Prioritization models for vaccine development against emerging infections

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Contents

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List of papers

I. Gouglas D, Hoyt K, Peacocke E, Kaloudis A, Ottersen T, Røttingen JA. Setting Strategic Objectives for the Coalition for Epidemic Preparedness Innovations: An Exploratory Decision Analysis Process. INFORMS Journal on Applied Analytics. 2019; 49(6):397-459; https://doi.org/10.1287/inte.2019.1011.

II. Gouglas D, Thanh Le T, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen JA. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. The Lancet Global Health. 2018; 6(12): e1386-e1396; https://doi.org/10.1016/S2214-109X(18)30346-2.

III. Gouglas D, Marsh K. Prioritizing investments in new vaccines against epidemic infectious diseases: A multi-criteria decision analysis. Journal of Multi-Criteria Decision Analysis. 2019; 26(3-4):153-163; https://doi.org/10.1002/mcda.1683.

IV. Gouglas D, Marsh K. Prioritizing investments in rapid response vaccine technologies for emerging infections: a portfolio decision analysis. PLOS One. 2021; 16(2): e0246235; https://doi.org/10.1371/journal.pone.0246235.

List of abbreviations

ACT	Access to COVID-19 Tools
AHP	Analytic Hierarchy Process
CEPI	Coalition for Epidemic Preparedness Innovations
CHNRI	Child Health and Nutrition Research Initiative
COVID-19	Coronavirus Disease 2019
DALYs	Disability Adjusted Life Years
DCE	Discrete Choice Experiment
DNA	Deoxyribonucleic acid
EIDs	Emerging Infectious Diseases
eNPV	Expected Net Present Value
HRPS	Health Research Priority Setting
mAbs	Monoclonal Antibodies
MACBETH	Measuring attractiveness through a categorical-based evaluation technique
MCDA	Multi-Criteria Decision Analysis
MERS	Middle East Respiratory Syndrome
NPV	Net Present Value
PDA	Portfolio Decision Analysis
PoS	Probability of Success
PSA	Probabilistic Sensitivity Analysis
QALYs	Quality Adjusted Life Years
R&D	Research and Development
RNA	Ribonucleic acid
RoV	Real Options Value
RSV	Respiratory Syncytial Virus
SMART	Strategic Multi-Attribute Ranking Tool
TPP	Target Product Profile
VFT	Value Focused Thinking
WHO	World Health Organization

Summary

Background: The COVID-19 pandemic is just the most recent, stark reminder of the threat that Emerging Infectious Diseases (EIDs) increasingly pose to the world. Vaccine development can serve an essential part in efforts to respond to these threats. Despite the momentum generated through institutional responses to EIDs in recent years, the world needs to get its EID vaccine development priorities right, given the range of threats and the limited resources available to address them. This points to the need for new research to better understand the nature and magnitude of the EID vaccine R&D prioritization problem, including the relevant objectives, funding needs, and the value of EID vaccine R&D alternatives. It also underscores the need for appropriate tools that can support high-impact R&D investment decisions in real-life settings.

Objective: The objective of this PhD project is to develop and apply a prioritization framework for investment in EID vaccine development within a newly established, international multi-stakeholder setting.

Methods: To develop the framework, the thesis draws on established approaches in the fields of Health Research Priority Setting, Decision Analysis and Operations Research; and proposes a conceptual frame for addressing interconnected problems of strategic objective setting, investment boundary setting, project and portfolio selection. Specific prioritization models are then employed to support solutions to each of these problems. An Exploratory Decision Analysis process combines Value-Focused Thinking and Discrete Choice Experiment methods to identify, structure and explore the relative importance of strategic objectives for EID vaccine R&D investments (**Paper I**). A stochastic optimization model estimates the minimum cost for advancing vaccines successfully through clinical safety and immunogenicity studies in a portfolio of 11 priority EIDs, setting the boundaries within which consequent investment decisions can be made (**Paper II**). A Multi-Criteria Decision Analysis combines multi-attribute utility and Monte Carlo simulation methods to support the selection of vaccine candidate projects for investment against Lassa, Middle East Respiratory Syndrome (MERS) and Nipah (**Paper III**). A Portfolio Decision Analysis combines simulation-optimization and Discrete Choice Experiment methods to support the selection of an optimal portfolio of rapid response vaccine technology platforms for investment against newly emerging infections (**Paper IV**).

