup some of the costs incurred. For other developers this may be an explicit strategy to take development through a specific stage and to then sell the asset as an exit strategy.
- **Stop development** is a common outcome, often linked to challenges with technical feasibility, opportunity cost or the value creation potential

Chapter 3: Challenges faced by developers

During the part of development from transition into Phase 2 clinical development to first country introductions, vaccine developers face challenges across various areas: regulatory, clinical, manufacturing, market and finance. These challenges have different root causes.

Literature review summary

A literature review conducted between December 2019 and February 2020 comprising more than 300 documents from 2009-2019 was the primary source for identifying and assessing challenges faced by developers. The results of the literature review are described here and the identified challenges are further articulated in this chapter.

Scientific feasibility and costs of achieving licensure and initial use are strongly influenced by a lack of clear regulatory standards, particularly for episodic, low-prevalence and poorly characterised diseases. The frequent absence of established pathways to licensure and the limited availability of surrogates or correlates of efficacy represent two significant obstacles, which can be further complicated by a poor understanding of the relationship of animal to human immunogenicity. Development can be further constrained by a lack of assays and reagents through which both manufacturing and clinical success is measured.

Few NRAs globally have the experience and scientific expertise needed for primary licensure of vaccines for unconventional diseases. The absence of a global cooperative regulatory scheme and lack of appropriate regulatory harmonisation adds time and costs to clinical trial implementation and product registration. Finally, in the event of outbreaks, emergency schemes to permit the use of unregistered vaccines, such as the Emergency Use Assessment and Listing procedure (EUAL), are unclear and untested.

Because of their episodic nature, clinical trials for outbreak-prone diseases face the challenge of being conducted in an ethical and logistically feasible manner. Diseases with low or intermediate incidence (e.g. Group B strep) or future clinical manifestations (e.g. HPV-associated cancers) require either very large and long traditional trials with classic endpoints or innovative solutions, such as the use of animal or human challenge models or surrogate endpoints. Finally, safety evaluations for vaccines intended to be used first in low-income settings may require larger pre-licensure safety studies to compensate for the weak post-licensure pharmacovigilance systems in many low- and middle-income countries.

Few vaccine developers, CMOs and regulators are experienced in vaccine manufacturing. Major decisions on manufacturing, including the process, how to measure consistency and anticipated plant capacity must be made prior to or during Phase 2 clinical trials. The need for early decisions has lasting effects on the costs of goods manufactured (COGM) and cost of goods sold (COGS) through the efficiency of the process and the capacity chosen, particularly because vaccine manufacturing has distinct economies of scale. Any subsequent changes to the materials, process or facility require regulatory approval of “variations” and can sometimes require subsequent clinical trials. Further, different requirements from various regulatory agencies – few of which are experienced in vaccine manufacturing – add ongoing costs to vaccine production.

The uncertainty of revenues and the generally lower revenues and high development costs for vaccines against episodic diseases or targeted primarily at low-income countries disadvantages them against more lucrative vaccines or drugs available to developers. External funding is often required to support vaccine development and typically comes in small amounts over short time horizons from different funders. This financing scheme does not match the long development timelines and investment requirements for vaccine development, in particular for large pivotal trials required in later phases. As a result, the number of developers able to activate the necessary capital to finish development has decreased, thus concentrating financial risk over a smaller number of companies. Early development entities including academia, PDPs and biotechs, which typically rely on external funding sources, are incentivised to make development decisions with shorter time horizons, transferring investments and risks associated with final product development and manufacturing to the mid- or large-size organisations that tend to finish development after early phase partnering.

Factors impacting market predictability and policy support are strongly related to the feasibility of recouping costs. Because vaccine markets are largely dependent on policy recommendations, an uncertain policy environment translates directly into market uncertainty. Policy recommendations are less clear for vaccines that do not have a clearly defined target population, initially target low-income countries, need new implementation strategies and those for which the impact of vaccination can be affected by the performance of immunisation programmes. Vaccines whose benefits are narrowly defined or not well documented can foster an under-valuation of vaccination that in turn creates hesitation in policy decisions, over-emphasises low per dose vaccine pricing or both.

Non-commercial factors can be challenges or facilitators in vaccine development. The advocacy of disease and vaccine champions and key opinion leaders is often required to positively impact development and implementation but can fail without end-to-end support, including through the licensing and implementation phases.

Additional challenges relate to IP, technology transfer and access to biologic material. Freedom to operate is increasingly problematic, particularly for manufacturers of follow-on vaccines. In addition, the small number of companies capable and willing to accept technology transfer from early phase developers creates delays in completing development. The legal risks faced by vaccine manufacturers adds to the overall risk profile of vaccine development and commercialisation. Finally, impediments to accessing new strains of virus or bacteria, an unintended consequence of the Nagoya Protocol, may cause delays or block development of vaccines, in particular for emergent diseases.

Description of challenges

Each challenge can represent a complex set of factors in the vaccine development ecosystem and may be multi-factorial and not entirely able to be separated from other challenges. Nevertheless, the descriptions below correspond to the point-of-view taken for each challenge in this analysis, organised by the challenge category.

Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use (Regulatory)

1. **Lack of recognised surrogates or correlates of efficacy** – The ability to assess the protective efficacy of a vaccine by measuring a particular immune response in vaccine recipients, without having to measure clinical outcomes, has significant advantages. The availability and quality of such endpoints greatly facilitates vaccine development, licensure and subsequent effectiveness monitoring. Absent recognised surrogates or correlates of efficacy, trials must be powered to show protection against disease. This means having to conduct larger and more costly effectiveness trials. Under these circumstances longer time is needed before a vaccine becomes available and higher per dose prices can be expected to allow for recovery of the extra costs.
2. **Lack of animal models that correspond with immunogenicity in humans** – Animal models are often used to predict vaccine immunogenicity and efficacy in humans. When animal models have limited predictive capacity with respect to human immune responses, clinical development has a higher likelihood of failure. This may translate – in particular for diseases that have limited market potential – into reduced interest from developers resulting in lower likelihood that a vaccine will be available, or increased time to widespread availability.
3. **Lack of standardised assays, standards and reagents for antigen testing** – Immunoassays are used to quantify molecules of biological interest based on the specificity and selectivity of antibody responses generated. Those assays are necessary for the manufacturing process (potency and characterisation assays). This is a regulatory requirement for the demonstration of consistency between manufactured batches of a candidate vaccine, as well as for the measurement of clinical outcomes (viral load, antibody and cell-mediated immune response assays). The absence of standardised assays, standards and reagents means that the clinical development process is more complicated and regulatory submissions are more likely to experience delays and/or to fail. Consequently, fewer vaccines will be available on the market for a specific disease and time to availability will be increased.
4. **Lack of standards by which platform technologies are transferable from one disease target to another** (e.g. viral vectors, mRNA) – Because regulators approve vaccines both as a process and resulting product, all vaccine licensure processes are de novo, even if based on a previously approved platform. Although this system does not constitute a barrier in itself to the development of individual vaccines, the inability of leveraging common parts of the development process results in more costly and lengthy development with a number of repeated activities. Vaccine price and time required to make products widely available are likely to increase.
5. **Lack of support for alternative clinical pathways** (e.g. HIS, adaptive trials) – Human infection Studies (HIS) are useful for proof of concept, pathogenesis, down-selection, immunogenicity and efficacy studies. Adaptive clinical trial design with a single control group, step-wedge design and other features are also more frequently considered to speed-up

development and to allow assessment of multiple vaccines in parallel (e.g. Ebola, COVID-19). However, many regulators show reluctance to accept these non-conventional clinical pathways as pivotal trials, favouring demonstration of vaccine effectiveness against naturally acquired disease in a traditional fashion. This forces developers to conduct longer, more expensive efficacy trials, resulting in a longer lead time to vaccine availability and higher prices once available.

6. **Few NRAs able to effectively and efficiently regulate primary licensure of novel vaccines** – Regulatory capability for novel vaccines is highly concentrated among a small group of government regulators. Although WHO has sought to expand regulatory capability and to evaluate regulatory authorities' performance and, if positive, confer WHO Listed Authority (WLA) status, a sufficient level of regulatory knowledge and capabilities remains a pre-requisite to developing the sophisticated approach needed to guide developers in regulation of novel vaccines. The relative dearth of authorities able to license innovative vaccines efficiently means that developers are limited in their options and that they must choose between a more sophisticated NRA in a country where the need may be less, thus delaying access to other countries, or choose an NRA lacking strong competencies, which then delays the process, increasing time to availability and leading to higher prices.
7. **Few NRAs for primary or secondary licensures of follow-on vaccines eligible for pre-qualification by WHO** – The paucity of capable regulators means that developers, in particular those located in countries where the NRA has not met the criteria established by WHO, are not able to seek prequalification. Where NRAs are not qualified, prequalification will be delayed pending the lengthy process of WHO accreditation of the NRA. Ultimately, this constraint results in reduced vaccine availability and longer lead-times.
8. **Lack of mechanisms allowing for use exclusively outside country of origin** (e.g. EMA Article 58, Korea) – The European Medicines Association (EMA) can render a scientific opinion about the suitability of vaccines not intended for use within their jurisdictions. This system serves as a proxy for regulatory approval, thus providing developers an efficient means of obtaining licensure in the countries of intended use. Because this mechanism is limited to very few NRAs, developers of novel vaccines are normally required to license their vaccine in the country of origin where the risk/benefit could be significantly different from those in user country/ies, requiring a high burden of proof relative to little benefit.
9. **Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals and diagnostics across NRAs** – The lack of adherence to international or regional standards means developers must often meet specific local requirements and potentially conduct bespoke clinical trials in specific jurisdictions irrespective of the clinical or epidemiological needs. Developers may need to establish different safety monitoring processes and meet unique labelling and packaging requirements. Those additional process-driven costs result in higher costs of development, correspondingly higher prices, longer access timelines and the risk of reduced access (developers may decide not to license the product in certain jurisdictions).
10. **Lack of harmonisation on documentation of quality, efficacy, labelling, packaging and safety of biologicals and diagnostics across NRAs** – Similarly, the lack of harmonisation between NRAs regarding documentation and lack of adherence to standards established in the common technical dossier (CTD) results in duplication of developers' effort, time and expense to meet the unique documentation requirements of each NRA, resulting in access delays and higher prices.

Feasibility and/or costs of testing under current clinical trial requirements (Clinical)

11. **Conducting efficacy trials requires an active outbreak** (presence of disease) – For many infectious diseases, efficacy trials can be conducted only in the presence of cases, e.g. an active outbreak, which may be sporadic in time, erratic in location and unpredictable in numbers of people at risk/infected. The inability to plan for the duration, location and costs of clinical trials and the need to wait, sometimes for several years, before being able to perform a trial raises developer uncertainty and risk. Furthermore, the compressed timeline of an outbreak increases the likelihood of failure in clinical development. These constraints reduce developer interest and lessen the likelihood of vaccine availability.
12. **Conducting efficacy trials for diseases with poorly established, low or sporadic disease incidence** – The lack of solid epidemiologic information about disease incidence and diseases that occur with low or sporadic prevalence pose challenges for demonstrating vaccine efficacy and increases the chances of failure in clinical development. Much longer trials are required to be able to reach the necessary sample size and to produce the necessary evidence. These circumstances increase costs and lengthen clinical development and, thus, they have an impact on prices and result in delayed availability of the vaccine. These complexities are also likely to reduce the developers' interest in these diseases.
13. **Real or perceived ethical concerns about trial design** (e.g. administration of placebos, HIS) – Real or perceived ethical concerns may exist about the risks versus the benefits to the individuals participating in clinical trials. For instance, for low prevalence diseases, for which individual risk of diseases is low, HIS can be perceived as exposing study subjects to high risks without any guarantee of benefit. Ethical concerns constrain developers to adopt classical approaches to vaccine development, which make clinical development longer and more expensive, delaying access and increasing vaccine prices.
14. **Conducting efficacy trials for diseases involving animal transmission** – When disease transmission includes one or more animal species the complexity of clinical development increases greatly. As in the case of Rift Valley fever, the interactions between humans and livestock and the dynamics of disease transmission complicates study design. Information about cross-species disease transmission is often incomplete, raising questions about the real impact of a vaccine and the most appropriate measurements of endemicity, transmission and efficacy. As a result, complex study designs are generally warranted, increasing the chances of failure and the costs of clinical development, lead times and prices.
15. **Conducting efficacy trials for diseases with varied epidemiologic profiles** – Differences in populations' immune responses, disease epidemiology and health-seeking behaviours require developers to perform parallel clinical trials at multiple sites. Beyond the higher costs compared to a single site study, some geographies may not be suitable or lack capacity to perform Phase 3 trials altogether. Such complexity may discourage vaccine development for these diseases with variable epidemiology or result in costlier development. The impact for the public is potentially higher prices and longer delay in vaccine development and availability.
16. **Additional requirements for use of new technologies** (e.g. adjuvants, mRNA) – Regulatory uncertainty regarding the safety and efficacy of new technologies can result in larger, longer clinical studies. Technologies that are firsts for human vaccine, such as mRNA, may come under greater scrutiny by regulators given their unproven nature, especially if there are alternatives with known technology. This leads to increasing prices and time-to-availability.
17. **Lack of qualified in-country human resources to perform trials in LMICs** – Insufficient know-how and experience in clinical development in LMICs leads to longer development time, particularly if developers have to build or

contribute to building country-level capacity. In some instances, lack of capacity will limit the ability of developers to conduct clinical trials in the most epidemiologically appropriate locations. Those circumstances can reduce developer interest, lengthen development time and costs, resulting in increased vaccine price and/or preclude access if development stalls or fails.

18. **Lack of epidemiologic surveillance systems in LMICs to adequately quantify disease occurrence during or after clinical trials** – Inadequate disease surveillance (data completeness, quality, timeliness) and epidemiologic characterisation (disease transmission, incidence, prevalence) before, during and after clinical trials hinders the ability of developers and regulators to define a baseline of disease occurrence and to measure the impact of the vaccine on the population. This means development is more likely to fail and/or clinical trials are likely to be longer and larger, increasing costs and ultimately prices and lead-time to availability.
19. **Lack of diagnostic capabilities to adequately quantify disease occurrence during clinical trials** – If clinical development is undertaken in countries where the diagnostic capabilities of the country are inadequate, because of insufficient infrastructure (e.g. testing only possible in centralised location by specialised labs) or lack of capacity and know-how (e.g. too few technicians capable of conducting testing), development will require larger, longer studies and is more likely to fail, with the same downstream consequences.
20. **Insufficient WHO guidance to LMIC countries on performance of clinical trials** – LMICs lacking strong capabilities on clinical trial approvals and performance rely greatly on WHO guidance on a variety of aspects. Without this guidance, development can stall because developers must press for clarity with local authorities and clinical staff. Under some circumstances where WHO is the trial sponsor, it's role in protocol design, endpoint selection and analysis and GCP (Good Clinical Practice) is essential to efficient conduct of trials. Under some conditions, delays are likely to occur, impacting cost and time to access.
21. **Increased pre-implementation studies for vaccines first used in LICs** – Inadequate capability to monitor safety on an ongoing basis after vaccine introduction may cause policy makers or regulators to perform pilot introduction programmes in advance of widespread national implementation, or to impose a set of post-marketing conditions such as long, large Phase 4 studies to confirm safety. As a consequence of these additional requirements, costs and duration of the trials increase with impact on price and time to access.

Feasibility and/or costs of manufacturing the vaccine to the right standard and volume (Manufacturing)

22. **Lack of personnel in the NRAs with expertise and experience to regulate manufacturing** – In-depth understanding of manufacturing and quality control of biological products is a very limited resource globally. Lack of NRA capability means that developers face increased likelihood of compliance failure in clinical trials and first commercial lots due to inadequate oversight from their NRA of reference. Non-compliance and quality issues have costs related to discarded product in the early phases of commercialisation and can delay licensure and reduce the likelihood of vaccine availability.
23. **Process changes require regulatory approvals and/or "bridging" clinical trials** – Changes in manufacturing processes typically require regulatory approval. The requirements reduce manufacturers' incentives to improve processes that could potentially lower cost of goods or bring other benefits. This is especially problematic since pressure during the clinical development to move forward quickly is at odds with taking additional time for process optimisation. Ideally,

to achieve optimal results, manufacturing process development should be an iterative process. Because any necessary process change adds time and costs to development, meaningful continuous process improvements are very uncommon, resulting in inefficient processes with higher costs and per dose price.

24. **Raw material/components changes require regulatory approvals** – Changes in manufacturing materials require regulatory approval. Developers have less control over material changes than process changes because these are sometimes forced by the supply chains. Furthermore, this may constitute an obstacle to improvement of the processes. The result is more expensive products and potential need for additional regulatory work to maintain licensure with additional costs for the developers.
25. **Need for high biosafety conditions** – High biosafety levels (BSL) may be required depending on the nature of the pathogen (seven out of 33 in-scope vaccines require BSL 3/4 facilities). Meeting those requirements increases development costs and time to ensure compliance. As a consequence, developers may be less interested in the development of vaccines requiring these conditions; development under these conditions increases time to market and price.
26. **Lack of ability to share production processes and/or facilities for multiple vaccines** – Because vaccines utilise many different production technologies (e.g. fermentation in yeast, growth in cell culture or in eggs, lyophilization) facilities often require unique equipment. Where vaccine manufacturing processes can share equipment or facility space, an extensive changeover cleaning procedure between manufacturing of different vaccines is required for quality control and often renders any benefits of a shared facility moot due to the long time period spent in transition. The fewer the opportunities to share production processes, the greater the time and costs developers must invest in establishing unique manufacturing lines or facilities, increasing time to market and vaccine price. Additionally, this raises the risk profile of those investments, reducing the likelihood of "go" decisions.
27. **Low volume or sporadic demand creates production inefficiency** – Vaccine manufacturing operates most efficiently at a constant rate, and changes to pace or stopping and starting production create costly disruptions. Furthermore, manufacturing plants have a minimal size below which their operation is economically very inefficient. Because vaccines have limited shelf-life, low volume and sporadic demand can often cause the expiration of unused products that must then be written off; COGM and COGS increase with production volume significantly lower than planned.
28. **Inability to quickly access new (seasonal) variants/strains** – Because many vaccines, particularly those against epidemic or novel diseases, depend on organic starting materials, international treaties such as the Nagoya Protocol that seek to ensure access to starting biological materials are critical. In the absence of pre-existing frameworks regulating those transfers with clarity (e.g. the Pandemic Influenza Preparedness framework), lack of understanding or differing interpretations of those treaties can result in delayed or stopping of development if developers cannot access those starting materials in a timely fashion. This constraint can result in fewer developers, reduced competition and reduced access overall.
29. **Long lead-time for establishing manufacturing capacity** – Dedicated vaccine manufacturing lines or facilities require significant time to build (typically five years). Unless decisions to start construction are taken at risk, waiting to invest in the manufacturing plant after initial clinical success is demonstrated can increase development time because at least some Phase 3 clinical trial material must come from the manufacturing plant where the licensed vaccine will be produced. This can reduce access because developers may not choose/be able to make the necessary investment; even with investment, time to market is lengthened.
30. **Lack of Good Manufacturing Practice (GMP)-compliant contract manufacturers available to produce clinical trial material** – Lack of readily

available and GMP-compliant manufacturing organisations means that developers who cannot manufacture GMP-compliant clinical trial material in-house will experience longer development time while they wait to identify willing and able contract partners, ultimately increasing the time and reducing the likelihood of availability.

31. **Lack of partners available/capable of receiving technology transfer** – Developers who are not capable of, or interested in, manufacturing their product require manufacturing partnerships for both clinical and commercial material (see challenge 48). The general dearth of vaccine manufacturers globally and, in particular, of manufacturers capable of handling a specific technology, limits the potential for partnerships.
32. **Lack of freedom to operate and/or existence of IP barriers** – Identified areas where a proposed product composition or manufacturing method may violate IP held by other entities can create delays in development as alternatives are explored, licenses are negotiated, or novel IP is created prior to commercialisation. In extreme cases where no solution can be found, vaccine development may stop.

Factors impacting the predictability of the market and the likelihood of policy support for use (Market & Policy)

33. **Insufficient public budgets for purchase and implementation of immunisation programmes** (willingness to pay) – Pressure on health budgets or on the overall public finances may constrain governments' willingness to implement new immunisation programmes. Different stakeholders and developers may seek to develop advocacy at country level to shape policy, programming and political will so that sufficient financial resources are allocated for a specific immunisation programme. In absence of those advocacy efforts, and mindful of the need for this additional expense and uncertainty, fewer developers may pursue "less popular" vaccines, resulting in reduced competition for some vaccines or, for others, a longer time to reach populations in need (or both).
34. **Lack of policy entrepreneurs or immunisation champions to mobilise political and funding support** – Absent clear and consistent voices supporting the development and adoption of a given vaccine, developers can experience significant uncertainty in individual markets and either abandon their efforts or seek to develop advocates (key opinion leaders, policy influencers) to shape public opinion. Absence of champions may result in reduced interest for specific vaccines and, as a consequence, reduced competition and vaccine availability/access.
35. **Lack of political attention to non-epidemic diseases** – Non-epidemic diseases often attract less political attention than epidemic diseases, because they do not result in public perception of an imminent risk to health. Absent public and/or government concern about a disease, a corresponding vaccine is less likely to be adopted. Fewer developers may be attracted by those diseases for which the flow of revenues may be small, because vaccines lack country adoptions.
36. **Lack of global political attention to diseases that don't cross over into HICs** – Epidemic diseases that have little likelihood of affecting populations in HICs (e.g. Ebola) often attract less political attention than global epidemic or pandemic diseases, because they are not perceived to pose an imminent health-related economic threat in countries where vaccine ROI is higher. Developers may be less interested in these diseases, and so access to vaccines can be limited or delayed.
37. **Growing vaccine hesitancy and spill-over of other vaccine issues impact acceptance and overall demand** – Public and policymaker scepticism and, in some cases, outright hostility to immunisation generally, and some vaccines particularly, is widely reported in the media and may over time reduce vaccine use. Developers may be more reluctant to engage in development

programmes for vaccines most associated with negative public perception or that are the subject of anti-vaccination movements in view of the reduced revenue potential and risks to corporate image and reputation.

38. **Target groups not well articulated by public health entities i.e. through a Target Product Profile** (TPP) – In the absence of clear guidance from public health authorities at global and national levels on desirable target populations and product characteristics, developers run the risk of developing a vaccine that policymakers will not accept, adopt and implement. Reluctance to engage in development of vaccines lacking clarity on targets, limits or delays access to those vaccines.
39. **Lack of data for assessing potential impact of vaccination in particular specific target populations** – In the absence of sound epidemiological data, developers are challenged to demonstrate the true impact of vaccination. Establishment or strengthening of epidemiology and surveillance capabilities are necessary in order to increase the likelihood that vaccines will be adopted and implemented. Absence of these data may result in increased development costs and/or development delay.
40. **Value of vaccination needs to be demonstrated against alternative interventions** (e.g. monoclonal antibodies, chemotherapy, improved sanitation) – When other interventions are already available, even if potentially less impactful than immunisation, policy makers often question the need for a new intervention. The potential value of vaccination, therefore, needs to be demonstrated against other alternative solutions. Additional costs and time are required to generate these data, which negatively impacts the timing and the availability of a vaccine and the price given the additional costs.
41. **Lack of use of appropriate models for economic valuation (e.g. cost effectiveness vs. cost-benefit) globally or in certain countries** – Economic models that fail to consider the broader societal benefits of immunisation result in under-valuation of immunisation and decrease the likelihood that vaccines will be adopted and used. Reliance on cost-effectiveness assessments for decision-making undervalue the contributions of vaccines to societal outcomes. By reducing the perceived value of vaccines and influencing policy makers' decisions, these approaches reduce the attractiveness of vaccines as targets of developers, who may rationally direct resources to other products. As a result, access to vaccines can be hindered or delayed.

Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery (Return on Investment)

42. **Potential need for IP licence to commercialise** – Developers may be required to expend significant resources to secure needed process or composition IP through licensing and/or royalty payments prior to commercialisation. This risk is higher when more recent technology is used because it is unlikely that the associated patents will have expired. The need to access IP ultimately adds to development costs and potentially restricts access due to higher and less controllable costs. The IP barriers to entry and the additional costs to overcome the challenges may limit the number of developers, resulting in less competition.
43. **Restrictions imposed by public funders on IP "reuse"** – Use of previously owned or newly generated IP from the public or publicly-financed originator/s as well as from private foundations and charities may be possible only if developers agree to a set of constraints defined by the funder. Those constraints generally include restrictions on prices and further applications of the IP, and requirements for access and distribution in various geographies. Developers may be reluctant to agree to those conditions and, as a result, they may prefer not to use the IP with consequent delays or termination of

development or incur additional cost to access alternate technology/IP.

44. **Opportunity costs outweigh the vaccine's economic rationale** – Developers' resource allocation decisions are informed by the financial imperatives that dictate that limited resources must be spent on the projects with an acceptable ROI, and generally on those with the highest return. Because of the large size of clinical trials, significant single-purpose manufacturing plant investments and higher risk profile compared to other therapeutic areas, vaccines are generally more expensive to develop and when combined with the high degree of uncertainty on revenues owing to the non-incremental nature of demand, less profitable than other medical products (e.g. drugs for oncology or chronic conditions). This can limit investment in vaccines compared to other classes of medical products. As a result, availability of vaccines in general, and vaccines for certain conditions in particular, is hindered or delayed.
45. **Unpredictability of public tender markets** – In view of the significant anticipated investment in dedicated manufacturing facilities and of the long lead-time for production, developers are required to allocate significant financial resources well in advance of public tenders. At the same time, tender awards are primarily based on price and often limited to one or few winners. Developers must invest significant resources without any certainty of a tender award. Uncertainty limits developer interest in development of new and improved vaccines, reducing the number of developers and competition.
46. **Reference pricing can reduce the value of HIC markets** – Increasingly, tenders and procurement activities refer to available market prices of similar products to set a price ceiling or reference level. While this approach may sound reasonable, in reality differences in prices may reflect substantially different contractual conditions (e.g. multi-year volume commitments) that are not comparable as well as widely different economic conditions of the procuring countries. By not clearly reflecting those differences, reference pricing may induce developers to delay or avoid sales or even registration in countries with lowest prices so as to avoid establishing a low reference. The consequence of price referencing may limit developer interest in low-priced markets and reduce the number of developers and competition, reducing access to countries and increasing prices.
47. **Pricing pressure may discourage innovation for improvements** – Buyers are often unwilling to pay a premium for improvements, including cost-saving features, that translate into systemic net savings at a higher per dose price (e.g. a higher per dose price for a single-dose schedule than the per dose price for a three-dose schedule). This limits developers' interest in making improvements and reduces the number of developers and level of competition.
48. **Limited availability of aligned partners to commercialise vaccine** – Vaccine developers that do not have or are not interested in building capacity for licensure and commercialisation of the vaccine – in particular public and academic institutions – must find available/interested/capable partners that can commercialise the vaccine. This means a legal entity capable of assuming the ownership of the product, licensing it and directly or indirectly commercialising the vaccine. Globally fewer than one hundred companies commercialise vaccines, and many of them are small entities focusing on their domestic markets and lacking the interest or the capability to act as partners. The limited number of capable partners available globally can delay or hinder completely the availability of certain vaccines.
49. **Insufficient access to funds for late-stage development** – Phase 3 is the most expensive part of vaccine development with financial requirements that range between 30 to 500 million USD depending on the vaccine, the trial and the NRA requirements. Very few small and mid-size developers can fully self-fund this development stage and those who can rely on private funding sources. Identifying and securing funding from the financial markets (as equity or debt) is challenging and uncertain because investors often seek more immediate returns than from lengthy vaccine development, and lenders seek less risky ventures. This is especially true for companies based in emerging markets, where

financial markets are less sophisticated and less interested in risky enterprises (e.g. India).

50. **Lack of private funding sources for vaccines targeted at LMICs** – Increasingly, venture capital and investment banking are a source of financing for small companies in the early phases of clinical development for new vaccines. Unfortunately, the lack of information about and presumed lower ROI from low- and middle-income markets suppresses interest from those investors, in particular for those vaccines for epidemic diseases where those geographies represent the largest share of the market. This misalignment of goals results in a reduced likelihood that those vaccines will be developed and available.
51. **Need to make expensive manufacturing investments prior to clinical success or demand certainty** – Investments are at significant risk, given the forward planning required to complete a manufacturing facility. The time to complete a manufacturing facility can be as long as five years, and construction is undertaken well before data from Phase 3 are available or licensing has been achieved. Overall, the probability a vaccine candidate will fail in Phase 2 is 42%[6], and this means that production capacity decisions must be taken when the risk of failure in clinical development is still quite high. Few large developers can invest at risk and others must seek outside support that, as mentioned, may be limited in size and to certain diseases. The result is delay or cancelation of vaccine development programmes.
52. **Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer** – In view of the sizeable development investments, the economic case for in-scope vaccines relies on the steady markets and buyers with sufficient ability and willingness to purchase over time. Lacking these conditions, vaccine developers tend to concentrate on buyers able to pay higher prices. The establishment of financial incentives on the demand side – such as the Advance Market Commitment (AMC) for Pneumococcal Conjugate vaccine – has been used as an instrument to positively alter the vaccine development enterprise's economics, triggering vaccine developers to develop and commercialise vaccines beyond the high-income markets. To function, these incentives should address the underlying challenges that block developers' decisions. If this result is not fully achieved, vaccine developers may decide either not to continue with clinical development or to target higher prices for markets that can afford/are willing to pay.
53. **Risks of legal action associated with widespread use of unlicensed vaccines** (e.g. under EUAL or other schemes) – Vaccines used under EUAL procedures are neither licensed nor undergoing a clinical trial. The risks associated with legal action and liabilities arising from an adverse event following immunisation – substantiated or not – under those conditions are very high for a vaccine developer. Some high-income jurisdictions have created protections for specific circumstances for licensed vaccines or unlicensed vaccines used in emergencies, but most countries lack such a mechanism. This results in few developers willing to expose themselves to this risk and reduced vaccine availability in countries lacking protection for producers, providers and patients.
54. **Exposure to risk to HIC markets from unsubstantiated issues in low-income markets** – Unsubstantiated allegation about risks from vaccination in environments with weak surveillance and pharmacovigilance systems can put developers at risk for litigation and threaten sales in high-income markets if allegations spill over globally. This limits developers' interest, reduces competition and suppresses access for LMICs.

Root causes, and challenges by type of developer

Root causes (i.e. those factors that underlie one or multiple challenges) were analysed for each of the challenges and totalled 31 in number. The root-cause analysis serves as a foundation for the identification of the potential solutions later in the research. Seven root-causes are cross-cutting, effecting more than one challenge (Table 3).

Table 3: Cross-cutting root causes

Category	Root Cause	# challenges effected
Regulatory	Desire of NRAs to assert local control/NRA lack of understanding of global guidance and documentation	3
	Fundamental deficiencies in knowledge or practices	3
Clinical	Insufficient human and technical resources to perform trials in MICs/LMICs	3
Manufacturing	Vaccine development is niche area of technology and science	3
Market & Policy	Vaccination not perceived to be politically rewarding	4
Financial outcomes	Limited private capital because of high risk, long-term investments	4
	Comparatively low market value of vaccines	5

For the financial outcomes' category, most root causes are legal and financial in nature. The manufacturing category is characterised by a set of legal and policy root causes along with foundational ones, requiring interventions with a longer-term perspective. In the clinical category, there is a mix of foundational root causes and capacity issues for which the challenges will require different types of interventions. For regulatory challenges, with a partial exception of the desire of NRAs to assert control, the root causes all reflect underlying capability shortcomings. Of all categories of challenges this is the one with a majority of intrinsic issues. In the market and policy category, many of the root causes are linked to perceptions, requiring a very specific set of actions to address them. Table 4 describes the relationship between the root causes and challenges.

Arguably, the first cause among all root causes is the comparatively low market value of vaccines. This fundamental reality of the vaccine ecosystem has knock-on effects – most clearly in limiting the capital available to vaccine developers. Rational investors motivated by returns rather than social impact allocate money to other investments that are less risky and more profitable. This is true within companies, as funds flow to other therapeutic areas, and for outside investors as well. Even if all other challenges could be solved – scientific breakthroughs such as platform technologies that may lower the cost of goods manufactured and sold, advances in regulatory science that reduce licensing inefficiencies, improvements in capacity for clinical trials and so on – this hard economic truth means that vaccine development will likely remain constrained. Even if demand increased and was more predictable, rational investors would still be drawn to higher margin, less risky investments, whether in the health sector or some other. A truly radical reformation of the vaccine ecosystem would start from the premise that immunity is a public good and work backward from there to explicate how that public good should be provided and funded, and the instrumental goods that are required to achieve it.

Developers vary in nontrivial ways, which affects their individual degrees of freedom to respond to systemic challenges. Some challenges are faced by every

developer, no matter the type of organisation. For example, all developers must contend with the challenge of a lack of recognised surrogates or correlates of efficacy. Other challenges, however, are experienced by certain developers but not others. For example, academic, PDP and governmental developers must find partners in order to commercialise vaccines, a challenge not typical for large and mid-sized developers. In Table 4, below, for each challenge the challenge topic, root cause and likely affected developers are indicated. In some instances, the location of the developer is a more important criteria and that is noted. The categories of developers below are:

- Large: large established manufacturers
- Mid: mid-sized private and parastatal developers
- Small: mid/small biotech
- Academic: academic/government developers and PDP

Table 4: Challenges to vaccine development

Topic	Root cause	Challenge	Affected developers
1. Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use			
Regulatory standards and practices	Fundamental deficiencies in knowledge or practices	1. Lack of recognised surrogates or correlates of efficacy	All
		2. Lack of animal models that correspond with immunogenicity in humans	
		3. Lack of standardised assays, standards, and reagents for antigen testing	
	Uncertainties about pathway to licensure for new/untested areas of knowledge or practices	4. Lack of standards by which platform technologies (e.g. adjuvants, mRNA) are transferable from one disease target to another	
		5. Lack of support for alternative clinical pathways (e.g. HIS, animal rule, animal bridge to human immunogenicity)	
NRA's capacity	Lack of experienced personnel and financial/technical resources	6. Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine	Large, mid, small
		7. Few NRAs able to regulate primary or secondary licensures of follow-on vaccines eligible for prequalification	
Alignment of NRAs	Desire of NRAs to assert local control/NRA lack of understanding of global guidance and documentation	8. Lack of mechanisms that allow for use exclusively outside of the country of origin (e.g. EMA Article 58)	Developers in HICs
		9. Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs	Large, mid, small
		10. Lack of harmonisation on documentation of quality, efficacy, labelling, packaging and safety of biologicals & diagnostic across NRAs	Large, mid, small

Topic	Root cause	Challenge	Affected developers
2. Feasibility and/or costs of testing under current clinical trial requirements			
Trial design and endpoint selection	Uncertainty/unpredictability of disease occurrence or low incidence	11. Conducting efficacy trials requires an active outbreak (presence of disease)	All
		12. Conducting efficacy trials for diseases with poorly established, low or sporadic disease incidence	
	Uncertainty in the application of ethical guidelines	13. Real or perceived ethical concerns about trial design (e.g. administration of placebos, HIS)	
	Complex disease epidemiology	14. Conducting efficacy trials for diseases involving animal transmission	
		15. Conducting efficacy trials for diseases with varied epidemiological profiles	
	Use of novel technologies	16. Additional requirements for use of new technologies (e.g. adjuvants, mRNA)	All
Country-level capacity and capability	Insufficient human and technical resources to perform trials in MICs/LMICs	17. Lack of qualified in-country human resources to perform trials in MICs/LICs	
		18. Lack of epidemiological surveillance systems in MICs/LICs to adequately quantify disease occurrence during or after clinical trials	
		19. Lack of diagnostics capabilities to adequately quantify disease occurrence during clinical trials	
	Insufficient technical guidance on clinical conduct	20. Insufficient WHO guidance to MICs/LICs on performance of clinical trials	
	Weaknesses in pharmacovigilance systems in the countries where the vaccine is implemented	21. Increased pre-implementation safety studies for vaccines used first in LIC	

Topic	Root cause	Challenge	Affected developers
3. Feasibility and/or costs of manufacturing the vaccine to the right standard and volume			
Regulation of manufacturing	Insufficient capacity in MICs/LMICs to regulate manufacturing	22. Lack of personnel in the NRAs with expertise and experience to regulate manufacturing	Developers with plants in MICs/LICs
	Management of variations requirements	23. Process changes require regulatory approvals and/or "bridging" clinical trials	Large, mid, small
		24. Raw material/components changes require regulatory approvals	
Manufacturing for commercialisation	Few countries/organisations with high BSL facilities	25. Need for high biosafety conditions (e.g. BSL 3/4)	
	Inherent uniqueness of each vaccine antigen	26. Lack of possibility to share production process and/or facilities	
	Scaled, steady production is most efficient	27. Low volume or sporadic demand creates production inefficiency	
	Under Nagoya protocol countries may limit access to new strains/variants if benefits of sharing are not sufficiently recovered	28. Inability to quickly access new (seasonal) variants/strains	
	Vaccine development is niche area of technology and science	29. Long-lead time for establishing manufacturing capacity	
Partnerships	Vaccine development is niche area of technology and science	30. Lack of GMP-compliant contract manufacturers to produce clinical trial material	Small, Academic
		31. Lack of partners available/capable of receiving technology transfer	
Freedom to operate	Limitations in accessing IP on processes or technologies useful to vaccine production	32. Lack of freedom to operate (existence of intellectual property barriers)	All

Topic	Root cause	Challenge	Affected developers
4. Factors impacting the predictability of the market and the likelihood of policy support for use			
Uncertainty of demand	Vaccination not perceived to be politically rewarding	33. Insufficient public budgets for purchase and implementation of immunisation programmes (Willingness to pay)	Large, mid, small
		34. Lack of policy entrepreneurs or immunisation champions to mobilise political and funding support	
		35. Lack of political attention to non-epidemic diseases	
		36. Lack of global political attention to diseases that don't cross-over into high-income countries (e.g. COVID-19 vs. Ebola)	
	Decreasing public appreciation for the value of vaccines	37. Growing vaccine hesitancy and spill-over of other vaccine issues impact acceptance and overall demand	
	Lack of early policy direction	38. Target groups not well articulated by public health entities (i.e., through a TPP)	
Uncertainty of policy recommendations	Weak epidemiological surveillance	39. Lack of data for assessing potential impact of vaccination in particular in specific target populations	
	Alternatives to vaccination are available	40. Value of vaccination needs to be demonstrated against alternative interventions to (monoclonal antibodies, treatments, improved sanitation etc.)	
	Uncertainties about vaccine full, long-term value	41. Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries	

Topic	Root cause	Challenge	Affected developers
5. Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery			
Freedom to operate	Intellectual property on processes or technologies	42. Potential need for IP license to commercialise	All
	Publicly funded research may result in limits on the use of IP	43. Restrictions imposed by public funders on IP "reuse"	
Return on investment (ROI)	Comparatively low market value of vaccines	44. Opportunity costs outweigh the vaccine's economic rationale	Large, mid
		45. Unpredictability of public tender markets	Large, mid, small
		46. Reference pricing can reduce the value of HIC markets	Large
		47. Pricing pressure may discourage innovation for improvements	Large, mid, small
		48. Limited availability of aligned partners to commercialise vaccine	Small, Academic
Long-term horizon of vaccine development	Limited private capital because of high risk, long-term investments	49. Insufficient access to funds for late-stage development	Mid, small
		50. Lack of private funding sources for vaccines targeted at LMICs	
		51. Need to make expensive manufacturing investments prior to clinical success or demand certainty	Large, mid, small
		52. Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	Large, mid
Liability risks linked to preventive medicine	Uncertainty of legal framework for unlicensed vaccine	53. Risks of legal action associated with widespread use of unlicensed vaccines (e.g. under EUAL or other schemes)	Large, mid, small
	Weak pharmacovigilance in LMIC	54. Exposure to risk to high-income markets from unsubstantiated issues in low-income markets	Large

Chapter 4: Impact of challenges

Challenges faced by vaccine developers differ in scope. Some are very specific, and some are universal across all diseases. The challenges also vary in terms of their collective impact on development cost and time and their public health relevance. Developers are confronted with decisions whether to overcome these challenges, one by one and collectively. Developer decisions are influenced by the estimated time and cost impact of overcoming the challenges and by how strategic those vaccine candidates are for the individual developers. As a consequence, some challenges are more important to developers than others and improvements in the overall vaccine ecosystem requires targeting those priority challenges.

Challenges by disease/archetype analysis

Not all diseases or the vaccines associated with them are equally affected by individual challenges. Some diseases/vaccines face unique challenges and others tend to face primarily the same challenges, and thus form an archetype. For instance, diseases that occur sporadically and without predictability pose a unique clinical development challenge because efficacy and safety must be assessed during outbreaks of diseases. Based on an analysis of the commonalities of challenges shared by diseases/vaccines, four archetypes were initially hypothesised from the analysis of the 33 diseases in scope:

1. vaccines for emerging infectious diseases with epidemic potential (EID)
2. vaccines for neglected diseases (ND)
3. vaccines for diseases that are AMR-related (AMR)
4. improved vaccines

However, the fourth archetype did not exhibit significant commonalities across challenges once an in-depth analysis was performed and was thus eliminated. Instead the analysis revealed a different fourth archetype: “vaccines for mixed markets”, meaning those vaccines that will be used in both low- and high-income markets. These archetypes have been defined based on the common challenges faced in vaccine development, which are often, but not always and not only, driven by disease features. Several vaccines appear in both a specific archetype and also in the mixed-market archetype; some in-scope vaccines did not fit into an archetype and are not listed below. Diseases in each archetype are shown in Table 5 below.

Table 5: List of diseases by archetype

EID	ND	AMR	Mixed market (MIX)
Chikungunya	Group A Strep	Clostridium difficile	Chikungunya
Ebola	Hookworm	E coli	Clostridium difficile
Lassa fever	Leishmaniasis	Group A strep	Dengue
MERS	Nontyphoidal Salmonella	Group B strep	ETEC
Nipah	Salmonella paratyphi	Pseudomonas aeruginosa	Group B strep
Plague	Schistosomiasis	S. aureus	HPV
Rift Valley fever	Shigella	S. pneumoniae	Japanese Encephalitis
Zika			Measles
			Multivalent Meningococcal
			Pseudomonas aeruginosa
			S. aureus
			S. pneumoniae

Each archetype is confronted with challenges in unique ways (Table 6 describes the relationship between archetypes and challenges). When all in-scope vaccines are affected by a challenge it is called a universal challenge and is further discussed in the next section.

- Vaccines for EID – diseases that occur predominantly in outbreaks and are sporadic and unpredictable in nature – are confronted with 23 of the 36 non-universal challenges. The need for an active outbreak to conduct efficacy trials, poor epidemiological surveillance in middle- income countries (MIC) and LICs, and the need to demonstrate value against other interventions are among the challenges specific to this archetype.
- Vaccines for ND – diseases predominantly occurring in LIC or MIC, and often disproportionately affecting impoverished subgroups within those countries, also face a large number of challenges, accounting for 16 of the 36 non-universal challenges. Lack of animal models that correspond to human immunogenicity, lack of standardised assays, reagents and standards for antigen testing and lack of political attention for diseases that do not cross-over to HICs are some of the most relevant specific challenges to this archetype, which is specially affected by challenges related to the feasibility of the clinical trials and of the predictability of the market.
- Vaccines for AMR are confronted with 19 of the 36 non-universal challenges, and more particularly are affected by challenges of market predictability and financial outcomes. Specifically, the need for target groups to be better articulated by public health authorities, the impact of reference pricing on the value of the HIC markets, and the risk for HIC markets from unsubstantiated issues in LIC markets.
- Vaccines for mixed markets – that is, those having markets in both high and low-income countries – are affected by eight of the 36 non-universal challenges. Vaccines in this archetype offer the possibility of recouping investment in high markets but, simultaneously, are affected by the challenges of market predictability and of financial outcomes over the long-term.

Overall, the EIDs and ND archetypes were predominantly affected by challenges specific to the nature of the diseases, such as their sporadic occurrence or their occurrence predominantly in the most impoverished groups within LICs. The AMR and mixed-market archetypes, on the other hand, are predominantly impacted by universal challenges, which pertain mostly to system weaknesses, such as insufficient capacity to develop and/or regulate. As such, the challenges faced by the EID and ND archetypes are more often archetype-specific whereas those faced by AMR and mixed-market diseases are less specific to the archetype.

Table 6 Mapping of most relevant challenges by archetype

In Table 7, challenges marked with ● indicate that 100% of diseases in the archetype are affected by the challenge; ◕ when 75% or more of the diseases in an archetype are affected by the challenge; blank cells indicate that less than 75% of diseases in an archetype are affected. When all 33 in-scope diseases are affected by a challenge it is indicated as "Universal" and discussed below.

Challenge	EID	ND	AMR	Mix
Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use				
Lack of recognised surrogates or correlates of efficacy	●	◕	◕	
Lack of animal models that correspond with immunogenicity in humans		◕		
Lack of standardised assays, standards, and reagents for antigen testing		◕		
Lack of standards by which platform technologies (e.g. adjuvants, mRNA) are transferable from one disease target to another	◕		◕	
Lack of support for alternative clinical pathways (e.g. HIS, animal rule, animal bridge to human immunogenicity)	◕		◕	
Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine		Universal		
Few NRAs able to regulate primary or secondary licensures of follow-on vaccines eligible for prequalification		Universal		
Lack of mechanisms that allow for use exclusively outside of the country of origin (e.g. EMA Article 58)	◕	◕		
Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs		Universal		
Lack of harmonisation on documentation of quality, efficacy, labelling, packaging and safety of biologicals & diagnostic across NRAs		Universal		
Feasibility and/or costs of testing under current clinical trial requirements				
Conducting efficacy trials requires an active outbreak (presence of disease)	●			
Conducting efficacy trials for diseases with poorly established, low or sporadic disease incidence	◕			
Real or perceived ethical concerns about trial design (e.g. administration of placebos, HIS)	◕	◕	◕	
Conducting efficacy trials for diseases involving animal transmission	◕			
Conducting efficacy trials for diseases with varied epidemiological profiles		◕	◕	◕
Additional requirements for use of new technologies (e.g. adjuvants, mRNA)	●		◕	◕
Lack of qualified in-country human resources to perform trials in MICs/LICs		Universal		
Lack of epidemiological surveillance systems in MICs/LICs to adequately quantify disease occurrence during or after clinical trials	●	◕	◕	
Lack of diagnostics capabilities to adequately quantify disease occurrence during clinical trials				
Insufficient WHO guidance to MICs/LICs on performance of clinical trials		Universal		
Increased pre-implementation safety studies for vaccines used first in LIC	◕	◕	◕	

Challenge	EID	ND	AMR	Mix
Feasibility and/or costs of manufacturing the vaccine to the right standard and volume				
Lack of personnel in the NRAs with expertise and experience to regulate manufacturing		Universal		
Process changes require regulatory approvals and/or “bridging” clinical trials		Universal		
Raw material/components changes require regulatory approvals		Universal		
Need for high Biosafety Level conditions (e.g. BSL 3/4)	◔			
Lack of possibility to share production process and/or facilities		Universal		
Low volume or sporadic demand creates production inefficiency	◔			
Inability to quickly access new (seasonal) variants/strains				
Long-lead time for establishing manufacturing capacity		Universal		
Lack of GMP-compliant contract manufacturers to produce clinical trial material		Universal		
Lack of partners available/capable of receiving technology transfer		Universal		
Lack of freedom to operate (existence of IP barriers)				
Factors impacting the predictability of the market and the likelihood of policy support for use				
Insufficient public budgets for purchase and implementation of immunisation programmes (Willingness to pay)		●	●	◔
Lack of policy entrepreneurs or immunisation champions to mobilise political and funding support	●	●		◔
Lack of political attention to non-epidemic diseases[3]	●	◔	◔	
Lack of global political attention to diseases that don’t cross-over into high-income countries (e.g. COVID-19 vs. Ebola)[4]		●	◔	
Growing vaccine hesitancy and spill-over of other vaccine issues impact acceptance and overall demand		◔		
Target groups not well articulated by public health entities (i.e., through a TPP)			●	◔
Lack of data for assessing potential impact of vaccination in particular in specific target populations		◔	◔	
Value of vaccination needs to be demonstrated against alternative interventions to (monoclonal antibodies, treatments, improved sanitation etc.)	●		◔	
Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries		Universal		

3. The lack of sustained political attention to EIDs post-outbreak and to non-epidemic diseases (e.g. rabies) that are not contagious means developers pursue solutions to these conditions with the risk that policymakers may not find them valuable.
4. Similarly, even serious epidemic diseases that are not seen as threats to developed nations - such as Ebola - do not receive sustained political attention, funding or prioritisation.