Findings: There are three sets of key findings that can be drawn from the thesis. First, it is possible to integrate diverse normative and methodological approaches to prioritization to develop a coherent framework within which prioritization models for EID vaccine development can be designed. Second, it is possible to employ this framework to generate evidence to inform EID vaccine R&D priorities and investment decisions through the systematic combination and adaptation of procedural and rigorous analytic tools. Third, the results of the application of this framework provide new evidence on EID vaccine development objectives, costs, risks and preferences. In terms of strategic objectives, vaccine R&D preparedness emerges as the highest priority, if advanced in parallel with market predictability, response and equity objectives. Vaccine development investment boundaries are estimated at $319–469M ($137M–$1·1BN range) per EID, reflecting expectations of

costs through mid-stage clinical development after accounting for likely project failures. The average probability of success of EID vaccines through mid-stage clinical development is estimated at 33% (14-66% range) – as demonstrated by expert assessments on a number of Lassa, MERS and Nipah vaccines. When investing in vaccines, there is more value to this probability than to the probability that the technology platforms supporting these vaccines will be suitable for vaccine development against other, newly emerging infections. The probability of vaccine technology platform projects rapidly responding to multiple emerging infections is low and varies between platform types: <1-36% for Viral Vectors; <1-26% for Protein; <1-23% for Ribonucleic acid (RNA); <1-12% for Deoxyribonucleic acid (DNA); <1-7% for gene-encoded monoclonal antibodies (mAb). The value of investing in RNA is higher than Viral Vector platforms, and investment in RNA and Viral Vectors is more desirable than in DNA, Protein or gene-encoded mAbs. Platform diversification is desirable in face of substantial uncertainty and diminishing returns from investing in projects of single platform types.

Implications: Findings demonstrate how prioritization models can rationalize the allocation of resources in a complex global health R&D setting, characterized by multiple stakeholder values, funding constraints and uncertainty in cost and performance of vaccine technologies. As global governance structures for outbreak preparedness and response continue to evolve, the findings of this thesis can help these structures make improved decisions that maximize value for global health.

More broadly, three implications can be drawn for future research and practice. First, the reported prioritization framework points to a set of theoretical foundations that others can consider when developing methods for prioritizing investments in newly established entities supporting R&D more generally; especially where a structured approach to planning and management of investments will be needed, and where societally valued goals are present but monetary gains are less important. Second, the real-life application of this framework in a specific organizational context should offer some reassurance to researchers and practitioners about the feasibility of employing both participatory and rigorous analytical tools to support real-world R&D decisions. Further research and applications will also be beneficial for testing the practical utility and validity of these tools across different R&D domains. Third, the findings from application of the framework can serve as inputs and points of departure in future prioritization processes. For instance, the evidence on costs, risks, and preferences for prioritizing new EID vaccine development investments presented in the thesis serve a valuable entry point for planning and prioritizing R&D investments in response to the COVID-19 pandemic. However, further validation, and potential updates to these estimates may be needed given the world's experience with COVID-19 and its likely impact on EID vaccine development priorities in the future.

1. Introduction

1.1. Background

1.1.1. The challenge

The world is currently shaken by the emergence and global spread of a novel coronavirus known as COVID-19. The COVID-19 pandemic is the most recent, stark reminder of the proliferating threat that Emerging Infectious Diseases (EIDs) increasingly pose to global health security [1]. Vaccine development can serve an essential part in efforts to respond to emerging epidemics [2]. This has been demonstrated by the vaccine Research and Development (R&D) response to the 2014–15 Ebola epidemic in West Africa and by the prominent role it is playing in the global COVID-19 pandemic response [3,4]. In doing so, vaccine R&D can act as a driving force of health security improvements worldwide. However, EID vaccine R&D faces challenges. Substantial investments are required for EID vaccine development [5-7]. In addition, vaccine development is inherently risky, with, for instance, at least two-thirds of preclinical vaccine candidates likely to fail before reaching clinical proof of concept, according to published industry data [8,9]. The scientific risks and operational complexities entailed generally in developing vaccines are well documented in the literature (e.g. see [10-12]).

Despite the world's unprecedented response to the COVID-19 pandemic, no vaccine has ever been developed in time to alter the course of a new disease outbreak for several additional reasons. First, coordination of stakeholder responses across institutions and sectors has traditionally lagged behind the epidemic curves of EIDs [13]. Second, R&D priorities for improving preparedness have been driven primarily by national security concerns, leaving sparse product development pipelines for EIDs that fell outside country-specific security agendas [14]. Third, development of EID vaccines has been unappealing for manufacturers, who see little commercial benefit due to the sporadic disease burden and lengthy, risky, and costly product development [12,15].