Challenge	EID	ND	AMR	Mix
Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery				
Potential need for IP license to commercialise	●	◕	◕	
Restrictions imposed by public funders on IP "reuse"	●	◕	◕	
Opportunity costs outweigh the vaccine's economic rationale	●	◕		
Unpredictability of public tender markets	◕	◕	●	●
Reference pricing can reduce the value of HIC markets			●	◕
Pricing pressure may discourage innovation for improvements		Universal		
Limited availability of aligned partners to commercialise vaccine		Universal		
Insufficient access to funds for late-stage development		Universal		
Lack of private funding sources for vaccines targeted at LMICs	●	●		
Need to make expensive manufacturing investments prior to clinical success or demand certainty		Universal		
Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	◕	●	◕	
Risks of legal action associated with widespread use of unlicensed vaccines (e.g. under EUAL or other schemes)	◕			
Exposure to risk to high-income markets from unsubstantiated issues in low-income markets			●	◕

Universal challenges

Some challenges are relevant for all in-scope vaccines and are more reflective of a general weakness in the system, independent of the archetype of vaccine under development. For instance, the challenge "Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals and diagnostics across NRAs" is a challenge that affects all vaccine licensures. The 18 universal challenges are presented in Table 7 below. Resolution of these universal challenges will have the potential to positively impact the entire vaccine development ecosystem.

In this table and throughout the remainder of this document universal challenges are denoted with an * after the challenge.

Table 7: Universal challenges

Topic	Root cause	Universal challenges faced on the way to vaccine introduction
Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use		
National Regulatory Authorities (NRAs) capacity	Lack of experienced personnel and financial/technical resources	Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*
		Few NRAs able to regulate primary or secondary licensures of follow-on vaccines eligible for prequalification*
Alignment of NRAs'	Desire of NRAs to assert local control/ NRA lack of understanding of global guidance and documentation	Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs*
		Lack of harmonisation on documentation of quality, efficacy, labelling, packaging and safety of biologicals & diagnostic across NRAs*
Feasibility and/or costs of testing under current clinical trial requirements		
Country-level capacity and capability	Insufficient human and technical resources to perform trials in MICs/ LMICs	Lack of qualified in-country human resources to perform trials in MICs/LICs*
	Insufficient technical guidance on clinical conduct	Insufficient WHO guidance to LMICs on performance of clinical trials*
Feasibility and/or costs of manufacturing the vaccine to the right standard and volume		
Regulation of manufacturing	Insufficient capacity in MICs/LMICs to regulate manufacturing	Lack of personnel in the NRAs with expertise and experience to regulate manufacturing*
	Management of variations requirements	Process changes require regulatory approvals and/or "bridging" clinical trials*
		Raw material/components changes require regulatory approvals*

Topic	Root cause	Universal challenges faced on the way to vaccine introduction
Manufacturing for commercialisation	Inherent uniqueness of each vaccine antigen	Lack of possibility to share production process and/or facilities*
	Vaccine development is niche area of technology and science	Long-lead time for establishing manufacturing capacity*
Partnerships		Lack of GMP-compliant contract manufacturers to produce clinical trial material*
		Lack of partners available/capable of receiving technology transfer*
Factors impacting the predictability of the market and the likelihood of policy support for use		
Uncertainty of policy recommendations	Uncertainties about vaccine full, long-term value	Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries*
Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery		
Return on investment (ROI)	Comparatively low market value of vaccines	Pricing pressure may discourage innovation for improvements*
		Limited availability of aligned partners to commercialise vaccine*
Long-term horizon of vaccine development	Limited private capital because of high risk, long-term investments	Insufficient access to funds for late-stage development*
		Need to make expensive manufacturing investments prior to clinical success or demand certainty*

Measurement of the impact of challenges

Because not all development challenges are equal, the relative importance of each was assessed based on three metrics: the theoretical financial cost and time required to technically overcome the challenge assuming a developer moved forward in vaccine development irrespective of the business rationale; and the collective impact of the challenge on public health. This assessment considered all of the vaccines affected by each challenge. For more information see below and for details on the methods for estimating these measures, refer to the Annex.

Impact of challenges on developers

The cost and time of overcoming each challenge were evaluated from the perspective of the developer. Literature review and/or expert judgement were used to estimate a low and high financial cost and time needed for the developer to persist in development, overcome the challenge and carry development forward. In some cases, overcoming the challenge was assessed as being exclusively a time delay and thus measured in number of additional years of development. In other cases, overcoming the challenge involved both time and money and in rare cases, just money was judged necessary to overcome the challenge. Given the specificity of each vaccine development pathway, the valuation of challenges was done using wide ranges meant to cover many circumstances.

Figure 14: Top 19 challenges by cost and time impact on developers

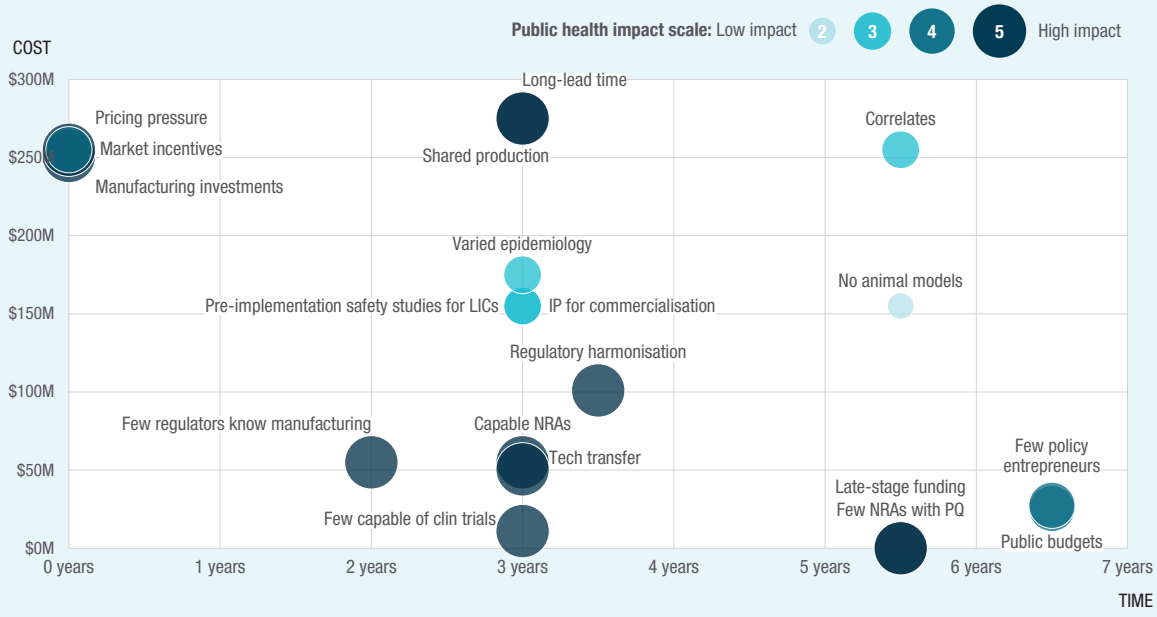


Figure 14 displays the 19 top challenges for developers with their cost and time implications.

While grounded in reality, the estimates are not meant to suggest that there will ever be a developer willing to spend the time or money required to overcome the challenge. In most circumstances the required investment will be too high, and the development would not proceed. The quantification allows for a comparison of the relative values of each challenge and can directionally indicate the benefits that could accrue from solving the challenge, however there is no direct link to indicate that solving a challenge would bring any specific financial or time benefits. See Chapter 5 for more on estimating the benefits of solutions.

The highest impact in term of costs are related to challenges associated with risky investment in costly manufacturing facilities, larger clinical trials and acceptance of lower revenue streams from HICs or in comparison to other products in the developer's portfolio.

The challenges with the largest time impact are those associated with the predictability of the market and the likelihood of policy support for use, with a median impact of 6.5 years. Unlike some other challenges that are largely controlled by the developers themselves, challenges related to the market or policy always involve a large number of stakeholders with diverse views and seeking to influence those views simply takes time.

Impact of challenges on global health

The impact of a challenge on global health is the third dimension in the measurement of the overall impact of challenges.

This measurement is based on an assessment of in-scope disease along six dimensions:

- Mortality: measured in absolute number of deaths – indicating the epidemiological importance of each of each disease.
- Public health priority: measured in terms of level of priority on WHO prequalification list and inclusion of the disease on priority pathogen lists of WHO and other public health institutions – indicating the attributed level of priority for public health.
- Relevance for AMR: measured based on the inclusion on Wellcome's list of priority diseases for AMR – indicating the contribution that a vaccine can give to reducing the AMR threat and alignment with one of the pillars of Wellcome's strategy.
- Level of global health support: measured as being backed by some exiting initiative – indicating the presence/absence of advocacy and financing efforts supporting the vaccine development and deployment.
- Relevance for impoverished populations: measured as being endemic in particular impoverished areas of the world – indicating the alignment with one of the pillars of Wellcome's mission.
- Fear of disease: measured on the potential geographical spread of an outbreak – indicating the perceived level of risk by key decision-makers.

Depending on the disease, each challenge received a score corresponding to the total of the disease scores. Since scores for each challenge reflect the scores of diseases associated with that challenge, the frequency of the challenge across diseases in scope is reflected.

In addition to the 18 universal challenges that received by design the highest score (being impacted by all diseases), challenges of market predictability and the long-term horizon of vaccine development emerged as the most impactful from a public health standpoint i.e.

- Insufficient public budgets for purchase and implementation of immunisation programmes (Willingness to pay)
- Lack of policy entrepreneurs or immunisation champions to mobilise political and funding support
- Unpredictability of public tender markets
- Lack of private funding sources for vaccines targeted at LMICs
- Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer

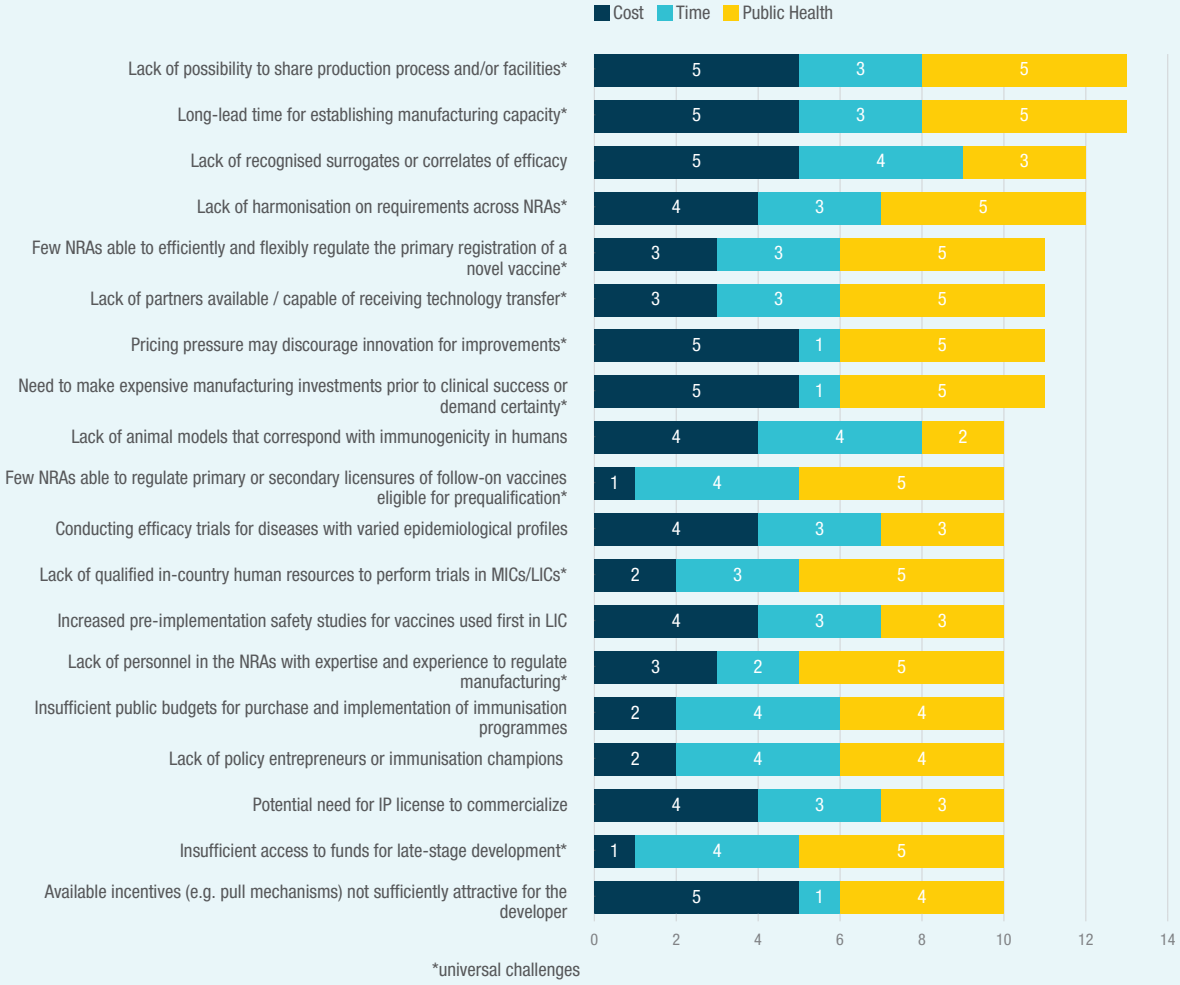
Overall challenges that relate to regulatory and/or financial outcomes showed a larger public health impact compared to other categories, the latter in view of the largest number of universal challenges included in this category.

Table 8 shows the average public health scoring for each category and the top 5 scoring challenges.

Table 8: Average public health scoring for each category and the top scoring challenges

Category	Nr. challenges	Nr Univ. challenges	Avg. score	Top scoring challenges
1. Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use	10	4	0.75	
5. Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery	13	4	0.75	• Unpredictability of public tender markets • Lack of private funding sources for vaccines targeted at LMICs • Available incentives not sufficiently attractive for the developer
3. Feasibility and/or costs of manufacturing the vaccine to the right standard and volume	11	7	0.71	
2. Feasibility and/or costs of testing under current clinical trial requirements	11	2	0.66	
4. Factors impacting the predictability of the market and the likelihood of policy support for use	9	1	0.65	• Insufficient public budgets for purchase and implementation of immunisation programmes • Lack of policy entrepreneurs or immunisation champions to mobilise political and funding support

Figure 15: Composite score of highest scored challenges



*universal challenges

Combined developers and public health impact

The combined impact of each challenge was a result of the consolidation of the impact across the three dimensions. Each challenge was assigned a composite score composed of cost (C), time (T) and public health (PH) based on a score of 1 – 5 for each component.

Figure 15 shows the highest scored challenges i.e. a score ≥ 10. See the Annex for the full scoring per challenge as well as the details into the implications of each challenge for the developer and the global community.

Challenges and decision making

In parallel, each challenge was assessed based on its influence on vaccine developers' decisions. This dimension is somewhat independent from the impact on developers' cost and time and on the public health impact, but it plays an equally important role in defining whether a specific development programme is financed. If a challenge is considered to be affecting an area of special importance for developers, even a smaller impact may be sufficient to trigger a negative decision.

The relationship of each challenge with the factors influencing decision-making was defined based on the findings from case studies, complemented with insights from the literature review and expert judgement of the MMGH team. Based on the level of importance of the different factors (discussed in Chapter 2), the level of influence of each challenge on vaccine developers' decisions was defined. Seven challenges were categorised as having a high influence, 34 challenges had a medium influence and 13 challenges are perceived to have a lower influence. Individual and topic level results are shown in the Annex (Table 20).

Value creation potential and technical feasibility emerged as the most influential factors and regulatory standard and practices, trial design and endpoint selection and uncertainty of demand emerged as the most influential sub-factors for developer decision-making.

Certain challenges emerged as more important because of their link to the most influential factors in the decision-making process. In particular, 5 challenges emerged as the most influential:

- **Opportunity costs outweigh the vaccine's economic rationale** – This influences overall value creation potential and the decisions related to the strategic fit (both organisational and portfolio fit). The ubiquitous nature of this challenge results in it being a factor in nearly all vaccine development programmes and thus it is highly influential, particularly in the later stages of development and for developers that have choices of where to invest.
- **Lack of recognised surrogates or correlates of efficacy** – This influences technical feasibility (both clinical and regulatory) and value creation potential (for the required additional investments). Although this is a technical challenge, its implications mean development is higher risk (more likely to fail), higher costs and longer time to licensure. It is a singular challenge that can be thought of as one of the riskiest aspects of vaccine development.
- **Lack of partners available/capable of receiving technology transfer** – This has a strong impact on strategic fit (both from an organisation as well as from a portfolio standpoint). For small or academic developers without manufacturing capabilities, the only choice in continuing development is to find a partner. This factor is highly influential because of the high costs associated with building vaccine manufacturing capabilities and the unavoidable necessity of finding a manufacturing outlet to continue in the development effort.
- **Lack of data for assessing potential impact of vaccination, particularly in specific target populations** – This reflects the cross-cutting challenges of sizing the target population, assessing the public health fit and assessing the revenue potential of the vaccine under development. This factor is a common reason for the uncertainty of potential future impact and therefore the certainty and value of a vaccine market. The problem is exacerbated for diseases with unpredictable disease patterns.
- **Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries** – This factor is affected by the ability to measure the burden of disease and cost-benefit balance, and hence value creation potential. Similar to the challenge of lack of data, lack of appropriate use of those data is another fundamental issue that can create uncertainty about the market.

Addressing these challenges could have a bigger impact on the vaccine ecosystem hence their identification complemented the impact measurement.

Priority challenges

Priority challenges were thus identified based on the combined measurement of the impact in cost, time and public health impact and their impact on decision-making.

Of the 54 challenges, the top eight scoring challenges (with scores > 10) for impact on cost, time or public health were prioritised together with the five with the highest impact on decision making. Two challenges belonged to both groups, leading to a first shortlist of 11. Five additional challenges were then added to the priority list out of the ones having the next score level on impact (10) and a medium impact on decision-making: two that were universal plus three additional challenges selected based on expert judgement. As a result, 16 priority challenges were identified (Figure 16).

Because they affect all vaccines/diseases, universal challenges tend to be among the priority challenges. Among the 16 priority challenges, 10 are universal.

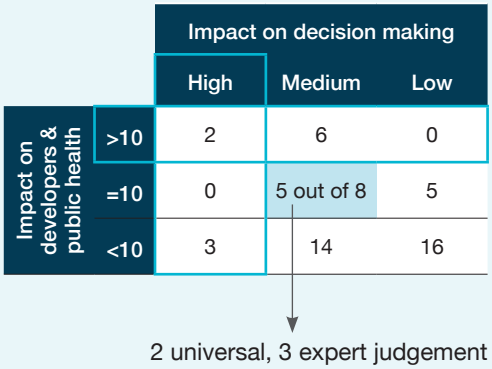
Table 9 lists the 16 priority challenges, with the median cost and time impact, and the stage at which the challenge impacts the developers decision-making process.

Priority challenges spanned across four of the categories i.e. no priority challenges were identified under the category “Feasibility and/or costs of testing under current clinical trial requirements”. This is because these challenges are more specific in nature and are sometimes limited to a smaller set of diseases, do not show the highest public health impact, and have an overall lower level of influence on the decision-making process.

Similarly, by the phase of clinical development of interest for this analysis (Phase 2 and beyond), the majority of clinical challenges have been resolved. Some priority challenges reflect the importance of clinical development on regulatory licensing and are reflected as regulatory challenges.

Mapping the priority challenges to the archetypes, as shown in Table 10, shows that all the priority challenges are affecting the majority of diseases included in the EID, ND and AMR archetypes, confirming the importance of addressing these challenges for organisations involved in these areas.

Figure 16: Challenges prioritisation process logic and outcome



The most critical challenges for EID:

- **Lack of recognised surrogates or correlates of efficacy** and the resulting difficulties in meeting the criteria for licensure through a field efficacy trial that, by definition, is dependent on presence of disease and is particularly unpredictable.
- **Opportunity costs outweighing the vaccine’s economic rationale** is especially important for EID because it reflects a situation where the development and availability of vaccine is effectively an insurance policy against a future outbreak of disease that may (or may not) cause adverse health and economic consequences in any specific country. It is most likely not worth the investment of any single country to develop these vaccines for itself, leaving the task to supranational funders whose investments would benefit multiple countries. Further, lacking steady demand the same supranational funders would need to pay for the establishment and replenishment of a stockpile of vaccine. While

Table 9: Cost and time implication for each priority challenge at each stage of development

Technical feasibility: Value creation 'Unmet need' and 'strategic fit' are not impacted.

Priority challenge	Median cost ($ millions)	Median time (years)	Decision-making stage			
			Pre-pivotal	Pivotal	Registration	1st country introduction
Lack of recognised surrogates or correlates of efficacy	255	5.5				
Lack of support for alternative clinical pathways	155	2				
Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*	55	3				
Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs*	50.5	3				
Lack of possibility to share production process and/or facilities*	275	3				
Long-lead time for establishing manufacturing capacity*	275	3				
Lack of partners available/capable of receiving technology transfer*	50.5	3				
Insufficient public budgets for purchase and implementation of immunisation programmes	25.5	6.5				
Lack of data for assessing potential impact of vaccination in particular in specific target populations	55	6.5				
Lack of use of appropriate models for economic valuation globally or in certain countries*	25.5	2				
Opportunity costs outweigh the vaccine's economic rationale	300	0				
Pricing pressure may discourage innovation for improvements*	251	0				
Limited availability of aligned partners to commercialise vaccine*	0	3				
Insufficient access to funds for late-stage development*	0	5.5				
Need to make expensive manufacturing investments prior to clinical success or demand certainty*	255	0				
Available incentives not sufficiently attractive for the developer	255	0				

Table 10: Mapping of priority challenges to archetypes

Challenges are marked with ◕ when 75% or more of the diseases in an archetype are affected by the challenge; ● indicates that 100% of diseases in archetype are affected by the challenge.

Priority Challenges	EID	ND	AMR	Mix
Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use				
Lack of recognised surrogates or correlates of efficacy	●	◕	◕	
Lack of support for alternative clinical pathways (e.g. HIS, animal rule, animal bridge to human immunogenicity)	◕	◕	◕	
Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine		Universal		
Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs		Universal		
Feasibility and/or costs of testing under current clinical trial requirements		**N/A**		
Feasibility and/or costs of manufacturing the vaccine to the right standard and volume				
Lack of possibility to share production process and/or facilities		Universal		
Long-lead time for establishing manufacturing capacity		Universal		
Lack of partners available/capable of receiving technology transfer		Universal		
Factors impacting the predictability of the market and the likelihood of policy support for use				
Insufficient public budgets for purchase and implementation of immunisation programmes (Willingness to pay)		●	●	◕
Lack of data for assessing potential impact of vaccination in particular in specific target populations		◕	◕	
Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries		Universal		
Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery				
Opportunity costs outweigh the vaccine's economic rationale	●	◕		
Pricing pressure may discourage innovation for improvements		Universal		
Limited availability of aligned partners to commercialise vaccine		Universal		
Insufficient access to funds for late-stage development		Universal		
Need to make expensive manufacturing investments prior to clinical success or demand certainty		Universal		
Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	◕	●	◕	

solutions have been proposed to overcome the challenges (e.g. Ebola vaccines) the long-term desire of funders to continue replenishing a stockpile that may not be used in the future has not been tested.

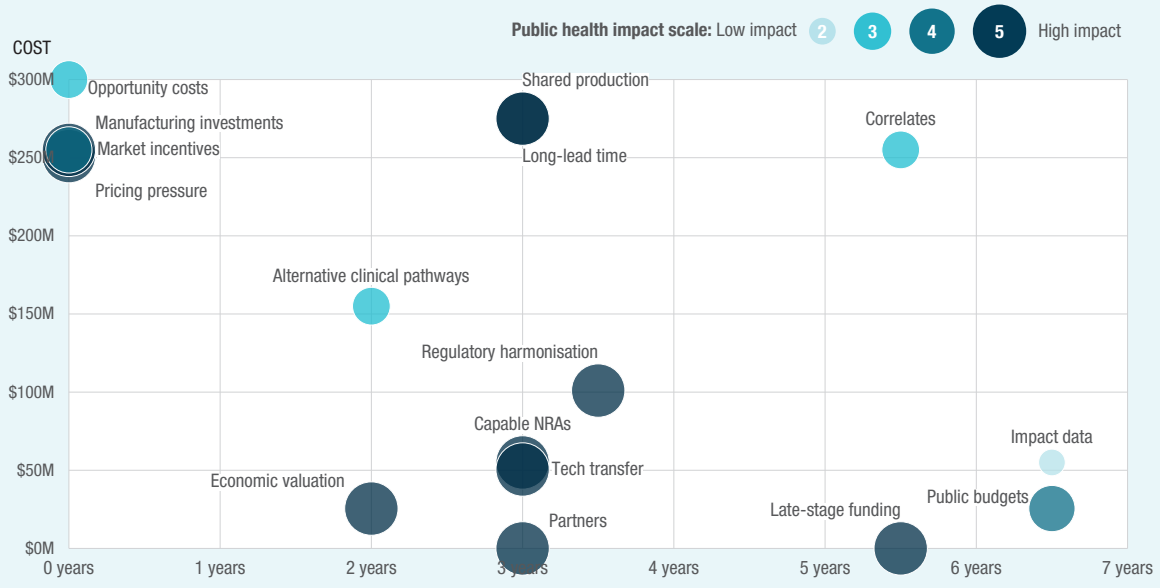
The most critical challenges for ND:

- **Insufficient public budgets for purchase and implementation of immunisation programmes,** reflecting the reality of competing priorities in countries' budgets, the likely lack of data supporting the impact of disease and therefore potential benefits of vaccination and, in many cases, the availability of inexpensive treatments that serve as the current mainstays of disease control.
- **Available incentives not sufficiently attractive for the developer** is a factor directly related to the insufficiency of public budgets. Developers with technically feasible vaccine approaches struggle to attract potential returns that would make financial sense to compensate their development expenses. Often the costs of vaccine development would need to be shared across much smaller sub-sets of populations, leading either to revenues too low to attract the developer or vaccine prices too high for country budgets.

For AMR the critical challenges mostly parallel to those of ND and for similar reasons. In the absence of clear data and a clear local problem on AMR, countries are likely to give priority to diseases causing morbidity and mortality now and to deprioritise a more theoretical or future problem. Similarly, the size of target populations and therefore market size for AMR vaccines in development are uncertain. Developers would be responsive to sufficient incentives; however, those have not yet been developed for vaccines directly targeting diseases of interest for AMR.

The mapping of the cost and time impact on developers of the priority challenges is shown in Figure 17.

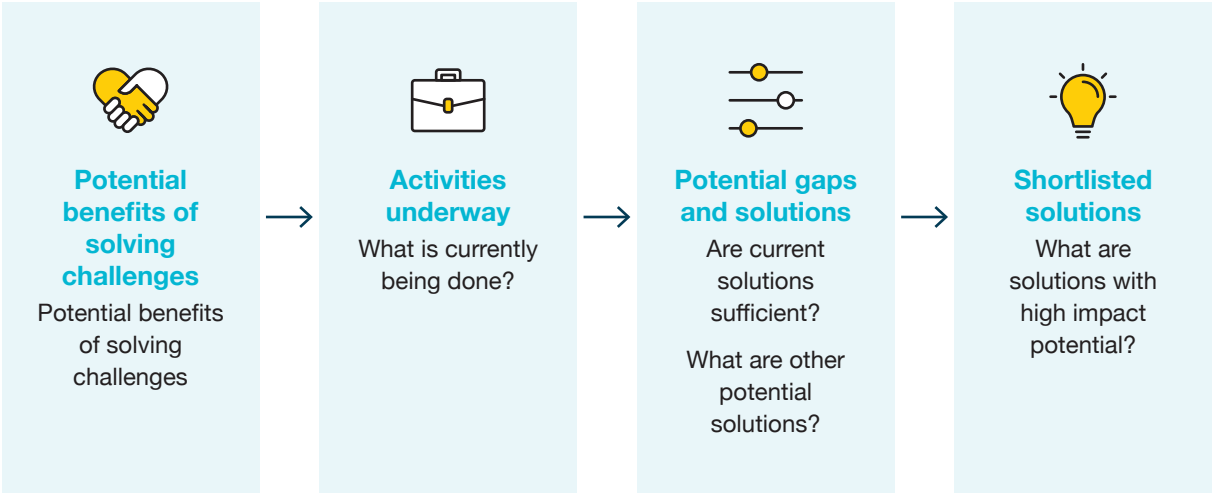
Figure 17: Cost and time analysis of each priority challenge



Chapter 5: Potential solutions

Interventions addressing priority challenges that are not successfully addressed by existing initiatives could positively impact the vaccine ecosystem. Potential solutions are presented for consideration.

Potential benefits from solving challenges



The following section assesses potential benefits in cost, time and public health in solving vaccine ecosystem challenges; describes activities that are currently underway to address challenges; addresses the completeness and impact of those activities and, last, proposes gap-filling solutionsto be considered.

Assigning exact quantitative benefits to solution sets would be misleading, but a directional perspective on where benefits would accrue could help to ground decisions on where to focus solutions.

Table 11 displays how solving each challenge would be expected to bring benefits to the ecosystem in cost, time and impact on public health.

Table 11: Benefits to cost, time and public health should the challenge be resolved

A full-circle ● indicates a large cost or time requirement, or bigger public health impact; relative to a half-circle ◐ and an empty-circle ○ which indicates a lesser cost or time requirement, or a lesser public health impact.

Challenge	Cost	Time	Public health
Lack of recognised surrogates or correlates of efficacy	●	●	◐
Lack of support for alternative clinical pathways	●	○	◐
Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*	◐	◐	●
Lack of harmonisation on requirements across NRAs*	●	◐	●
Lack of possibility to share production process and/or facilities*	●	◐	●
Long-lead time for establishing manufacturing capacity*	●	◐	●
Lack of partners available/capable of receiving technology transfer*	◐	◐	●
Insufficient public budgets for purchase and implementation of immunisation programmes	○	●	●
Lack of data for assessing potential impact of vaccination in particular in specific target populations	◐	●	○
Lack of use of appropriate models for economic valuation globally or in certain countries*	○	○	●
Opportunity costs outweigh the vaccine's economic rationale	●	○	◐
Pricing pressure may discourage innovation for improvements*	●	○	●
Limited availability of aligned partners to commercialise vaccine*	○	◐	●
Insufficient access to funds for late-stage development*	○	●	●
Need to make expensive manufacturing investments prior to clinical success or demand certainty*	●	○	●
Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	●	○	●

Activities underway and potential gaps to be filled

Many efforts to address challenges are led by individual institutions with little global coordination on addressing a specific challenge or across related challenges (Figure 18). Thus, initiatives and activities are unsystematic, discordant and can be duplicative. Few challenges are being addressed by more coordinated efforts, and even those may be insufficient to address complex inter-related challenges. For example, a large consortium like the Human Vaccines Project has multiple areas of interest; a single challenge area such as correlates of protection may be addressed from a science standpoint, but without needed attention to the regulatory hurdles that developers would face. This is

Figure 18: Organisations providing solutions mapped to priority challenges

	Academics	FDA/EMA	Gavi	Global initiatives/ collaborations	Governments	Large foundations	NGOs	PH research institutes	WHO
Aligned partners						●			
Alternative clinical pathways		●		●		●		●	
Correlates of efficacy	●	●		●				●	
Economic evaluation	●					●			●
Few capable national regulatory authorities		●		●					●
Impact data			●	●	●				●
Late stage funding			●						●
Long leadtime									
Manufacturing investment					●				
Market incentives			●			●			
Opportunity cost				●	●	●			
Price pressure			●			●			●
Public budgets									●
Regulatory harmonisation		●		●	●				●
Shared production					●				
Tech transfer						●	●	●	●

particularly an issue with the capabilities' challenges, where much of the effort must be directed at fundamental science to address the challenges.

A number of interventions attempting to overcome the priority challenges were identified and are discussed below. The interventions cluster around improving scientific and technical understanding and government agency and expanding institutional collaboration on regulatory and (occasionally on) manufacturing challenges. Vaccine developers themselves attempt to provide solutions or at least mitigate market, policy and financial challenges and WHO and countries play a role in improving data for decision-making. Solutions tend to be focused on individual components of the ecosystem or on those vertically affecting a particular disease, with fewer systematic, synergistic and horizontally focused solutions.

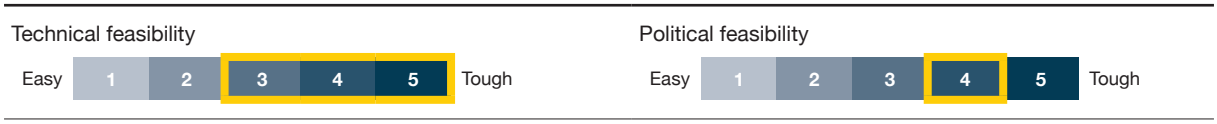
Each challenge has been evaluated based on its technical and political feasibility of solutions. Included in the assessment of technical feasibility are aspects such as the strength of the existing science, data and evidence as well as structural components such as information technology and human capital, including knowledge, skills and abilities. Political feasibility was evaluated in areas such as policymaker and stakeholder support, difficulty of collective action and solution management, funding requirements, who "loses" if the problem is solved and the complexity of legal changes (if needed).

The Likert scale refers to the feasibility of implementing a solution based on technical and political feasibility. * indicates that a challenge is universal.

Likert scale for assessing technical and political feasibility

1	Challenge is technically/politically feasible; easily accomplished
2	Challenge is technically/politically feasible but specific components are slowing progress; others are addressing
3	Challenge has faced technical/political blocks in the past
4	Challenge faces important technical/political hurdles; progress has been slow
5	Challenge is difficult to address technically/politically; will require significant resources (fiscal, human, technical, political) and many years to address

1. Lack of recognised surrogates or correlates of efficacy



Activities underway:

Targeted, fundamental research aimed at identifying surrogates or correlates of protection against targeted diseases is ongoing. WHO guidance [7] provides a general framework for action, together with a set of definitions from regulators (e.g. FDA, EMA). In addition to developers, academic institutions and public research institutes are active. These include the Vaccine Research Institute, Institut Pasteur, National Institute of Allergy and Infectious Disease (NIAID), disease-focused initiatives (e.g. TuBerculosis Vaccine Initiative, TBVI for TB), targeted efforts by the Innovative Medicines Initiative (IMI), and the Human Vaccines Project.

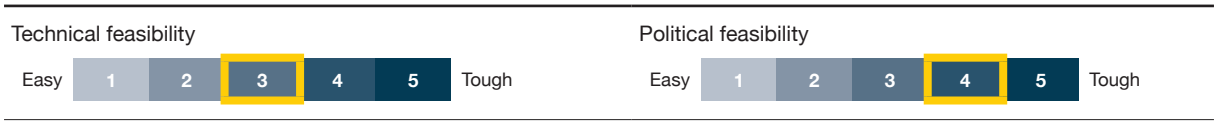
A disease-by-disease approach to researching surrogates or correlates of efficacy is technically feasible, though easier for some diseases than for others (3), and Wellcome has ongoing projects in this area. But an approach spanning multiple diseases or the human genome is extraordinarily technically complex (5) and would require significant resource allocation over many years. Politically, owing to other institutions' historical engagement and perceived "ownership," this challenge is assessed as difficult (4).

Potential gaps to be filled and other solutions:

This challenge has a very broad scope because protective immune responses are typically disease specific. Research undertaken in large consortia of academics, developers and public health research institutes (such as the Innovative Medicines Initiative or Human Vaccine Project) is often motivated by specific interests or a desire to increase knowledge about immune function in general, and it may not be sufficiently specific to solve unique vaccine development challenges. Additionally, this research tends to be lengthy, often requiring the pooling of knowledge over several years before unique discoveries are made. In reality, developers themselves spend much time and effort in isolation studying the nature of animal and human responses to a disease antigen, in the hopes of discovering a surrogate of protection. If too lengthy, developers may move ahead with clinical development at-risk, hoping that their vaccine candidate will show effectiveness in a field trial. Greater information sharing between researchers, including by individual developers, could greatly benefit all vaccine development and additional forms of research, such as modelling by artificial intelligence, could greatly contribute to accelerating discoveries around protective immune responses.

Individual developers, however, are unlikely to be very forthcoming with their own discoveries since they operate in a competitive environment. Public health institutes and large consortia with information-sharing agreements play critical roles in communicating discoveries of this nature, but as mentioned above, their research is unlikely to be sufficiently timely or specific to meet the needs of developers. This leaves a gap in the current solution space. Innovative mechanisms, such as research prizes or other incentive mechanisms, to accelerate discoveries that could benefit all vaccine development, could be considered targeting research institutions to facilitate progress on the basic science. On the other hand, individual developers are unlikely to postpone vaccine development while awaiting outcomes of incentivised research. An extremely focused research coalition, with the full engagement of vaccine developers, pursuing a mandate to solve very specific challenges for a limited number of priority diseases might be the most effective means to solve this challenge. Such a coalition could be funded in aggregate by governments with like-minded disease priority development objectives or by large private foundations. Outputs of the research initiative would need to be in the public domain for use by developers.

2. Lack of support for alternative clinical pathways (e.g. HIS, animal rule, animal bridge to human immunogenicity)



Activities underway:

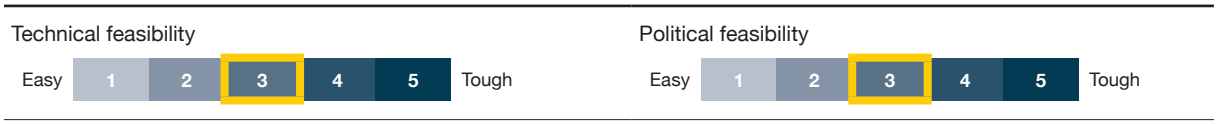
The US FDA guidance [8] on the "animal rule" and EMA implementation of a consultative approach for specific, bespoke solutions are examples of regulatory support for alternative pathways. Developers must identify and propose alternatives to regulators with good justification for how the alternative design will provide needed assurances. Many funders of scientific research, such as the Academy of Medical Sciences, the Wellcome Trust (with a special focus on HIS), the BMGF, public research institutes (e.g. INSERM, NIAID, UK Medical Research Council (MRC)) are actively doing research on the fundamental principles of alternate approaches. The Human Vaccines Project is also playing a catalytic role with the creation of a network of leading university and academic research centres whose work is focused on progressing clinical development.

As science advances, regulators have signalled some openness to alternative clinical pathways, earning this a technical feasibility score of 3. Politically it is slightly more difficult (4) because risk-averse manufacturers and regulators are reluctant to make changes they perceive may produce results that are less reliable in terms of guaranteeing vaccines' safety and efficacy. Nonetheless, the urgency to bring COVID-19 vaccines into widescale use and the world's subsequent experience with compressing traditional phases of development may open up possibilities to pursue alternative clinical pathways.

Potential gaps to be filled and other solutions:

Incremental changes have been fostered through regulatory science and developer creativity in suggesting novel approaches to regulators in specific countries. Modernising the approach to clinically demonstrating the efficacy and safety of vaccines for regulatory purposes has progressed in the past ten years, but a gap remains, and progress needs a change of pace to accelerate licensure of vaccines against additional diseases. Although vaccine developers and regulators are the important actors, a consortium of scientists from different disciplines (e.g. artificial intelligence) may provide a catalyst to break away from incremental changes and approach transformational change. This consortium could be convened and funded by foundations or governments. A broader-based constituency of actors from disciplines outside of vaccines is likely needed. Picking several notoriously difficult vaccines and putting those as a challenge in front of a group could be a way to spark new ideas for both regulators and developers for them to ultimately implement. This type of activity is beyond the scope of any single regulatory agency or developer but would likely be welcomed by both groups. Change in this area is feasible but will develop over a decade and will be tied to vaccines licensed through novel pathways that provide precedents and open the door for other agencies to adopt similar approaches to the same disease or for similar approaches to be applied to other diseases.

3. Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*



Activities underway:

Various interventions have been implemented by WHO and EMA and through bilateral regulatory cooperation agreements (e.g. Health Canada with the Indian NRA) to strengthen NRAs in developing countries where vaccine manufacturers are located. Other approaches include the centralised procedure of the EMA [9,10] that combines resources of all EU member countries. A centralised procedure is being explored in other regions such as Africa through the African Vaccine Regulatory Forum (AVAREF). The International Coalition of Medicines Regulatory Authorities (ICMRA), AVAREF and the Pan American Network for Drug Regulation Harmonization (PANDRH) play important roles in knowledge transfer and peer learning among their members.

Building regulatory capacity and capability in LMICs has been the work of many years already, without great success. Technically, building capacity (adding staff, IT resources, etc.) and building capability (improving education and experience) are not difficult with sufficient resources (mostly financial), netting this out at 3. Politically, strengthening in-country regulatory systems is also not terribly complex, given the appeal to national self-sufficiency – but the requirement of adequate public budgets to support regulatory excellence is a stumbling block, also judged at 3.

Potential gaps to be filled and other solutions:

The solutions offered are primarily focused on capacity building of NRAs in LMICs by WHO and some regulators and are insufficient for short- or mid-term easing of the challenges. It will be more than a decade to achieve change sufficient to meet the regulatory challenges of vaccines.

In the short-term, important incremental changes could be realised by focusing on challenges associated with specific antigens/vaccines and those specific to a certain component of regulatory science that may touch several vaccines. CEPI has done this for two of the vaccines in its portfolio. A methodical approach, undergirded by a sound research agenda and undertaken by a third-party convener, could yield more systematic gains.

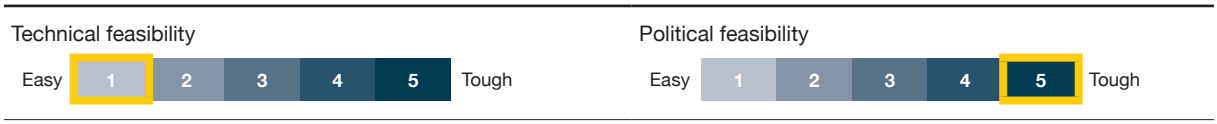
Additionally, there are a number of mid-term solutions, while regulatory systems are being strengthened at country level, that could benefit from higher profile convening and focused discussion or targeted funding to spur adoption:

EMA encourages developers to seek review and a positive opinion through Article 58 and works closely with WHO to conduct risk-benefit analysis for target countries outside the EU, facilitating a streamlined WHO PQ evaluation and licensure in target countries. Expanding Article 58-like mechanisms to other Stringent Regulatory Authorities (SRAs) would give developers more options and reduce at least one aspect of regulatory uncertainty.

Similarly, when evaluating an intervention for a pathogen with high morbidity and mortality that will be used primarily in LMICs (e.g. Ebola vaccines), SRAs should consider the risk-benefit profile for use in at-risk countries rather than in their jurisdictions. Codifying this practice into regulatory science and strategy would further reduce developers' uncertainty about licensure.

Regional regulatory systems, functioning for a group of countries, could be further encouraged and supported to share resources and provide needed oversight for the bloc. Pooled regulatory science resources, just as pooled procurement, is a wise use of scarce public health infrastructure.

4. Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs*



Activities underway:

Mutual recognition (e.g. between EMA and FDA), or collaborative agreements (e.g. animal testing performed in the exporting country's national control laboratory and accepted by the importing country) to align requirements and accept dossiers from other NRAs technically go beyond harmonisation but are effective ways to achieve a similar goal. Several organisations (FDA, International Council for Harmonization (ICH), EMA, Therapeutic Goods Administration (TGA), National Institute of Infectious Disease (NIID), International Pharmaceutical Regulators Program (IPRP)) have been involved in dialogues aimed at progressing along those lines. Initiatives have been started at global and regional levels, such as WHO.

Solutions to this challenge are imminently technically feasible (1). No major technical hurdles exist to harmonising requirements, but the political hurdles are significant, given countries' preference for regulatory self-determination as well as nation-specific policies, procedures and regulations. Furthermore, NRA staffing requirements would likely fall with harmonised requirements – once a lead entity established benchmarks, the rest would follow suit – which could be expected to draw resistance from public sector regulatory employees and unions. Finally, players already active in this space could be expected to defend their turf (5).

Potential gaps to be filled and other solutions:

For many years the need for harmonisation has been highlighted, the benefits agreed to and potential areas of work identified and discussed. Outside the European region the efforts toward centralised procedure led to the establishment of preliminary dialogues in particular in Africa (with AVAREF) and in the Americas (PANDRH) but did not translate into implementation of any specific centralised procedure. For these centralised approaches, political buy-in at country level is the main pre-requisite, with countries needing to be willing to accept some form of supra-national process. However, this change may be seen as reducing national power/control and may result in reduction of some financial proceeds from the licensure process. For those reasons, evolution is slow and requires a balanced approach.

Harmonisation of individual procedures could greatly benefit the ecosystem and can be pursued along three dimensions: (a) the requirements for licensure (e.g. accepting the same clinical studies and outcomes); (b) the extent of NRA's review of the dossier (e.g. will a country accept a site inspection report from another agency and forego a bespoke inspection); (c) the extent of dependence on another NRA's approval (e.g. if a product is approved in country X, then country Y will automatically approve it). Increasing levels of harmonisation and mutual recognition can be pursued across the three areas.

Table 12: Target state of harmonisation on the 3 dimensions

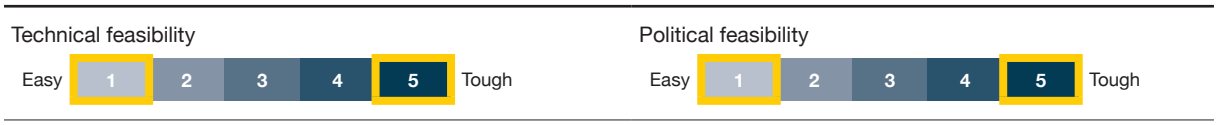
	Requirements	Review	Approval
No Harmonisation	**Differ**	**Each country does full review**	**Each country separately**
Harmonisation	**No bespoke requirements**	**Relying on another country or joint entity**	**Approved based on another country or joint entity**

The long-term, very ambitious full-harmonisation goal is the creation of truly global mutual recognition process. Regional mutual recognition procedures can represent an intermediate step of great impact. Those improvements should be pursued beyond vaccines and could have far-reaching effects, reducing duplicative clinical, manufacturing and regulatory activities.

However, a change of this magnitude will likely require significant political advocacy and the time to see results materialising will be a decade or more. Success in the short-term is improbable, but it is likely that a long-term, well-orchestrated process could build on existing efforts such as the ICH and produce results. This advocacy also should be supported by an evidence base, which has been partially created [11].

A neutral entity aligned with neither the developers nor countries can potentially play a catalytic role to produce an independent evidence base and shepherd the players through advocacy over the long time required to achieve such a goal. A foundation or an academic institution can play a critical role in this space. Donors who support procurement of healthcare commodities including vaccines in LMICs would also be well-placed to lead this activity as they, and countries, would realise benefits from eventual implementation. Any entity will have to work closely with leading regulatory agencies and with WHO.

5. Lack of possibility to share production process and/or facilities*



Activities underway:

Public-private partnerships have been created to establish production facilities in advance of the potential need for manufacturing. The UK Vaccine Network brings together 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. The UK government committed £120 million between 2016 and 2021 for the development of new vaccines for such diseases, in line with the expert advice provided by the UK Vaccines Network. The US Biomedical Advanced Research and Development Authority (BARDA) established the Centers of Innovation for Advanced Development and Manufacturing, a partnership in which the US government and private sector partners share facility construction costs.

Sharing production facilities is technically quite feasible for sharing across homogenous platforms and/or pathogens (1) but faces nontrivial hurdles for sharing across heterogenous platforms and pathogens (5). Similarly, political feasibility varies, depending on circumstances: Sharing production lines or facilities is very difficult in free market economies in which manufacturers are operating competitively (5) but could be politically simple (1) in planned economies and/or with state-controlled developers.

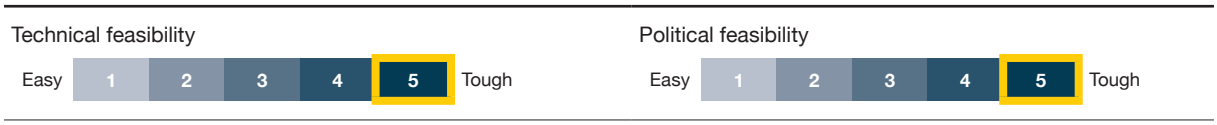
Potential gaps to be filled and other solutions:

Current solutions, such as the UK Vaccine Network and the Centers of Innovation for Advanced Development and Manufacturing, attempt to alleviate the burden on the developer by sharing costs between public and private sectors. These arrangements between industry, academia and relevant funding bodies make targeted investments in specific priority vaccines or establish production facilities in advance of the potential need for manufacture. However, they are limited to the priorities of the funders and as such, they will always be limited in scope. Other solutions include the eventual acceptance of platform vaccine manufacturing technologies that could share some aspects of manufacturing.

There is a solution gap that falls primarily on developers to solve. Developers that are sufficiently confident in the market will look to overcome this challenge by securing the necessary resources for the manufacturing facility. But vaccines with limited market potential will likely be abandoned by developers.

Individual developers may apply innovative manufacturing technology solutions to manufacturing but since manufacturing is most often considered proprietary by developers, there is unlikely to be much sharing among individual developers. Among external stakeholders, a constellation of think tanks, along with regulators and technology developers, are seeking to overcome these issues, and may be useful to inform better strategies to reduce costs of establishing manufacturing capacity.

6. Long-lead time for establishing manufacturing capacity*



Activities underway:

Individual developers seek to compress timelines to establish manufacturing when possible, but some delays are non-compressible without novel paradigms for vaccine manufacturing. In addition novel, multi-purpose manufacturing technology [12] biospecifics, fusion proteins, and nanobodies. This diverse portfolio carries a greater range of product demands (kg/year is increasingly being used by some manufacturers as are platform vaccine technologies (e.g. nucleic acid vaccines).

Current science makes this solving this challenge exceedingly difficult (5), but that has the possibility of ameliorating over time as technology evolves. Similarly, the political feasibility is limited (5), given that timely development of manufacturing capacity is not fundamentally a function of governments, except in the instance of state-owned facilities or government-funded production to respond to biosecurity threats.

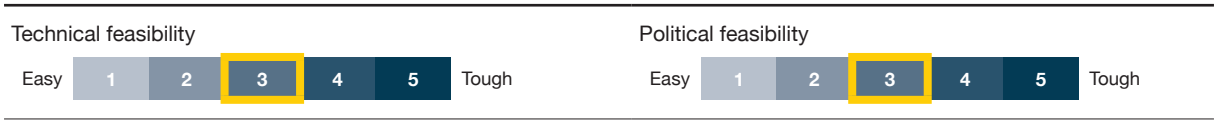
Potential gaps to be filled and other solutions:

Current solutions include seeking to apply know-how and best practices across as many products as possible to reduce unexpected delays when establishing manufacturing or applying novel, multi-purpose manufacturing technologies [12] biospecifics, fusion proteins, and nanobodies. This diverse portfolio carries a greater range of product demands (kg/year to reduce time. However, these solutions have relatively minor impact on the long lead time required to establish manufacturing capacity.

Thus, a current solution gap exists. In the absence of novel manufacturing technology and processes, or major changes to regulatory requirements, development times for priority diseases are likely to remain lengthy. External stakeholders could take stock of all proposed solutions to accelerate the development of a COVID-19 vaccine to assess their potential applicability to other priority vaccines. This could be spearheaded by organisations already devoted to accelerating vaccine development, like CEPI, or large foundations that have other major investments in priority diseases.

Predicting the impact of this challenge across vaccines in development is theoretically possible by pooling data on sunk costs and time lost, with an additional variable to incorporate opportunity costs when candidates fail in later stages. However, manufacturers do not make this data public and the generic probability of failure may or may not be applicable for a given vaccine candidate.

7. Lack of partners available/capable of receiving technology transfer*



Activities underway:

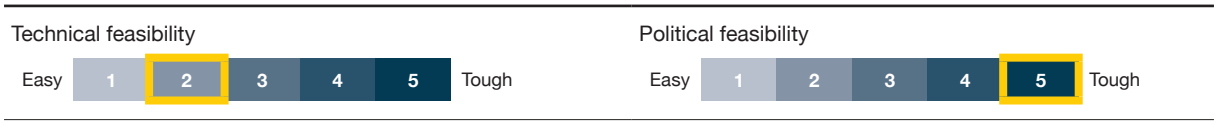
Over the past 15 years, several initiatives have been established by UN agencies, governmental and research organisations and foundations to facilitate transfer of vaccine manufacturing process and know-how, thus expanding the number of potential vaccine manufacturing partners. WHO's Technology Transfer Hub for Influenza [13], the National Institutes of Health's (NIH) Rotavirus Technology Transfer programme [14], the Global Polio Eradication Initiative's ongoing support transfer technology for polio vaccine production, the work of the US Centers for Disease Control and Prevention (CDC) Technology Transfer Office (TTO) in particular for assays and diagnostics (e.g. pandemic flu), the International Vaccine Institute (IVI) work on Cholera and Typhoid, the many initiatives directly or indirectly led by the BMGF (many of them via PATH) and the work of the Hilleman Labs are all examples of this drive aimed at enlarging the manufacturing base for vaccines.

Just as with building NRA capacity, strengthening the capacity and capability of LMIC vaccine developers is fairly readily accomplished from a technical standpoint (3), given sufficient time and resources. It is possible that the requirement for global supply of COVID-19 vaccines may spur further growth in the number of producing partners. Politically, this is also largely feasible (3), with the right structures to increase the cooperation of current manufacturers. Absent market-based incentives, established manufacturers, whether MNCs or DCVMs, see little attractiveness in creating greater competition.

Potential gaps to be filled and other solutions:

Initiatives have resulted in a large number of technology transfers across many of the vaccines currently available, with a positive impact on the number of manufacturers available as partners. Even so, there remains a dearth of qualified vaccine manufacturers to meet global needs. An independent party with sufficient clout in the vaccine space could spearhead the effort: aligning stakeholders, designing the appropriate incentives, refining legal constructs and assembling a programme aimed at further increasing the base of manufacturers, most likely in collaboration with academic institutions. Facilitation by the DCVMN could be possible.

8. Insufficient public budgets for purchase and implementation of immunisation programmes



Activities underway:

Many efforts have been implemented to address fiscal space for immunisation: for example, the Sustainable Development Goal push for health budget increases, Gavi support to eligible countries, UNICEF pooled procurement for MICs and the Vaccine Independence Initiative [15], the Pan American Health Organization (PAHO) Revolving Fund, the Immunization Financing Resource Guide, which explores financing sources and associated costs of immunisation programmes, other joint procurement initiatives (e.g. Baltic countries and the Gulf Cooperation Council), WHO Middle Income strategy, Market Information for Access to Vaccines (MI4A) [16] and Sabin's Sustainable Immunization Financing Program. Actions aimed at increasing the willingness to pay are focused on local advocacy efforts from public health agencies, NGOs, manufacturers, key opinion leaders, public figures and, at the global level, on disease-specific initiatives (e.g. Accelerated Development and Introduction Plans, ADIPs, WHO goals for HPV elimination).

Transitioning vaccine cost-effectiveness evaluation to represent the full societal value of vaccination will help solve this challenge and is largely technically feasible, though building better and more integrated databases across a variety of socioeconomic variables remains a gap, thus earning this a 2 for technical feasibility. Political feasibility, however, is harder (5). No document is more policy and polity explicit than a budget. Governments' choices about spending are constrained, particularly in the current pandemic, but they are, nonetheless, choices.

Potential gaps to be filled and other solutions:

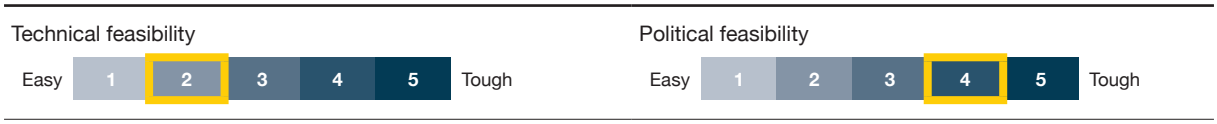
Countries eligible for Gavi support have been very successful in growing their vaccination budgets – albeit in the limited fashion required from co-financing requirements. However, MICs not supported by Gavi have lagged, and efforts have had limited success in increasing immunisation budgets and vaccine adoptions.

In its new strategy Gavi plans to introduce forms of catalytic support for some MICs that have graduated from its support or for other countries never eligible for Gavi support that remain below the 4 000 USD GNI threshold. Gavi is also exploring engagement with countries that have GNI per capita of 4 000 to 6 000 USD, with a special focus on advocacy for immunisation financing. PAHO has historically played an important and successful role in advocating for immunisation financing in South and Central America and the Caribbean. At the global level, WHO developed a MIC strategy discussed at WHO's Strategic Advisory Group of Experts on Immunization (SAGE) in 2015. Finally, a recent effort in the Southeastern European countries led to the creation of a health network to bring countries together to discuss common problems and encourage them to share best practices, including budgeting.

Despite those efforts, not much success has been achieved in changing the practice of under-investing in health and in preventive medicine specifically. There is potentially space for an independent party, which doesn't directly interact with countries and thus is not influenced by any relationship, to transparently report on expenditures on immunisation programmes and health in absolute numbers and as a percentage of the total public budget, particularly against other expenditures. Some work has been initiated in this field by WHO as part of the MI4A

initiative and can serve as a base. This effort would improve upon the data available through WHO. It would be important to understand how those funds are derived; for example, whether people are paying for vaccination out of pocket or are taxed through vehicles such as consumption taxes. The creation of a yearly Country Vaccination Index, allowing countries to see exactly where they stand in comparison to others, can play quite an important role in highlighting the laggards and providing ministries of health and advocates with an additional tool to leverage in budget negotiations.

9. Lack of data for assessing potential impact of vaccination specific target populations



Activities underway:

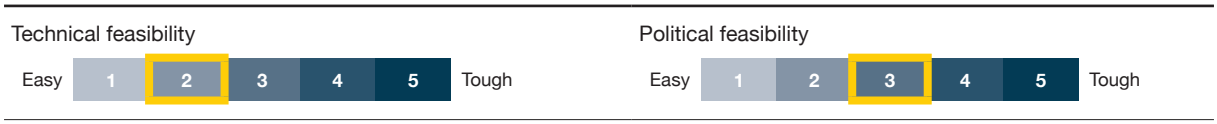
Several initiatives focus on strengthening country capacity for routine monitoring and evaluation of the epidemiology of diseases, particularly in specific target populations, as well as the generation of epidemiologic data to inform evidence-based decision-making. The following groups offer specific technical support in their respective focus areas and/or regions: WHO sentinel site surveillance network and GISRS network: Gavi's strategic focus area on data, USAID's MEASURE initiative, programmes by the US CDC, the East African Integrated Disease Surveillance Network (EAIDSNet), the REDISSE project, funded by the World Bank, the West African Health Organization (WAHO) and the Asian Development Bank and Africa CDC.

Building strong surveillance and epidemiological systems has been the work of decades for public health institutions, with slow progress being made. There are unique challenges to truly rare or episodic diseases, but these are solvable. The technical complexities are not significant (2). The biggest challenge is political and is simply devoting sufficient resources to strengthen both capacity and capability. In addition, in some countries, officials may be reluctant to fully characterise a given health problem because they will then have to allocate spending to address it. This was assessed as a 4 for political feasibility.

Potential gaps to be filled and other solutions:

For the developer, this challenge may severely limit interest in diseases for which little is known about the epidemiology in specific sub-populations. Particularly for vaccines with limited markets, developers are not likely to make an effort to ascertain the needs for specific target groups. Several actors currently occupy the solution space for this challenge. Initiatives have focused on strengthening country capacity for routine monitoring and evaluation of the epidemiology of diseases. But the scope and sustainability of supporting routine monitoring is beyond the capability of any single solver. Additionally, data is not sufficient to incentivise developers. The solution to the challenge is likely to require an assessment into how more timely, complete and accurate data can meaningfully inform better policy-making. This requires elaborating a research agenda – as MMGH is doing with Wellcome for cholera. Only then would it be possible for the necessary data to be collected in a systematic way to address the research questions. This would require bringing together developers and policymakers to determine how better direction could be provided on specific target populations, such as pregnant women or displaced populations, through TPPs or other guidance. A comprehensive data clearinghouse that would provide developers, health authorities and funders with a broader, societal view of the full value of vaccination should be contemplated. Public sector actors, or large private foundations like Wellcome may be ideally suited to creating this type of space.

10. Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries*



Activities underway:

Organisations are trying to address shortcomings and define a more robust approach, particularly regarding the prominence of cost-effectiveness analyses, rather than full-value cost-benefit analyses, retained in many ministries of health. These organisations include academic institutions, WHO, Wellcome, BMGF and vaccine manufacturers as well as published tools on economic evaluation of vaccine.

Overall, this is not particularly technically challenging, but the lack of robust socioeconomic databases, a particular challenge in nations with large informal sectors, is a limiting factor, earning this a score of 2. In terms of political feasibility, dislodging the entrenched cost-benefit models used by many nations and WHO will be challenging. Additionally, constraints on health budgets militate against using full-value models because they make such a clear case for vaccines compared to many restorative interventions. Solutions are available, but implementation will likely be slow (3).

Potential gaps to be filled and other solutions:

Existing solutions to dislodge the entrenched cost-effectiveness models used by many health authorities have been marginally effective. It is essential that models describing the full value of vaccination (or, more accurately, immunity from disease) be established as the standard of practice. Governments experiencing budgetary pressures may discourage societal view cost-benefit analyses that demonstrate overwhelming benefits of vaccination. Models are necessary but insufficient to make the case. A concerted effort to "globalise" full-value estimations could drive a more evidence-based perspective on vaccination, its costs and benefits to countries. Among the possible interventions:

Model economic valuation curricula – short courses for practitioners as well as incorporation into all public health degree-granting institutions.

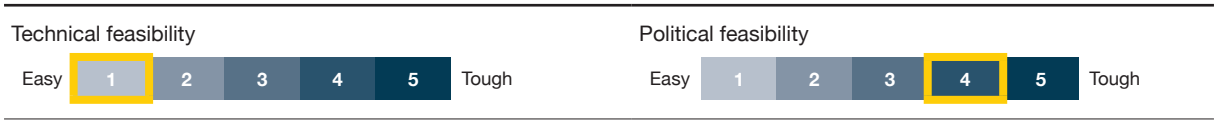
Fellowships for LMIC students and staff for locum tenens study at leading academic institutions and certification in vaccination valuation.

Incorporating into WHO guidance on immunisation programmes.

A "Stop Selling Vaccination Short" campaign with a broad consortium of stakeholders that explicates the full societal value of immunisation and the types of health economics analyses appropriate for developing those estimates should target the media and, through them, policymakers and the public.

Trusted third-parties – academia, foundations – should lead the charge. For this to be successful, these third parties would need to strengthen the collection and use of data for decision-making in LMICs and support making it policy-ready (informatics), along with assessing the role of advocacy in supporting data-informed decision-making. Some quasi-permanent structure, such as a global immunisation value centre, might be considered.

11. Opportunity costs outweigh the vaccine's economic rationale



Activities underway:

Financial incentives (discussed below) provide some improvement in market certainty and therefore lower opportunity costs for developers. Other mechanisms for increasing financial rewards are priority review vouchers by the US FDA [17]. Funding to reduce development costs (push funding) is done by BARDA, CEPI, foundations such as BMGF and Wellcome and multilateral country-specific investment funds such as the Global Health Innovation Technology Fund (GHIT) and RIGHT Fund.

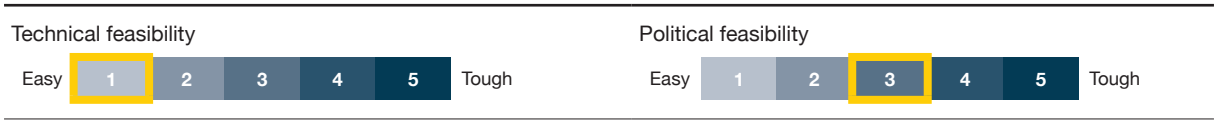
Provided governments or others are willing to devote the resources to incentivise manufacturers to pursue vaccines, this challenge is technically not difficult (1). However, in a free-market structure, the political feasibility is more problematic and would require a shift in thinking about the underlying validity of a market-based approach to vaccine development and supply (4).

Potential gaps to be filled and other solutions:

Piecemeal efforts in this area have achieved some progress for vaccines one-by-one. To encourage developers to sustain efforts on vaccines over time, however, will require end-to-end solutions. Many developers are faced with the economic reality of directing resources to higher value oncology candidates or vaccine candidates with a known and high set of development costs and a much less certain compensating revenue stream over which they have little control. Similarly, as Gavi has done for low-income countries, if the combined demand of middle-income countries was more certain, that would assure developers of an ongoing market that could balance some of the opportunity costs. This idea might have even more attractiveness if aggregated demand was not vaccine by vaccine but rather across a manufacturer's portfolio, which could be achieved by a creatively structured central contracting or procurement agency.

Conventional market-based vaccine development is unlikely to succeed where the market (i.e. demand for the vaccine at a price sustainable for the developer) is uncertain. Therefore, new paradigms are required for vaccines with low market predictability. Think tanks and other consortia are needed to develop consensus on alternatives to market-based development, manufacturing and use that will serve those most in need.

12. Pricing pressure may discourage innovation for improvements*



Activties underay:

Incentives targeted at innovations and improvements of existing vaccines can positively alter the current situation. The Wellcome Trust (via the Hilleman Labs), BMGF, Gavi and WHO are active in this space. Initiatives like the Grand Challenge, Gavi's Vaccine Innovation Prioritization Strategy (VIPS) [18], and WHO Total System Effectiveness Initiative [19], now known as CAPACITI, provide direct or direct incentives for innovation and improvements.

Although many innovations are technically fairly easy (1), in a market-based system where buyers are indifferent to innovation, there is no rational economic incentive for developers to innovate. Improving buyers' willingness to pay by demonstrating the full value of the innovation in the context of vaccination programmes (e.g. ease of administration, heat stability, etc.) can help coax developers to make improvements, but may require "topping up" by donors – that is, making up the difference between what LMICs are willing and able to pay, at least for a while, and manufacturers' innovation price point, earning this a 3 for political feasibility.

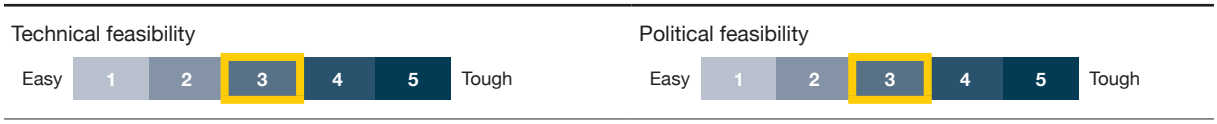
Potential gaps to be filled and other solutions:

Efforts such as Gavi's VIPS, which articulates improvements that are valued and will be compensated by the global health community through higher vaccine prices, are helpful to developers because they theoretically provide information about which improvements are desired and worth additional costs to buyers. The data informing these efforts, however, needs to be grounded in the reality of what a country or donor is willing to pay and not a theoretical approach. To help countries make an informed choice on where paying more makes sense because of other benefits or cost savings requires additional work. Efforts, primarily through WHO, to provide an analytical framework for this issue need additional development and implementation. Innovation prizes structured as a pull mechanism have not yielded important products to date, though with better structuring and links to eventual demand, they could be revisited. In the rare case that there are a sufficient number of competitors in a vaccine market, one of them being a "first-mover" in advancing an improvement can cause others to follow, but this situation is rare in vaccine markets.

This area is ripe for relatively simple and near-term solutions that should support or be integrated into the ongoing work such as the Total Systems Effectiveness framework at WHO that is now known as CAPACITI. Further data on the costs of vaccination would be a useful policy tool that could drive more evidence-based decisions. A systematic policy analysis of vaccine procurement laws/regulations and practices could inform questions about how procurers make decisions, including the unintended consequences of anti-corruption laws that require public purchasers to take the lowest bid for products considered equivalent.

In addition to the systematic solutions described above, simple shifts in communication can be reinforcing and provide great help. For example, speaking about the cost of vaccination instead of the cost of vaccines shifts the conversation to a more holistic view of programme costs, including vaccines, delivery, adverse event following immunisation (AEFI), surveillance, campaigns, storage, vaccinators and other essential components.

13. Limited availability of aligned partners to commercialise vaccine*



Activities underway:

Little has been done systematically to address the inability or unwillingness of small developers (biotech, academia or public institutions) to move forward with the most complex and expensive phase of clinical development, the process of licensing the vaccine and subsequent commercialisation, thus requiring partners to assume responsibility for those tasks. The DCVMN provides support to its members, and PATH provides support to companies, usually funded by BMGF, to move into vaccine commercialisation, thus eliminating the need for a partner.

As with other challenges that are fundamentally the result of lack of capability and capacity, this challenge could be solved, over time, with sufficient resources, thus meriting a score of 3 for both technical and political feasibility. There are limiting factors, including the underlying market-based system, which deters entry of smaller developers, as well as the fact that partnerships to date have often been disease-specific and driven by a dedicated policy entrepreneur or vaccine champion.

Potential gaps to be filled and other solutions:

A number of successful individual partnerships have worked – Serum Institute of India (SII) with MenAfriVac [see box case study], NewLink-Merck/MSD for Ebola, Butantan and Merck/MSD for Dengue (in progress), Vaccine Projekt Management to SII for TB vaccine – whereby the appropriate partner has been found to continue development initiated in academia or by developers that did not have interest in moving the project forward. This has often resulted from the efforts and knowledge of a supporting entity (e.g. Wellcome, BMGF, PATH).

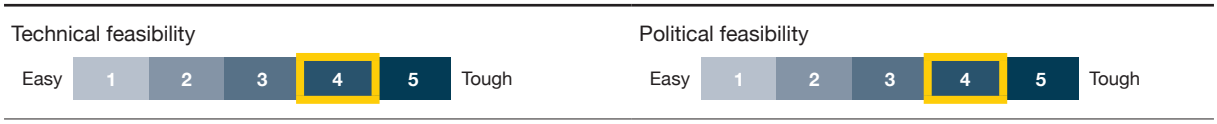
The current setup has delivered results but has not addressed the reality of an artificially constrained ecosystem where individual developers consider only a limited number of potential partners based on their level of knowledge of the partners and their strategic goals and interests. This is especially true for academic institutions and may result in missed opportunities.

To ensure the most effective matching between technologies in development and potential commercialising partners, there is the need to increase the visibility of large/mid-size developers' strategies and key personnel to academic institutions, public developers and smaller biotech to avoid partnering driven only by the larger companies. There is also the need for early phase developers to consider the longer-term economics of the vaccine they are developing and the likelihood that it will result in a commercially attractive vaccine for a partner.

The creation of an open exchange, where small vaccine developers can make contact with potential commercialisation partners, could improve the situation. Equipping innovators with stronger understanding of vaccine commercialisation economics and negotiation skills could result in more innovations being commercialised. This initiative would aim to be akin to the annual J.P Morgan or Goldman Sachs health conferences but focused exclusively on vaccines and on creating opportunities for productive dialogue between developers and potential partners.

An independent party, such as a foundation or an agency from the UN, in collaboration with WHO, industry associations, countries' economic ministries and possibly the World Economic Forum (WEF), can work towards the creation of such a marketplace. Some work in the field has been initiated by DCVMN and resulted in some successes, albeit limited to the DCVMN members and with limited impact and visibility in the broader academic/biotech world.

14. Insufficient access to funds for late-stage development*



Activities underway:

Some actions have been put in place to address this gap. Issuing bonds, such as Gavi's International Finance Facility for Immunization (IFFIm), has been used to support funding for both Gavi and CEPI. The International Finance Corporation (IFC) invests in private health companies in developing markets. Several private investors are both educated and active in this field, including Lions Head Global Partners and Adjuvant Capital.

Solutions to this challenge mostly suffer from market-based constraints rather than either technical or political limitations – but those underlying market checks are significant, earning this a score of 4 for both. Convincing venture capital firms that vaccines are a good investment will likely become easier over time as other challenges are addressed and reduce risk. For now, however, there is a need to educate both developers and financers about each other and about vaccine development and deployment and to continue to promote financial instruments such as social impact bonds to increase certainty for developers and funders.

Potential gaps to be filled and other solutions:

The efforts seeking to address this challenge are not linked together and thus are not comprehensive in scope or impact and are insufficient to develop needed vaccines. The significant costs of late-stage development – which can reach up to 500 million USD in Phase 3 and beyond – and the relative scarcity of funding remain serious challenges for developers.

Creative funding for late-stage development is needed to develop vaccines for which the economics of late-stage development and commercialisation are not justified for manufacturers alone to invest in and where market-based incentives do not attract investors. Think tanks or other groups could be created to generate new ideas, such as was done by the Center for Global Development on the design of the original AMC concept.

Case study: MenAfriVac

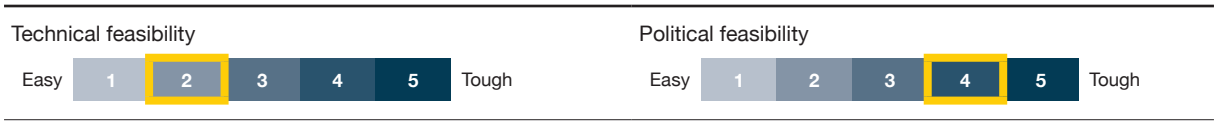
WHO and PATH created the Meningitis Vaccine Project (MVP) in 2000 with the goal of making available a conjugate meningococcal serotype vaccine costing 0.50 USD per dose. In pursuit of this goal, MVP met with manufacturers, however only the Serum Institute of India (SII) was willing to participate, necessitating additional funding, technology and development expertise and the support of the NRA in India. The MVP involved more than 30 partners [44] and five clinical trials between 2005 and 2009 leading to prequalification in 2010.

Financing for vaccine development was provided primarily through grants of 90 million USD and capital investment of ~30 million USD by SII. Financing for vaccine procurement was approved in 2008 by Gavi.

In this example donors funded a virtual vaccine developer and then the procurement of that vaccine. Some of the factors that led to success included:

- good timing on the need to secure financing for vaccine procurement at the same time as Gavi was recovering from a funding deficit,
- pre-defined demand of the vaccine for routine campaigns and a stockpile,
- fairly well-coordinated intentions across donors, developers and countries.

15. Need to make expensive manufacturing investments prior to clinical success or demand certainty*



Activities underway:

Government-owned facilities have recently been established to help with this issue, but they have not yet proven their effectiveness. The Vaccines Manufacturing Innovations Centre in the United Kingdom and the Advanced Development Manufacturing Center in the United States are two examples of such approaches. The latter has not delivered according to expectations [20]. Vaccine manufacturers have attempted to play a role by making manufacturing capacity available. This was meant to be the case for GSK's BioPreparedness Organization, an attempt to attract funding and have available a US-based facility for urgent manufacturing for emergent global health needs. The attempt failed but set a precedent for a potential private-public partnership in this area.

The biggest scientific hurdle associated with this challenge is how to keep facilities "warm based," that is, ready for production continuously, earning this a 2, because it is technically feasible but fiscally demanding. Politically, the challenge is greater for non-government-owned or -supported manufacturers, which operate in a commercial environment and respond to market incentives, thus assessed at level 4. Government support for "just in case" and "just in time" production historically has been a hard sell politically, though COVID-19 may well change that perception, at least in the short term.

Case study: Typhoid conjugate vaccine

In October 2017, WHO re-emphasised the use of typhoid vaccines in controlling endemic and epidemic disease. The Coalition Against Typhoid (CAT) and the Typhoid Vaccine Acceleration Consortium (TyVac) provided centralised coordination and advocacy for prevention of typhoid including improved epidemiologic data, cost-effectiveness of vaccination and supporting evidence-based introduction of TCV in countries.

The first TCV was licensed in India in 2013 and was prequalified in 2017. A second TCV, developed by a PDP and subject of a technology transfer in 2013, was licensed in India in 2019.

In 2009 Gavi committed to finance TCV procurement when there was a prequalified vaccine available and a recommendation from WHO. At the end of 2017, when vaccine availability and a recommendation were imminent, Gavi recommitted in advance to avoid delaying use of the vaccine. Gavi has committed 950 USD million in funding between 2019 and 2025 for routine introductions and associated catch-up campaigns; funding for a stockpile is not provided.

BMGF provided funding for CAT and TyVac and is supporting development of additional TCVs with one manufacturer and expanded capacity for the prequalified vaccine. Most vaccine development has been self-funded, so little data is available on development costs. One manufacturer who received a technology transfer from a PDP invested 40 million USD itself to establish the manufacturing facility.

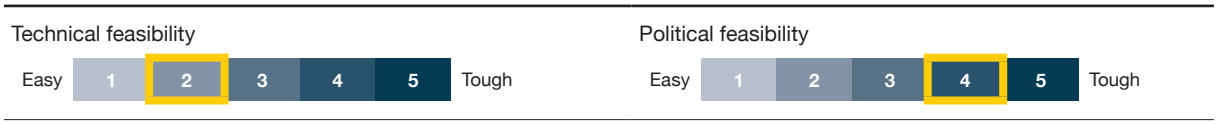
Potential gaps to be filled and other solutions:

Although several solutions are in progress, their likelihood of success is not yet known. In theory the solution of having a flexible manufacturing site capable of manufacturing Phase 3 clinical trial material and early commercialisation doses, while simultaneously planning for a technology transfer, is feasible although still requires that an entity be the legal owner or "sponsor" of the product while the manufacturing facility acts effectively as a contract manufacturing organisation. The certainty of the technology transfer is the important element in the longevity of the solution, and that faces the same uncertainties as the initial challenge poses, except for knowing that the outcome of the Phase 3 trial. A facility that bridges some of those concerns temporarily is only a part of the larger solution, which requires a partner willing and able to receive a technology transfer and be aligned commercially. Observing the success of the solutions in progress is likely a prudent pathway before creating parallel solutions.

There have been long-standing discussions about the value of multipurpose government-owned manufacturing facilities established primarily for emergency use. Outside of emergencies, these could be operated for other purposes, such as to produce clinical trial material. The primary challenge with this proposal is the increasingly specific nature of vaccine manufacturing (such that a generic vaccine facility would be difficult to design) and the cost-ineffectiveness of keeping facilities operationally ready while only using a small portion of their capacity. On a technical level, start-up of new vaccine manufacturing requires a period of several years to validate equipment, processes and technicians' competencies, and thus significant lead time would still be required to start-up production of any new vaccine. However, there could be some value in having production facilities on stand-by for urgent needs and group study appropriate models.

It is worthwhile exploring alternative models that would de-risk the manufacturing investment possibly by establishing a type of guaranteed pay-out from governments if the Phase 3 development fails, as is being done for some COVID-19 vaccines. This could be seen as a type of insurance for the developer, underwritten by a government or another entity with an interest in having a vaccine further developed that would only pay-out to the developer if there was a scientific failure. It would provide a type of downside risk mitigation sufficient for the developer to continue. While this would need be implemented on a vaccine by vaccine basis, the idea could be replicated for multiple vaccines.

16. Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer



Activities underway:

For certain vaccines and countries, the Gavi Vaccine Investment Strategy provides the promise of funding for vaccines that are prioritised and incentivised to finish development. While effective, this mechanism is often not enough to compel developers to move quickly (e.g. TCV [see sidebar]). BMGF and MedAccess both offer volume guarantees to manufacturers for licensed products with the incentive of lower pricing, so these structures help early implementation but do not have a strong effect on finishing development. AMCs and Advanced Purchases Commitments (APCs) each provide the promise of sales when a vaccine is licensed and implemented and does attract certain developers. The AMC for pneumococcal conjugate vaccines provided strong incentives for two developers that were already most advanced in their development, but it did not extend those incentives to other developers who were less advanced because they were unlikely to benefit from the incentive.

While technically feasible (2) with sufficient capital to support development and market guarantees, there are challenges associated with episodic diseases for which production and need are sporadic. Importantly, from a political standpoint, there remain questions about why “Big Pharma” should require support from governments or foundations, rather than producing vaccines as needed and at cost (or even free), making solutions for this challenge less politically feasible (4).

Potential gaps to be filled and other solutions:

Both push and pull incentives typically drive disease-specific solutions aimed at specific goals and compensating for specific issues that differ across diseases and vaccines. These solutions have been successfully as in the case for the AMC for pneumococcal conjugate vaccines, but not systematically used.

Entities with some information about, or influence on, the eventual demand for a product that is the subject of incentives are the most likely to succeed because they can benefit from the information asymmetry, which gives them a lower overall risk profile versus others. A consistent sponsoring entity that would scan the environment for opportunities or an approach to incentives that was consistent and understood by developers would bring benefits and more certainty to the ecosystem overall. This activity is partially done by MedAccess, among others, but there are no comprehensive or consistent approaches. Currently the ad hoc nature of incentives creates confusion among developers and could be ameliorated by a clearer communication strategy or by an overarching entity consistently structuring them. Incentives for development of vaccines should be continued along with push funding and should be designed carefully, taking into consideration the specific elements of each vaccine.

Potential solutions

Many priority challenges are inter-related and do cluster in specific ways; particularly regarding entities engaged in the challenges.

Regulatory challenges cluster into challenges in achieving primary licensure of a vaccine and the related expertise in regulatory science required to improve the efficiency of licensure, particularly of novel vaccines. This expertise is held in relatively few countries and thus favours manufacturers in those countries at the expense of developing a broader base of efficient regulators and developers. The limits on developers here has a strong link to the dearth of available partners.

Manufacturing challenges cluster around some basic challenges of current vaccine manufacturing technology and the costs and inefficiencies of those technologies. The expense of the manufacturing challenges has a strong link to the financial challenges.

Country-level decision-making poses challenges both in the harmonisation of regulatory requirements and in their public budgeting and decision-making where each country represents its own micro-challenge and collectively pose priority challenges for developers.

Data that informs regulatory science and that underpins country decision-making, including the basic disease burden and its uses for decision-making, are related. These are all actually dual challenges in first having the data and then in using it to foster change.

The **lack of partners** available either for manufacturing through technology transfer or for commercialisation touches on regulatory, manufacturing and financial challenges. Because of concentrated regulatory and manufacturing expertise and financial needs, the same large companies are often the final developers of vaccines and form a relatively closed set of organisations with expertise, leaving few choices for small developers seeking partners for manufacturing and commercialisation

Financial factors are particularly important in late-stage development and reflect both the large manufacturing investments and relatively low availability of funding for those investments, the timing of investment decisions, particularly as they relate to the uncertainty of potential revenue and finally the uncertainty of returns. Although developers and countries are currently the main interlocuters representing the sellers and buyers, a plethora of organisations are capable of intervening in this challenge.

The challenges and current solutions applied in the global vaccines ecosystem span those involving basic science, industrial development, collective

action, economics and political economy. Addressing those scientific and technical challenges is dependent on identifying either advances that can reduce the technical or financial burden to developers or that provide sufficient economic rewards to successful developers that persist in bringing vaccines to market. Solutions should address both of those fundamental aspects of the ecosystem and be packaged to enable successful implementation.

Unfortunately, to date, efforts to solve those challenges have largely been singular approaches that have produced benefits for single disease or single topic areas but have not produced system-wide gains. Changing the perspective to drive solutions across this complex system (or system of systems) can produce greater system-wide gains but comes with the challenge of defining the scope of any single initiative and being able to engage stakeholders across multiple functional and disease areas.

While no final conclusions can yet be drawn on the systematic effects of COVID-19 on vaccine development, preliminary thoughts are offered below for each of the four areas of priority challenges. Eventually, observing and applying the lessons learned at the conclusion of COVID-19 vaccine development and deployment may provide an important perspective on how to drive system change. This should consider that COVID-19 is a single, globally relevant disease and recognise the differences between COVID-19 and the less prominent diseases for which vaccines are desired.

Starting from those considerations, this research points at four axes of action, in relation to the vaccine ecosystem:

- **Convening** global stakeholders to work toward solving a specific challenge or set of challenges by facilitating a collective definition of a clear path forward and of clear accountability.
- **Advocating** to and educating stakeholders, decision makers and the public on the varied and interrelated aspects of vaccine research, development and deployment and the need for a systemic approach.
- **Funding** to improve understanding of the science of vaccine development or manufacturing, and to generate data and evidence supporting policy and access advocacy.
- Designing and establishing **incentives** aimed at activating the most appropriate economic and political levers driving systemic change.

Table 13: Proposed strategies and tactics to tackle challenges

Strategies	Tactics/area of action	Priority challenge addressed	Root cause addressed
REGULATORY 1. Lack of recognised surrogates or correlates of efficacy 2. Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs* 3. Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine 4. Lack of harmonisation on requirements for quality, efficacy, labelling, packaging and safety of biologicals & diagnostics across NRAs*			
Modernise the approach to clinically demonstrating efficacy and safety of vaccines for licensure	**Convene** a global forum mandated to design a concrete blueprint for the modernisation of the approach	1, 2	Fundamental deficiencies in knowledge and practices Uncertainty about pathway to licensure
	Fund research to increase the understanding of cross-cutting basic science	1, 2	
	Fund big data/artificial intelligence to look for patterns of immune response	1	
Enhance regulatory harmonisation	**Fund** policy research that defines the health and economic consequences of inaction on harmonisation	4	Desire of NRAs to assert local control NRA lack of understanding of global guidance and documentation
	Fund the creation of an evidence base for the set of economic indicators needed to offset any national revenue losses	4	
	Convene stakeholders to co-create harmonisation solutions over time	4	
	Fund a pilot programme to develop understanding about the collaborative review procedure for prequalified vaccines	4	
	Advocate to advance the organisations/initiatives involved in harmonising vaccine regulatory science	4	
Promote regulatory centralisation	**Fund** modelling the impacts of expanding existing alternatives to harmonisation	3, 4	Lack of experienced personnel & financial/ technical resources Desire of NRAs to assert local control
	Advocate for long-view efforts to build global/ regional regulatory approaches	3, 4	
	Fund long-term implementation of regional centralised regulatory procedures	3, 4	

Strategies	Tactics/area of action	Priority challenge addressed	Root cause addressed
MANUFACTURING 5. Lack of possibility to share production process and/or facilities* 6. Long-lead time for establishing manufacturing capacity* 7. Lack of partners available/capable of receiving technology transfer*			
Enhance manufacturing innovations **Fund** development of manufacturing platforms leading to more efficient production **Incentivise** vaccines based on platforms that are economically efficient **Convene** stakeholders to establish a partnering exchange for vaccine developers	**Fund** an analysis of innovations from other industrial sectors	5, 6	Inherent uniqueness of each vaccine antigen Vaccine development is niche area of technology and science
	Fund development of manufacturing platforms leading to more efficient production	5, 6	
	Incentivise vaccines based on platforms that are economically efficient	5, 6	
	Convene stakeholders to establish a partnering exchange for vaccine developers	5, 6	
Expand the manufacturing base **Convene** stakeholders to cultivate additional global manufacturers that are able to successfully and efficiently receive technology transfers	**Fund** efforts to increase the number of global vaccine manufacturers able to achieve prequalification	7, 13, 15	Vaccine development is niche area of technology and science Limited availability of partners to commercialise the vaccine Limited private capital because of high risk, long-term investments
	Convene stakeholders to cultivate additional global manufacturers that are able to successfully and efficiently receive technology transfers	7, 13, 15	
MARKET AND POLICY 8. Insufficient public budgets for purchase and implementation of immunisation programmes (willingness to pay) 9. Lack of data for assessing potential impact of vaccination in particular in specific target populations 10. Lack of use of appropriate models for economic valuation (e.g. cost-effectiveness vs. cost-benefit) globally or in certain countries*			
Promote evidence-based decision making	**Convene** stakeholders, with the goal of defining a comprehensive health portfolio evidence package	8	Vaccination not perceived to be politically rewarding Weak epidemiological surveillance
	Fund formative research to understand what data are needed by which decision makers	8, 9, 10	
	Fund country capacity in policy informatics: to collect and analyse data across disciplines such as health, economics, labour, education	8	

Strategies	Tactics/area of action	Priority challenge addressed	Root cause addressed
Increase country fiscal space for immunisation/ability to pay	**Fund** research into the impact of COVID-19 on health budgets	8, 9	Vaccination not perceived to be politically rewarding
	Fund research into a portfolio approach to health planning and purchasing	8	
	Fund research into the potential for pharmaceutical cross-subsidisation and tiered pricing	8	
	Fund research to identify the scope of financial saving possible through improved country procurement	8	
FINANCIAL OUTCOMES 11. Opportunity costs outweigh the vaccine's economic rationale 12. Pricing pressure may discourage innovation for improvements* 13. Limited availability of aligned partners to commercialise vaccine* 14. Insufficient access to funds for late-stage development* 15. Need to make expensive manufacturing investments prior to clinical success or demand certainty* 16. Limited availability of aligned partners to commercialise vaccine*			
Promote the value of innovation	**Incentivise** innovation through strategic prizes	12, 16	Comparatively low market value of vaccines Limited private capital because of high risk, long-term investments
	Fund economic analysis that demonstrates the broad value of innovation	11, 12	
	Fund a systemic policy analysis of vaccine procurement laws, regulations, and practices	12	
Drive creation of new funding models	**Convene** a consortium of funders, scientists, developers and regulators to develop new models of incentives to drive development of vaccines	11, 14, 16	Comparatively low market value of vaccines Limited private capital because of high risk, long-term investments
	Convene an open exchange of investing opportunities with leading venture capital firms and/or other funders	14, 15	
	Convene discussions to explore mechanisms to de-risk manufacturing investment	11, 15, 16	
Increase availability of partners for vaccine commercialisation	**Incentivise** greater alignment of goals of biotech/academia and pharma	7, 11, 13, 14, 16	Comparatively low market value of vaccines Limited private capital because of high risk, long-term investments
	Convene a marketplace covering end-to-end partnering needs of vaccine developers	7, 13	

*Universal challenges

Interventions aimed at addressing the "Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use"

Different tactics are required to address the various root causes. Those tactics are linked to each other and sometimes require a sequential approach. To reflect this, tactics are listed in order of recommended implementation.

Modernise the approach to demonstrating efficacy and safety of vaccines for licensure

- **Convene**, in collaboration with WHO/UN, a global forum (along the same lines of the commission on social determinants of health) of scientists, developers and regulators that has the mandate to design a concrete blueprint for modernising the approach to clinically demonstrating efficacy and safety of vaccines for licensure, with particular emphasis on adaptive clinical trials (Challenges 1, 2).
- **Fund** research to increase the understanding of cross-cutting basic science on correlates of protection, alternative clinical pathways/adaptive clinical trial designs and innovative manufacturing technologies (Challenges 1, 2).
- **Fund** additional work on big data/artificial intelligence to look for patterns of immune response. Wellcome is supporting work in this field as part of the development of an invasive non-typhoidal Salmonella vaccine, and this could provide a good starting point (Challenge 1).

These tactics could have a high impact in reducing cost of clinical development and a medium impact on reducing the duration of clinical development.

Enhance regulatory harmonisation

- **Fund** policy research that defines the health and economic consequences of inaction on harmonisation across the global regulatory system, along with savings governments could realise through harmonised approaches and national gains in health and economies from increasing access (Challenge 4).
- **Fund** the creation of an evidence base for the set of economic incentives needed to offset any national revenue losses resulting from mutual recognition in regulatory assessments. This is a necessary step toward addressing the incentives that can prevent regulatory harmonisation (Challenge 4).
- **Convene** regulators, WHO, donors, developers to co-create harmonisation solutions over time. A starting point could be to convene stakeholders to define a path to resolution for a small set of practical/administrative challenges (e.g. interoperable IT systems, reducing the reliance on paper requirements) that cause significant burden to vaccine developers – especially the small ones – in the process of licensure in multiple countries (Challenge 4).
- **Fund** a pilot programme in collaboration with WHO and a subset of countries to develop understanding about the barriers and facilitators to implementing the collaborative review procedure for prequalified vaccines (Challenge 4).
- **Advocate** at global, regional and national political levels to promote the organisations engaged in harmonising vaccine regulatory science globally and ensure that a clear accountability framework is in place to ensure that specific agencies have specific responsibilities in moving forward the agreed agenda and that the consequences of inaction are clearly understood and communicated (Challenge 4).

These tactics could have a high impact in reducing cost of clinical development and a medium impact on reducing the duration of clinical development.

Promote regulatory centralisation

- **Fund** the creation of the of an evidence base of the positive impact of expanding existing alternatives to harmonisation such as centralised procedures (e.g. Article 58), including cost savings, reducing time to implementation and salutary effects, thereby developing policy-ready evidence for action (Challenges 3, 4).

- **Advocate** for longer-term efforts to build global/regional regulatory approaches, as a way to pool talent and resources and a good use of scarce public health funding (Challenges 3, 4).
- **Fund** longer-term implementation of regionally centralised regulatory procedures (Challenges 3, 4).

These tactics could have a medium impact in reducing cost and duration of clinical development.

Interventions aimed at addressing the "Feasibility and/or costs of manufacturing the vaccine to the right standard and volume"

COVID-19 implications

Manufacturing – If vaccines using platform technologies such as DNA, RNA or viral vectors succeed, the development and manufacturing of vaccines against viral pathogens will be ripe for transformation. If they do not succeed clinically, this new approach to vaccine development and manufacturing may be abandoned. Regardless, the plethora of contract manufacturers engaged in COVID-19 may have a lasting effect on the availability of vaccine manufacturing partners.

Enhance manufacturing innovations

- **Fund** an analysis of manufacturing technology innovations from other industrial sectors (perhaps in collaboration with the WEF) to identify potential transferrable solutions (Challenges 5, 6).
- **Fund** development of manufacturing platforms leading to more efficient production (Challenges 5, 6).
- **Incentivise** vaccines based on platforms that are more likely to allow use of common production processes/shared plants over those that require bespoke production processes and do not easily allow common production. (Challenges 5, 6).
- **Convene** stakeholders to establish an exchange or marketplace for vaccine developers, manufacturers and contract manufacturers to meet and identify potential partnerships in vaccine manufacturing (Challenges 5, 6).

These tactics could have a high impact in reducing cost of clinical development and a medium impact on its duration.

Expand the manufacturing base

- **Fund** efforts (such as those of the DCVMN and PATH) to increase the number of global vaccine manufacturers able to achieve vaccine prequalification. This will increase the number of potential partners with vaccine manufacturing expertise as well as the financial means to accept resource-intensive technology transfers and those capable and willing to commercialise vaccines that are regionally focused (Challenge 7, 13, 15).
- **Convene** stakeholders to assess mechanisms that can cultivate additional global manufacturers that are able to successfully and efficiently receive technology transfers, and manufacture and commercialise a vaccine that may be have lower overall financial returns (Challenges 7, 13, 15).

These tactics could have a high impact in reducing cost of clinical development and a medium one on its duration.

Interventions aimed at addressing "Factors impacting the predictability of the market and the likelihood of policy support for use"

Promote evidence-based decision making

- **Convene** stakeholders, with the goal of defining a comprehensive health portfolio evidence package – inclusive of burden of disease evidence, health technology assessment (HTA), full cost of delivery, product and supply requirements, measurement of the full health and economic impact on different target populations – that allows for the comparative assessment of new and improved health interventions (including vaccination) for the prevention of diseases (Challenge 8).
- **Fund** formative research to understand what types of data are needed by vaccine developers vs. government policymakers. For example, as TPPs are being created, how do data needs differ between health decision-makers and vaccine developers, whose needs should be addressed first, and to identify which data are lacking that may be necessary for informed country decision-making on vaccine introductions and programmatic changes (e.g. vaccine innovations), building on existing efforts of WHO. Epidemiologic data is insufficient to make the case; additional evidence on the full societal value of vaccination is needed (Challenges 8, 9, 10).
- **Fund** country capacity to collect and analyse data beyond basic epidemiology, e.g. what type of data to collect; how data can be used; supporting the ability to collect and analyse various types of data: disease burden, cost, AMR data, data specific to target groups (Challenge 9, 10).

These tactics could have a high impact in reducing duration of clinical development and a medium one on its cost.

Increase country fiscal space for immunisation/ ability to pay

- **Fund** research into the impact of COVID-19 on health budgets, particularly immunisation budgets, and service delivery during and after the pandemic (Challenges 8,9).
- **Fund** research into a portfolio approach to health – that is, can governments derive greater health impact by pursuing an interconnected approach to prevention, care and treatment for vaccine-preventable diseases (Challenge 8).
- **Fund** research into the potential for pharmaceutical companies and/or development funders to find novel approaches to cross-subsidisation and tiered pricing not just across markets but within them (across different products) (Challenge 8).
- **Fund** research to identify the scope of financial savings possible through improved country procurement practices for health commodities and ancillary services (Challenge 8).

COVID-19 implications

Market and policy – While the value of vaccines to society has become starkly evident through the COVID-19 pandemic, the trust in and value of all vaccines to individuals may rest on their experience in COVID-19 vaccine deployment. Similarly, countries are experiencing the simultaneous increase in a willingness to pay for a COVID-19 vaccine and decrease in their ability to pay not only for COVID-19 vaccine for also for those against other life-threatening diseases.

Public perception and the markets for all vaccines may rest on the success (or failure) of COVID-19 vaccine development and deployment. Tracking and reporting on regulatory and manufacturing innovations will be critical during and after the COVID-19 response – those that fail, those that advance and then revert to status quo ante and those that advance and persist. Understanding how innovations succeed or fail and why will be critical to building a better vaccines ecosystem over time.

These tactics could have a high impact in reducing duration of clinical development and a medium one on its cost.

Increase awareness of the full value of vaccination/willingness to pay

- **Fund** a research, modelling and policy agenda to demonstrate the value of vaccination to public health and economic development globally, including vaccines in scope for this analysis, typically used vaccines and pandemic vaccines. This should encompass the full societal value of improved vaccines and the full societal value of vaccination as part of broader health tools and should include a clearinghouse for data and econometric approaches (Challenge 8, 9, 10).
- **Advocate** for immunisation through reporting health and immunisation expenditures in an annual Country Vaccination Index that highlights the relative underspend on health compared to other publicly provided services. Include information on people's out-of-pocket costs and the governments' share of health expenditures (Challenges 8, 10)**.**
- **Fund** a "Stop Selling Vaccination Short" global communication campaign (perhaps in collaboration with others) targeting the media, academics, public health decision makers, policymakers and the public that delivers messages and interventions demonstrating the full value of immunisation. Develop online learning modules and tools for each audience to inform and activate changes in standard cost-effectiveness analyses of immunisation (Challenges 8, 10).

These tactics could have a high impact in reducing duration of clinical development and a medium one on its cost.

Increase demand predictability

- **Convene** communities of practice to learn and develop best practices on predicting market certainty. The topic could include: how ministries of health make vaccine introduction and subsequent purchasing decisions and whether decisions are taken in isolation, product by product, or thorough a more holistic, "formulary" approach to contribute to a better understanding of individual and policymakers' risk-benefit calculations to inform potential demand (Challenges 8, 10).
- **Fund** and help progress initiatives aimed at increasing visibility of demand (e.g. WHO's Product Development for Vaccines Advisory Committee, PDVAC and Mi4A) (Challenges 8, 10).
- **Convene discussions about cross-country mechanisms (e.g. the African Medicine Supply Pool for COVID-19 vaccines) that can increase demand certainty globally (Challenges 8, 10).**
- These tactics could have a high impact in reducing duration of clinical development and a medium one on its cost.

Interventions aimed at addressing the "Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery"

Promote the value of innovation

- **Incentivise** innovation through strategic prizes. A "delivery innovation prize" could encourage new delivery technology that could increase vaccination, reduce costs or both. A "purchasing innovation prize" could encourage new pathways for buyers and sellers to explore and reduce the reliance on lowest-price-takes-all purchasing, e.g. through performance-based contracting/ purchasing (Challenges 12, 16).
- **Fund** economic analysis that demonstrates the broad value of the innovation – e.g. in lowering other immunisation system costs or broader societal costs (Challenges 11, 12).
- **Fund** a systemic policy analysis of vaccine procurement laws, regulations and practices to inform questions about how procurers make

decisions, including the unintended consequences of laws that require public purchasers to take the lowest bid (Challenge 12).

These tactics could have a high impact in reducing cost of clinical development and a limited one on its duration.

Drive creation of new funding models

- **Convene** a forum of funders, scientists, developers and regulators to develop new models of incentives to drive development of vaccines for which there are uncertain or limited economic rewards. Partnering will be important with the others that have previously led the thought-exercises (e.g. Center for Global Development, WEF through the Health Community) to create new solutions (Challenges 11, 14, 16)**.**
- **Convene** an open exchange to discuss vaccine ecosystem investment opportunities and tools such as social impact bonds by collaborating with leading venture capital firms and/or other funders to convene discussions at high-visibility fora – e.g. Davos, JP Morgan – and industry association meetings such as the BIO annual convention (Challenge 14, 15).
- **Convene** discussions with ecosystem actors to explore mechanisms to de-risk manufacturing investment, such as is happening now with COVID-19 vaccine development, to determine how to facilitate the adoption of those solutions in a wide-spread fashion going forward (Challenge 11, 15, 16).

These tactics could have a high impact in reducing cost of clinical development and a limited one on its duration.

Increase availability of partners for vaccine commercialisation

- **Incentivise** greater alignment of goals of biotech/academia and pharma to ensure successful partnerships that enable technology transfers and continued development of vaccines important for public health (Challenges 7, 11, 13, 14, 16).

COVID-19 implications

The plethora of funding available for COVID-19 vaccines, private funding advantages that the funding provides and subsequent huge number of developers engaged in development of COVID-19 vaccine provides a stark demonstration of the importance of transforming the economics of vaccine development. Where money flows, development will follow. Advance contracting with developers has the effect of reducing the uncertainty of demand and therefore incentivises developers to push through challenges.

Emerging from this experience it may be more difficult to attract vaccine development in the absence of substantial funding for late-stage development and manufacturing – those stages that provide the biggest challenges to developers.

- **Convene** a marketplace covering end-to-end partnering needs of vaccine developers seeking technical, financial or commercial partnerships to progress in their development efforts. The creation of an effective exchange space for the entire ecosystem – instead of existing initiatives generally limited to specific areas (e.g. financing) or players (e.g. biotech or developing countries manufacturers) – where potential partners can meet and explore opportunities for engagement across multiple dimensions, overcome existing barriers and reduce the risk that promising technologies are discarded (Challenges 7, 13).

These tactics could have a high impact in reducing cost and duration of clinical development.

Conclusion

Vaccines are recognised as one of the most cost-effective public health interventions available. However, a large number of scientifically possible candidates are not progressing beyond Phase 2 clinical development because of systemic constraints that prevent or retard their development. These challenges are not insurmountable but require focused attention on their root causes and radical change in perspective and priorities. Fashioning a more efficient, effective and equitable vaccine ecosystem will require focusing on systemic solutions that go beyond functional and organisational boundaries and interests and interrogating established and entrenched wisdoms.

Leveraging the sense of urgency instilled by the SARS-CoV-2 pandemic, needed rethinking and reformation could have the potential of addressing long-standing challenges that have hampered the vaccine ecosystem for decades. The push for development of COVID-19 vaccines has the potential to provide valuable learnings and cautionary tales – insights that will be clear only when vaccines are deployed globally.

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Annexes

Methodology

Methodologies used in the analysis of the reports can be found in each of the supporting documents for work packages 1, 2 and 3 and below.

Characterisation of the ecosystem

The diseases and vaccines of interest and in-scope for this analysis include new or improved vaccines focused on epidemic diseases, LICs and important for combatting AMR. Data for each disease and vaccine in scope were collected from databases including clinicaltrials.gov, WHO vaccine pipeline, BMGF pipeline database, WHO disease portal, the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) database and the Global Vaccines Market Model. These data were supplemented by investor analysis and data published in the literature. Expert judgement of the project team was applied to reconcile conflicting data.

Sixty-five vaccines were identified as having at least one vaccine in Phase 2 clinical development during the period 2009–2019. Of those, 32 were considered out of scope for this analysis for reasons including that the disease/pathogen/vaccine: is not focused on low-income settings; has a HIC commercial market; has very limited burden; is primarily a biodefense target and/or; has special eradication/prevention goals with unique priorities and decision drivers.

In an assessment of the entire vaccine ecosystem, we quantified the intensity of development effort against the rate of progress for all the vaccines in scope.

Development effort was quantified through:

- number of clinical trials at each stage (Phase 1, 2, 3);
- number of subjects enrolled at each stage (Phase 1, 2, 3);
- number of developers achieving expected outcomes at each stage (Phase 1, 2, 3).

The parameters used as a proxy for progress in development were:

- number of vaccine specific antigens advanced from Phase 1 to 2; Phase 2 to 3; Phase 3 to license;
- pace of advancement (number of antigens progressing, progressing slowly or stopped);
- whether vaccine development was funded by donors and to what amount.

To assess the relative status of development for each in-scope vaccine, we plotted intensity of vaccine development effort against progress, using the number of developers for each antigen against the number of Phase 3 trials for each antigen. Then, to elucidate possible reasons for clustering, we examined which challenges might be common to a cluster and whether clustering might represent vaccine archetypes.

We conducted regression analyses to examine whether market value for the in-scope vaccines is related to either number of deaths, number of developers or number of DALYs from disease. We used the natural log (ln) of each parameter to normalise the data. We then determined Pearson's correlation coefficient (r) of the ln-transformed values in Excel.

We excluded all in-scope vaccines for which the annual market was estimated at 100 million USD or less, since these vaccines are unlikely to be developed based on commercial attractiveness alone.

Several limitations of the quantitative analyses are listed below.

- Only the vaccines in scope were considered. The analyses may not be representative of the global vaccine ecosystem, particularly because they exclude many vaccines for HIC.
- Although the review period is 2009-2019, the analyses were static, comparing all vaccines within a 10-year window regardless of their entry time, reflecting all vaccine development at a single point in time and not comparing individual vaccine developments over equal periods of time.
- The assessment about the state of development progression was based on arbitrary cut-offs that

were set and on the team's assessment of progress based on personal knowledge of development. Progress was classified as: stopped; progressing slowly (3 or more years for progress to move from the end of one phase to the start of the next phase) or progressing.

The available quantitative data was limited and often of poor quality. Disease burden data was collected, when possible, from the IHME GBD database, using the 2017 mid-point estimate. However, estimates of DALYs from the IHME database were available for only 22 of the 33 diseases in scope, and for 19 of the 24 diseases in our quantitative analyses. For the remainder of the diseases we relied on estimates reported in the literature and these varied in methodology and in time. As such, the disease burden data is not comparable between diseases. For Chikungunya, Group B strep, Lassa, MERS, Nipah, Pseudomonas aeruginosa and S. aureus we were unable to reference any usable global estimates of DALYs. The same data quality issues were encountered for mortality.

Market values were challenging to estimate and were sourced from the literature (both peer reviewed and market analysis reports) in combination with the team's judgement about the reasonableness of the estimate. The estimates are thus not comparable between disease and should be taken as gross approximations.

Developer decision-making

Based on a structured review of the literature and on collection of expert knowledge, MMGH identified a draft list of factors that trigger and influence vaccine developers' decisions; how the importance of those factors change at different stages of the development process; the potential range of outcomes of each decision; and how factors and decisions differ depending on the characteristics of the developers. The preliminary view was presented to the EAG for input and revision. After this first refinement, the revised view was validated through a survey administered online via the QualtricsTM platform to a convenience sample composed of 135 individuals. The sample comprised primarily of representatives from pharmaceutical and biotech companies and PDPs (80% of the sample) complemented by professionals from academia, donor organisations, UN agencies and venture capital. Fifty responses were received (37% of the sample) with a sample representative of the different groups targeted (75% of the responses came from pharmaceutical companies, biotech and PDPs). Full results of the survey and the developer decision making are presented in detail in a separate report.

Challenges

Starting hypothesis

Eight categories of challenges were hypothesised to contribute to influence vaccine development. These categories were initially explored through literature as below and refined for valuation and prioritisation.

Identification

A systemic search of peer-reviewed literature and selective grey literature published between 1 January 2009 and 30 January 2020 formed the basis of the process. Over 4 000 documents were appraised, 450 were read for general insights and another 250 articles were reviewed on specific vaccines in scope. The final analysis included insights from 300 documents selected as those that provided the most relevant information. The outputs of this literature review were provided as a separate document.

Literature review

The identification, refining and quantifying of the challenges faced by vaccine developers in their decisions was performed through a multi-step, iterative process. A starting research structure was defined to inform the literature review and insight gathering, which resulted in eight categories of

challenges (based on the research questions) and 24 topics corresponding to the different areas influencing vaccine development between transition into Phase 2 clinical development and the early phases of commercialisation.

1. **The feasibility and/costs of meeting regulatory requirements to enable licensure and initial use, encompassing:**
    - a lack of clear regulatory standards for licensure
    - few National Regulatory Authorities (NRA) with suitable capacity
    - a lack of harmonisation among NRAs
2. **Feasibility and/or costs of testing under current clinical trial requirements, incorporating:**

- complex trial design and endpoint selection
- scarcity of resources to perform trials
- growing complexity from new technology use

3. **Feasibility and/or costs of manufacturing the vaccine to the right standard and volume, including:**
    - complex regulatory requirements on manufacturing process
    - need for early decisions in vaccine manufacturing
    - ongoing process rigidity and complexity
4. **Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery, comprising:**
    - a ROI typically lower than other products
    - uncertain financing horizons
    - vaccine-specific manufacturing investments
    - developers with different alignment to public health
5. **Factors impacting the predictability of the market and likelihood of policy support for use, including:**
    - uncertainty of demand for new vaccines
    - uncertainty of policy recommendations
    - the value of vaccines in the eyes of policymakers and the public
    - uncertainty on willingness and ability to pay
6. **Reliance on non-commercial drivers within the pharmaceutical industry, incorporating:**
    - the influence of strong advocacy
    - the strong link between politics and vaccines
7. **Additional challenged identified in the literature review included:**
    - freedom to operate
    - attrition in technology transfer
    - liability concerns
    - access to starting naturally derived starting material
8. **Whether challenges are viewed differently by different types and sizes of developers**

On this basis 120 individual challenges were identified. Those challenges were then refined and further categorised to assess the root cause and the relationship between each challenge and the in-scope diseases and associated vaccines. This process of refinement led to the consolidation of five categories of challenges, 14 topics and 54 challenges.

Vaccine archetype and universal challenge analysis

Each disease and corresponding vaccine was evaluated by the MMGH team against each challenge using both the literature review, case study results and expert judgement. Groups of vaccines that had similar challenges were grouped into archetypes. If a challenge was experienced by more than 80% of the diseases and vaccines, it was considered a universal challenge.

Valuation of challenges

Because not all development challenges are equal, the relative importance of each was evaluated quantitatively on three dimensions:

Additional cost to a developer if they were to "push through" the challenge and proceed with development

Additional time required by the developer if they were to "push through" the challenge and proceed with development

A composite evaluation of the public health value of eliminating each challenge

A five-point scale was used to give a score for each challenge for each of the three dimensions, with five representing the biggest highest cost, longest time and highest public health value if overcome. To assign a total score per challenge, the three dimensions were summed, resulting in the highest potential score of 15.

It is important to note that cost and time scores are not estimates of the true costs or time of overcoming each challenge, but rather offer a means to compare the relative gains of lessening or eliminating each challenge through systematic changes.

The cost score was derived from first estimating the low and high costs that could be associated with a developer overcoming a challenge. These estimates ranged from low of zero to 100 million USD and a high of zero to 500 million. Challenges estimated to have zero associated costs are those that money was deemed not useful in overcoming the challenge. Estimates were made by MMGH staff based on the literature review and expert judgement. The median costs was calculated for each challenge based on the low and high. Median costs ranged from 5.5 to 300 million USD. The five-point scale was then assigned based on the following criteria:

Table 14: Five-point scale for ranking of cost implications

Cost, USD M	Score
<10	1
11-50	2
51-100	3
101-250	4
>250	5

The time score was derived from first estimating the low and high time periods that could be associated with a developer overcoming a challenge. These estimates ranged from a low of less than one year and a high of zero to seven years or more. Challenges estimated to have zero associated time delay are those where additional time was not deemed useful in overcoming the challenge. Estimates were made by MMGH staff based on the literature review and expert judgement. The median time delay was calculated for each challenge based on the low and high. Median time delay was 6.5 years. The five-point scale was then assigned based on the following criteria:

Table 15: Five-point scale for ranking of time implications

Time, years	Score
<1	1
1.1-3	2
3.1-5	3
5.1-7	4
>7	5

The public health factor accounted for the number of vaccines impacted by each challenge. This public health factor was weighted by disease based on 5-point scale for three high priority factors (global mortality, global health priority, and impact on most impoverished populations) and a 2-point scale for three contextual factors (contributing to AMR, neglected by global donors, and the degree to which a disease invokes a public health response). The scale used for each of the disease factors is shown in Table 16.

Table 16: Weighting of disease factors

Weight factor	Criteria	Points
Deaths from disease	> 1 million annual deaths	5
	> 100k to 1 million annual deaths	4
	> 10k to 100k annual deaths	3
	> 1k to 10K annual deaths	2
	≤ 1 k annual deaths	1
On a priority list	'high' priority on WHO PQ list	5
	WHO emergency pathogen list	4
	'medium' priority on WHO PQ list	3
	on another organisation's priority list	2
	'low' priority on WHO PQ list	1
Affects the poor	risk is linked to conditions of poverty	5
	risk is equally distributed	0
Role in AMR	on Wellcome's AMR list	2
	not on Wellcome's AMR list	0
Lack of support	not on a priority list	2
	on a priority list	0
Fear of disease	outbreak of disease of international concern	2
	outbreak of disease of national/local concern	1
	does not occur in outbreak or not of concern	0

The weight of each disease in the public health score is shown in Table 17.

Table 17: Weight of diseases used on public health scores

Disease	Deaths from disease	On a priority list	Affects the poor	Role in AMR	Lack of support	Fear of disease	Total score
TB	5	3	5	2	0	1	16
Salmonella typhi (typhoid)	4	5	5	2	0	0	16
Nontyphoidal Salmonella	4	0	5	2	2	0	13
Shigella	4	0	5	2	2	0	13
Salmonella paratyphi	3	0	5	2	2	0	12
E. coli	3	0	5	2	2	0	12
Ebola	1	4	5	0	0	2	12
Cholera	3	3	5	0	0	1	12
S. pneumoniae	5	5	0	2	0	0	12
MERS	1	4	5	0	0	1	11
Lassa fever	2	4	5	0	0	0	11
Nipah	1	4	5	0	0	1	11
Measles	3	5	0	0	0	2	10
Malaria	4	5	0	0	0	1	10
HPV	4	5	0	0	0	1	10
Schistosomiasis	2	0	5	0	2	0	9
Leishmaniasis	2	0	5	0	2	0	9
Dengue	3	5	0	0	0	1	9
Rotavirus	3	5	0	0	0	1	9
Pseudomonas aeruginosa	4	0	0	2	2	0	8
Hookworm	1	0	5	0	2	0	8
S. aureus	3	0	0	2	2	0	7
Zika	1	4	0	0	0	2	7
Multivalent Meningococcal	3	3	0	0	0	1	7
Rabies	2	5	0	0	0	0	7

Disease	Deaths from disease	On a priority list	Affects the poor	Role in AMR	Lack of support	Fear of disease	Total score
Group B strep	4	0	0	0	2	0	6
Group A strep	4	0	0	0	2	0	6
Rift Valley fever	1	4	0	0	0	1	6
JE	3	1	0	0	0	1	5
whole cell Pertussis	3	1	0	0	0	1	5
Chikungunya	2	2	0	0	0	1	5
Clostridium difficile	2	0	0	0	2	0	4
Plague	1	2	0	0	0	0	3

As such, each challenge received a weighted composite score that was the sum of the disease scores for alldiseases encompassed by the challenge out of a possible total of 303 points. The weighted public health scores for each challenge was then ranked by quintile and challenges were assigned values of 1 to 5 in order of lowest to highest quintile.

The results of the analysis of 54 challenges and total scores by category are shown in Table 18.

Table 18: Scoring and frequency of challenges

C = Cost; T = Time; PH = Public Health score.

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
1. Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use				
Lack of recognised surrogates or correlates of efficacy	Clinical development is longer, more expensive	Higher price because of more costly development Longer time before vaccine becomes available	70%	C: 5 T: 4 PH: 3 = 12
Lack of animal models that correspond with immunogenicity in humans	Clinical development has higher likelihood of failure	Lower likelihood of vaccine availability/less competition Longer time before vaccine becomes available	42%	C: 4 T: 4 PH: 2 = 10
Lack of standardised assays, standards, and reagents for antigen testing	Regulatory submission has higher likelihood of delays and failure		58%	C: 3 T: 3 PH: 2 = 8

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
Lack of standards by which platform technologies (e.g. adjuvants, mRNA) are transferable from one disease target to another	Duplication of costs and time for licensure of each new product even if from same platform	Higher price because of more costly development Longer time before vaccine becomes available	58%	C: 4 T: 3 PH: 2 = 9
Lack of support for alternative clinical pathways	Clinical development is longer, more expensive		70%	C: 4 T: 3 PH: 3 = 10
Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*	Regulatory process longer and more complex (if NRA of choice lacks those competencies)		100%	C: 3 T: 3 PH: 5 = 11
Few NRAs able to regulate primary or secondary licensures of follow-on vaccines eligible for prequalification*	Developers located in some countries are not able to pursue PQ	Lower likelihood of vaccine availability/less competition	100%	C: 1 T: 4 PH: 5 = 10
Lack of mechanisms that allow for use exclusively outside of the country of origin (e.g. EMA Article 58)	Lower likelihood of obtaining regulatory approval because risk/benefit higher in country of origin than in country of disease		48%	C: 4 T: 3 PH: 2 = 9
Lack of harmonisation on requirements across NRAs*	Duplicates costs and time for licensure in each country	Longer time to access and potential for higher prices	100%	C: 4 T: 3 PH: 5 = 12
Lack of harmonisation on documentation of quality, efficacy, labelling, packaging and safety of biologicals & diagnostic across NRAs*	Duplicates costs and time for licensure in each country		100%	C: 2 T: 2 PH: 5 = 9
2. Feasibility and/or costs of testing under current clinical trial requirements				
Conducting efficacy trials requires an active outbreak	Inability to plan for duration and costs of clinical trials. Higher likelihood of failure in clinical development due to uncertainty of timing, duration and size of outbreak	Lower likelihood of vaccine availability	36%	C: 3 T: 4 PH: 1 = 8
Conducting efficacy trials for a disease with poorly established, low or sporadic disease incidence	Higher likelihood of failure in clinical development	Lower likelihood of vaccine availability or higher price because of more costly development	42%	C: 4 T: 2 PH: 2 = 8

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
Real or perceived ethical concerns about trial design (e.g. administration of placebos, Controlled Human Infection Model, CHIM)	Clinical development is longer, more expensive absent option to do more efficient trial	Higher price because of more costly development Longer time before vaccine becomes available	73%	C: 4 T: 2 PH: 3 = 9
Conducting efficacy trials for diseases involving animal transmission	Higher likelihood of failure in clinical development due to complex study design and need for a broader understanding of disease transmission (x-species)	Higher price because of more costly development	45%	C: 4 T: 4 PH: 1 = 9
Conducting efficacy trials for diseases with varied epidemiological profiles	Need to perform parallel trials in multiple sites (some of which may not be suitable)		64%	C: 4 T: 3 PH: 3 = 10
Additional requirements for use of new technologies (e.g. adjuvants, mRNA)	Longer, larger clinical studies needed due to unknown safety/ efficacy with new technology and lack of familiarity by regulators	Higher price because of more costly development Longer time before vaccine becomes available	67%	C: 4 T: 2 PH: 3 = 9
Lack of qualified in-country human resources to perform trials in MICs/LICs*	Development takes longer because developers have to first build/contribute to building in-country capacity	Less access because developer may not choose to make necessary investment Longer time before vaccine becomes available	100%	C: 2 T: 3 PH: 5 = 10
Lack of epidemiological surveillance systems in MICs/ LICs	Higher likelihood of failure in clinical development or need to do longer, more expensive trial	Lower likelihood of vaccine availability/less competition Longer time before vaccine becomes available	76%	C: 2 T: 2 PH: 3 = 7
Lack of diagnostics capabilities to adequately quantify disease occurrence during clinical trials	Need to do larger studies due to lack of quality data	Higher price because of more costly development Longer time before vaccine becomes available	48%	C: 2 T: 2 PH: 2 = 6
Insufficient WHO guidance to MICs/LICs on performance of clinical trials*	Development takes longer because developers have to first ensure that clarity is reached	Reduced access because developer may not choose /be able to make investment Longer time before vaccine becomes available	100%	C: 2 T: 2 PH: 5 = 9
Increased pre-implementation safety studies for vaccines used first in LIC	Need to do longer, larger studies due to lack of quality safety monitoring	Higher price because of more costly development Longer time before vaccine becomes available	70%	C: 4 T: 3 PH: 3 = 10

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
3. Feasibility and/or costs of manufacturing the vaccine to the right standard and volume				
Lack of personnel in the NRAs with expertise and experience to regulate manufacturing*	Higher likelihood of compliance failure (in clinical trials and first commercial lots) due to lack of quality oversight	Lower likelihood of vaccine availability	100%	C: 3 T: 2 PH: 5 = 10
Process changes require regulatory approvals and/or "bridging" clinical trials*	Changes and associated requirements add cost	Higher price because of more costly development/process	100%	C:2 T: 2 PH: 5 = 9
Raw material/components changes require regulatory approvals*	Changes and associated requirements add cost		100%	C: 2 T: 2 PH: 5 = 9
Need for high biosafety conditions (e.g. BSL 3/4)	Increases development cost and time to ensure biocontainment compliance	Fewer developers and less competition Longer time before vaccine become available	21%	C: 4 T: 2 PH: 1 = 7
Lack of possibility to share production process and/or facilities*	High costs and development time to develop new facilities	Higher price because of more costly development Longer time before vaccine becomes available	100%	C: 5 T: 3 PH: 5 = 13
Low volume or sporadic demand creates production inefficiency	Increases risk of product write offs or increases cost of goods through low volume production	Higher price because of inefficient production	45%	C: 3 T: 1 PH: 2 = 6
Inability to quickly access new (seasonal) variants/strains	Delays development waiting for strain access	Fewer developers and less competition	0%	C: 1 T: 3 PH: 1 = 5
Long-lead time for establishing manufacturing capacity*	Increases development time to invest after clinical success is established	Reduced access because developer may not choose to make necessary investment Longer time before vaccine becomes available	100%	C: 5 T: 3 PH: 5 = 13
Lack of GMP-compliant contract manufacturers to produce clinical trial material*	Increases development time to find available capacity	Lower likelihood of vaccine availability Longer time before vaccine becomes available	100%	C: 1 T: 2 PH: 5 = 8

5. https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
Lack of partners available/ capable of receiving technology transfer*	Development takes longer because developers have to wait for available partners Limitation in available capacity	Lower likelihood of vaccine availability Lower supply level Longer time before vaccine becomes available	100%	C: 3 T:3 PH: 5 = 11
Lack of freedom to operate	Delays in development to find an alternative/develop IP	Fewer developers and less competition	12%	C: 1 T: 2 PH: 1 = 4
4. Factors impacting the predictability of the market and the likelihood of policy support for use				
Insufficient public budgets for purchase and implementation of immunisation programmes	Reduces likelihood of vaccine being adopted and implemented	Lower likelihood of vaccine availability/less competition	76%	C: 2 T: 4 PH: 4 = 10
Lack of policy entrepreneurs or immunisation champions	Reduces likelihood of vaccine being adopted and implemented		79%	C: 2 T: 4 PH: 4 = 10
Lack of political attention to non-epidemic diseases	Reduces likelihood of vaccine being adopted and implemented		70%	C: 2 T: 4 PH: 3 = 9
Lack of global political attention to diseases that don't cross-over into high-income countries (e.g. COVID-19 vs. Ebola)	Reduces likelihood of vaccine being adopted and implemented		48%	C: 2 T: 4 PH: 2 = 8

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
Growing vaccine hesitancy	Reduces likelihood of vaccine being adopted and implemented	Lower likelihood of vaccine availability/less competition	33%	C: 2 T: 4 PH: 1 = 7
Target groups not well articulated by public health entities (i.e., through a TPP)	Increased risk of developing a vaccine with low acceptance from policy makers		48%	C: 1 T: 4 PH: 2 = 7
Lack of data for assessing potential impact of vaccination in particular in specific target populations	Increases costs to developer to establish/strengthen epidemiology systems		55%	C: 3 T: 4 PH: 2 = 9
Value of vaccination needs to be demonstrated against alternative interventions	Increases costs to establish value vs alternatives		73%	C: 2 T: 2 PH: 3 = 7
Lack of use of appropriate models for economic valuation globally or in certain countries*	Reduces likelihood that vaccine will be adopted and implemented		100%	C: 2 T: 2 PH: 5 = 9
5. Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery				
Potential need for IP license to commercialise	Imposes additional costs to license technology; risk that it might not be possible	Fewer developers and less competition	76%	C: 4 T: 3 PH: 3 = 10
Restrictions imposed by public funders on IP “reuse”	Limits the attractiveness to developers; can put development of commercial products at risk if they use same IP		70%	C: 3 T: 4 PH: 1 = 8
Opportunity costs outweigh the vaccine’s economic rationale	Limited resources should be spent in most productive projects		64%	C: 5 T: 1 PH: 3 = 9

Challenge	Why this is a challenge for the developer.	Implication for the global community (if the challenge is not solved)	Frequency of challenge	Total Score
Unpredictability of public tender markets	Raises uncertainty and requires production to begin before results of tender are known	Fewer developers and less competition	82%	C: 3 T: 1 PH: 4 = 8
Reference pricing can reduce the value of HIC markets	Preserve a ROI that is sufficient to justify development with lower value of HIC markets		52%	C: 5 T: 1 PH: 1 = 7
Pricing pressure may discourage innovation for improvements*	Innovation investments are unlikely to support higher pricing	Lower likelihood of vaccine availability	100%	C: 5 T: 1 PH: 5 = 11
Limited availability of aligned partners to commercialise vaccine*	Development takes longer because developers have to wait for available/interested/ capable partners	Lower likelihood of vaccine availability Longer time before vaccine becomes available	100%	C: 1 T: 4 PH: 5 = 10
Insufficient access to funds for late-stage development*	Identifying and securing funding	Lower likelihood of vaccine availability/less competition	100%	C: 1 T: 4 PH: 5 = 10
Lack of private funding sources for vaccines targeted at LMICs	Identifying and securing funding		76%	C: 1 T: 4 PH: 4 = 9
Need to make expensive manufacturing investments prior to clinical success or demand certainty*	Puts investments at high risk because of chance of development failure		100%	C: 5 T: 1 PH: 5 = 11
Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	Increases developer's uncertainty and risk	Lower likelihood of vaccine availability/less competition/ higher costs to those who can pay	76%	C: 5 T: 1 PH: 4 = 10
Risks of legal action associated with widespread use of unlicensed vaccines	Risk of litigation against developer	Lower likelihood of vaccine availability/less competition	18%	C: 4 T: 1 PH: 1 = 6
Exposure to risk to high-income markets from unsubstantiated issues in low-income markets	Both risk of litigation against developer and lost revenue in high-income countries		48%	C: 5 T: 3 PH: 1 = 9

Priority challenges and decision-making influences

Each challenge was assessed for its relationship to factors that could influence a decision to stall or stop development. The case studies were used as a basis for this assignment and expert judgement of the MMGH team used to assess other challenges. If a challenge was judged to be associated to an influencing factor, that challenge was assigned a score of 1-4 according to whether the factor was the most important (4) or the least important (1) within each influencing area based on survey results of developer decision-making, as below:

The result of each of those assignments was translated into High (H)/Medium (M)/Low (L) level of influence that the challenge is hypothesised to have on decisions to slow or stop development. This was translated as below.

Table 19: Challenge topics in relation to influencing factors

Technical Feasibility			
Licensure feasibility (4)	Clinical feasibility (3)	Manufacturing process (2)	Freedom to operate (1)
Value Creation Potential			
Revenue potential (4)	Required investment (3)	Availability of funding (2)	Non-financial returns (1)
Unmet Medical Needs			
Burden of disease (4)	Size of target population (3)	Alternative interventions (2)	Cost-benefit (1)
Strategic Fit			
Organisational fit (4)	Portfolio fit (3)	Public health fit (2)	Available suitable partners (1)

Table 20: Scale for ranking of decision-making implications

Topic score	Challenge score	Score
>33	>8.9	High
<33	>6.9	Medium
<16.6	<6.9	Low

The results of the analysis for all 54 challenges are shown in Table 21 below.

Table 21: Level of impact of challenge on decision making Universal challenges are marked with an *

Topic	Topic: Level of influence	Challenge	Challenge: Level of influence
1. Feasibility and/or costs of meeting regulatory requirements to enable licensure and initial use			
Regulatory standards and practices	High	Lack of recognised surrogates or correlates of efficacy	HIgh
		Lack of animal models that correspond with immunogenicity in humans	Medium
		Lack of standardised assays, standards, and reagents for antigen testing	Medium
		Lack of standards by which platform technologies (e.g. adjuvants, mRNA) are transferable from one disease target to another	Medium
		Lack of support for alternative clinical pathways	Medium
National Regulatory Authorities (NRAs) capacity	Low	Few NRAs able to efficiently and flexibly regulate the primary licensure of a novel vaccine*	Medium
		Few NRAs able to regulate primary or secondary licensures of follow-on vaccines eligible for prequalification*	Low
Alignment of NRAs'	Medium	Lack of mechanisms that allow for use exclusively outside of the country of origin (e.g. EMA Article 58)	Medium
		Lack of harmonisation on requirements across NRAs*	Medium
		Lack of harmonisation on documentation of quality, efficacy, labelling, packaging and safety of biologicals & diagnostic across NRAs*	Medium
2. Feasibility and/or costs of testing under current clinical trial requirements			
Trial design and endpoint selection	High	Conducting efficacy trials requires an active outbreak	Medium
		Conducting efficacy trials for a disease with poorly established, low or sporadic disease incidence	Medium
		Real or perceived ethical concerns about trial design (e.g. administration of placebos, CHIM)	Medium
		Conducting efficacy trials for diseases involving animal transmission	Medium
		Conducting efficacy trials for diseases with varied epidemiological profiles	Medium
		Additional requirements for use of new technologies (e.g. adjuvants, mRNA)	Medium

Topic	Topic: Level of influence	Challenge	Challenge: Level of influence
Country-level capacity and capability	Medium	Lack of qualified in-country human resources to perform trials in MICs/LICs*	Low
		Lack of epidemiological surveillance systems in MICs/LICs	Medium
		Lack of diagnostics capabilities to adequately quantify disease occurrence during clinical trials	Low
		Insufficient WHO guidance to MICs/LICs on performance of clinical trials*	Low
		Increased pre-implementation safety studies for vaccines used first in LIC	Low
3. Feasibility and/or costs of manufacturing the vaccine to the right standard and volume			
Regulation of manufacturing	Medium	Lack of personnel in the NRAs with expertise and experience to regulate manufacturing*	Medium
		Process changes require regulatory approvals and/or "bridging" clinical trials*	Medium
		Raw material/components changes require regulatory approvals*	Medium
Manufacturing for commercialisation	Medium	Need for high biosafety conditions (e.g. BSL 3/4)	Low
		Lack of possibility to share production process and/or facilities*	HIgh
		Low volume or sporadic demand creates production inefficiency	Medium
		Inability to quickly access new (seasonal) variants/strains	Low
		Long-lead time for establishing manufacturing capacity*	Medium
Partnerships	Low	Lack of GMP-compliant contract manufacturers to produce clinical trial material*	Low
		Lack of partners available/capable of receiving technology transfer*	HIgh
Freedom to operate	Medium	Lack of freedom to operate	Low
4. Factors impacting the predictability of the market and the likelihood of policy support for use			

Topic	Topic: Level of influence	Challenge	Challenge: Level of influence
Uncertainty of demand	High	Insufficient public budgets for purchase and implementation of immunisation programmes	Medium
		Lack of policy entrepreneurs or immunisation champions	Medium
		Lack of political attention to non-epidemic diseases	Medium
		Lack of global political attention to diseases that don't cross-over into high-income countries (e.g. COVID-19 vs. Ebola)	Medium
		Growing vaccine hesitancy	Medium
		Target groups not well articulated by public health entities (i.e., through a TPP)	Low
Uncertainty of policy recommendations	Medium	Lack of data for assessing potential impact of vaccination in particular in specific target populations	HIgh
		Value of vaccination needs to be demonstrated against alternative interventions	Medium
		Lack of use of appropriate models for economic valuation globally or in certain countries*	HIgh
5. Feasibility of recouping all costs, while resulting in a vaccine deemed worthwhile by those funding procurement and delivery			
Freedom to operate	Medium	Potential need for IP license to commercialise	Medium
		Restrictions imposed by public funders on IP "reuse"	Medium
Return on investment (ROI)	Medium	Opportunity costs outweigh the vaccine's economic rationale	HIgh
		Unpredictability of public tender markets	Low
		Reference pricing can reduce the value of HIC markets	Low
		Pricing pressure may discourage innovation for improvements*	Medium
		Limited availability of aligned partners to commercialise vaccine*	Medium
Long-term horizon of vaccine development	Medium	Insufficient access to funds for late-stage development*	HIgh
		Lack of private funding sources for vaccines targeted at LMICs	Low
		Need to make expensive manufacturing investments prior to clinical success or demand certainty*	Medium
		Available incentives (e.g. pull mechanisms) not sufficiently attractive for the developer	Medium
Liability risks linked to preventive medicine	Low	Risks of legal action associated with widespread use of unlicensed vaccines	Medium
		Exposure to risk to high-income markets from unsubstantiated issues in low-income markets	Medium

Case studies

These case-studies were simulated through a role-play with members of the EAG in which each case study simulated two distinct decision points and the results of each decision-point were mapped to the appropriate challenge. The case study discussions took place via teleconference as a consequence of COVID-19 travel restrictions. Challenges identified by the EAG and factors influencing the decisions were documented.

Four case studies, each based on an in-scope vaccine, preliminary hypotheses on archetypes, and type of developer, were designed to validate the draft archetypes, refine the challenges and link influencing factors with challenges.

1. The case study on leishmaniasis vaccine development, a neglected disease archetype, explored the efforts of an academic institution attempting to find a mid-size vaccine development partner for its vaccine. The case study highlighted market uncertainty, regulatory feasibility and capacity to recoup development costs as the top challenges, with market uncertainty representing the most significant challenge. Unmet medical need, strategic fit in the developer's portfolio and value potential emerged as the most prominent factors influencing the decision-making process. The outcome of the mid-sized developer's decision not to partner with the academic institution reflected the different level of attention paid to market potential by the two developers.
2. The case study on Staphylococcus aureus vaccine development, a vaccine targeting high- and low-income markets (mixed markets) and important for AMR, highlighted the strong impact of clinical trial feasibility, recouping development costs and market uncertainty challenges. Technical feasibility and value creation had the highest influence on decision making together with some consideration for public health fit. The outcome of the decision to limit development to a single indication and then to proceed to Phase 3 was driven primarily by financial considerations. This large developer sought to protect a vaccine with high revenue potential from the potential to have a second indication force a lower price to the product as a whole.
3. The case study on Zika vaccine development, a vaccine representative of the EID archetype, illuminated important challenges in clinical, regulatory and manufacturing feasibility typical of a novel technology being pursued by a biotech company. The feasibility of recouping development costs was prominent, particularly the need to secure funding for late-stage development. The factors influencing decisions paralleled the challenges and included technical feasibility but, ultimately, the value creation potential, and, specifically, the availability of funding, proved to be the strongest influencing factor in moving past the first decision point.
4. Finally, the case study on the Typhoid conjugate vaccine (TCV) presented the critical aspects of the proposed archetype of improved vaccines (dropped after the case study and the additional analytical work). Development for this type of vaccine normally faces relatively few challenges: predictability of the market, regulatory feasibility and feasibility of recouping development costs being among the most common ones. These challenges were ultimately considered manageable, even for a small parastatal vaccine developer. Factors that influenced the decisions to move forward in development included unmet medical need, technical feasibility and good strategic fit.

Across the case studies, feasibility of recouping all costs, followed by regulatory feasibility and market predictability were the most frequently discussed challenge categories. Clinical and manufacturing feasibility were the least frequently cited challenges but, where they appeared, were strongly linked to stalled development. Two individual challenges mentioned in at least three of the cases studies were the lack of funding for late-stage development and lack of a clear articulation of the interest for the vaccine by policy makers.

The most frequently occurring influencing factor that influenced three of the four outcomes was public health fit as defined in the decision-making section, followed by licensure feasibility, clinical feasibility and availability of funding that each influenced two of the four outcomes. These results were not entirely aligned with the factors identified as most influential through the survey. Specifically, public health fit was more influential than expected based on the survey results because it was a factor in influencing decisions in three of the four case studies yet was deemed one of the least influential factors in the survey.

MMGH team profiles

Stefano Malvolti

Stefano has over 20 years of experience in global health and the pharmaceutical industry in programme management, strategy, policy, finance and supply chain. He is currently a Member of the Board of Directors of the Fondazione Achile Sclavo in Siena, Italy, an NGO focused on facilitating vaccine development for neglected diseases.

In 2016, he served as Chief Executive Officer at Univac in Brussels, an early stage Biotech company developing a new vaccine platform for viral diseases. Under his tenure, the company redefined its governance mechanisms, its strategy and defined its preclinical development plan. Previously, he was the Director of Vaccine Implementation at Gavi, the Vaccine Alliance where he was responsible for the coordination of the roll-out of Gavi's 11 vaccine programmes with more than 150 country launches. He also led the Gavi Coverage and Equity initiative aimed at defining new approaches and country strategies to steer the Alliance towards its 2020 goal of number of children vaccinated. Mr. Malvolti chaired the Gavi Alliance's Vaccine Implementation Management Team. He was also a member of WHO's Global Polio Eradication Initiative's Immunization Management Group and the Ebola Vaccine Deployment Steering Group.

Prior to Gavi, he was Global Policy Director at Novartis Vaccines, responsible for the business unit's relations with WHO, UNICEF and GAVI and for the negotiation of the Pandemic Influenza Preparedness framework. In the starting years of his career he was Director of Strategic Vaccines Supply at PATH where he implemented state-of-the art processes that raised the reliability of Gavi's forecasts and was a member of UNICEF Supply Division procurement reference groups for Pneumococcal and Rotavirus vaccines. Before this, he served in various positions in Novartis Pharma and Baxter Healthcare in strategic forecasting, outsourcing, sales and operations, planning and finance.

Melissa Malhame

Melissa spent more than 20 years in market shaping, policy, regulatory, strategy and commercial roles in global public and private health at Gavi, Merck and Dynavax. She is a world-wide expert in market shaping and procurement and was a member of the Center for Global Development working group on the Future of Global Healthcare Procurement.

She led Gavi's market shaping efforts until late 2017. In that capacity, she was accountable for ensuring adequate and timely supply of vaccines at affordable prices for Gavi, for setting long-term access strategies for sixteen vaccines, for forecasting long-term demand and working closely with UNICEF Supply Division. She has served on numerous Procurement Reference Groups.

Prior to her role at Gavi, Melissa had a twenty-year career in the vaccine industry spanning commercial, policy, regulatory and strategy roles.

Shawn Gilchrist

Shawn has longstanding experience in developing countries, most extensively in Cameroon where he worked as a community physician and conducted a clinical trial on measles vaccines in the 1990s, and in other countries in West Africa, where he managed a training program in vaccinology for physicians in the early 2000s.

He has 14 years of experience in the vaccine industry, having held the position of Director of Corporate Public Policy at Sanofi Pasteur. While in industry, he acted as liaison with international organisations including the World Health Organization, Unicef, and the World Bank, on major international public health initiatives, such as the Global Polio Eradication Initiative and Gavi, and was the International Federation of Pharmaceutical Manufacturers and Associations representative on the Gavi working group.

Shawn is currently the President of S Gilchrist Consulting Services Inc, providing technical assistance and policy services to clients in both the public and private sector. Much of his work has focused on issues pertaining to improved access to vaccines. He has served as a member of the WHO SAGE Working Group on Monitoring and Evaluation of the Decade of Vaccines and on the Harvard Working Group on Middle-Income countries.

Lydia Ogden

Lydia Ogden is a proven public- and private-sector leader with three decades of experience in predicting and managing health system change and enabling successful health partnerships spanning the globe. Lydia joined Merck in November 2012, initially directing U.S. and ex-U.S. work in vaccines policy, partnerships, and government relations to globalise Merck's vaccines business and improve immunisation rates worldwide. From August 2017 to May 2019, she led company-wide strategic engagement with international organisations, foundations, institutions, and industry associations; directed overall access efforts; and served as the policy lead for Merck's Public Policy and Responsibility Council.

Prior to joining Merck, Lydia worked in public health for more than two decades at the U.S. Centers for Disease Control and Prevention, in environmental health, domestic and international HIV/AIDS, and leading the agency's health reform initiatives. Lydia has a doctorate in health services research and health policy from Emory University; a Master's degree in Public Policy from the Kennedy School of Government, Harvard University; a Master's degree in Literature from Vanderbilt University; and a bachelor's degree in English and Education (K-12) from Middle Tennessee State University. She holds an affiliate faculty appointment in health management and policy at the Dornsife School of Public Health of Drexel University and is an adjunct fellow at the Center for Public Health Initiatives and the Fels Institute of Government of the University of

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