Given the damage potential of EIDs as well as the scale of investment and coordination, risks and complexities inherent in vaccine R&D, there is a growing need by decision-makers of understanding what it would cost and agreeing on how to prioritize scarce resources to develop vaccines. This problem is of particular relevance in current times, since, traditionally, there has been a paucity of explicit, publicly available vaccine R&D Probability of Success (PoS) and cost data as well as little agreement between stakeholders on which R&D investments should be prioritised. These challenges are compounded by the historical absence of a global EID R&D portfolio strategy and coordination, and are amplified by the lack of evidence about the magnitude of the EID vaccine R&D prioritization problem and the feasibility of addressing it [16,17].

1.1.2. The opportunity

Challenges notwithstanding, the west African Ebola epidemic [2,16,17] and the COVID-19 pandemic [18] have led to a paradigm shift in EID vaccine development thinking. In response to Ebola, experimental vaccines were possible to deploy thanks to over a decade of R&D into

biodefence-related Ebola countermeasures [19]. In response to COVID-19, vaccines were possible to develop at unprecedented speed thanks to the accumulation of evidence on technology platform performance against a variety of related pathogens [20]. Successful efficacy testing of an Ebola vaccine [21] and of several COVID-19 vaccines [22-24] in midst of the two most notable epidemics of recent times suggest a pathway for better preparedness against future epidemics: namely, advancement of vaccine technologies through human trials in anticipation of emergencies and making the most promising of these quickly available for efficacy testing and use if and when emergencies occur [19].

With these successes in mind, a political, financial and scientific momentum has been generated to address the world's security challenge from future epidemic threats via institutional responses. One of these is the Coalition for Epidemic Preparedness Innovations (CEPI). CEPI was formally launched at the 2017 World Economic Forum meeting in Davos [25], with close to US$2 billion current funding from various governments and philanthropic foundations, seeking to diminish the danger that EIDs pose to the wellbeing of affected populations. Others are the Access to COVID-19 Tools (ACT) Accelerator [26] and its COVAX pillar for vaccine development [27], which CEPI has contributed to setting up in response to the COVID-19 pandemic. However, to fully seize on this momentum, the world must get its priorities for EID vaccine development right, given the range of EID threats and the limited resources available to address them.

1.1.3. The knowledge we need

To prioritize EID vaccine R&D investments appropriately, we need new research to understand the nature and magnitude of the EID vaccine R&D prioritization problem as well as to design appropriate tools that can support high-impact R&D investment decisions in real-life settings. In particular, two main knowledge gaps need to be addressed: a) evidence around appropriate objectives, funding needs and the value of EID vaccine R&D alternatives; and b) methods for eliciting these in a rational, systematic manner.

Indeed, the novelty of global institutional responses to EID threats brings with it an unchartered territory in terms of evidence around both what the most relevant objectives should be and their relative importance to help set some desirable goals towards which subsequent investment decisions can be made. The identification and structuring of strategic objectives – and the specification of trade-offs between these – requires the application of methods that explicitly account for stakeholder values in complex planning contexts characterized by strong interests and conflicting priorities.

Furthermore, not knowing what R&D alternatives are potentially available, and not knowing how much it would cost to successfully develop these to satisfy strategic targets, prevents the setting of boundaries within which reasonable R&D investment decisions can be made [6]. This requires new evidence on EID R&D pipelines and costs through models that identify optimal pipeline structures and funding needs, accounting for pipeline constraints and R&D uncertainties.

Models for valuing and prioritizing EID R&D investments, such as EID vaccines and rapid response technology platforms for newly or unexpectedly emerging EID threats, are also almost entirely lacking (see Chapter 2). Most of the handful of models previously proposed for vaccine development prioritization (e.g. the CHNRI methodology [28-30], or the SMART Vaccines framework [31-40]) do not lend themselves easily to the estimation of value of

vaccine R&D that is adjusted for the PoS of early stage, risky R&D candidates, which is typically the case of EID vaccines. Other cost-effectiveness [41-44] and decision-tree analysis methods (e.g. [45]) have attempted to more explicitly address such concerns. However, differences in the characteristics between these prioritization problems suggest that no single model can assume criteria, preferences and constraints to be equally relevant across different application contexts [46].

Despite the establishment of various Health Research Priority Setting (HRPS), Decision Analysis and Operations Research approaches to health product development prioritization (see Chapter 2), a practically oriented framework for EID vaccine development prioritization is lacking. Such a framework is needed for structuring the EID vaccine R&D prioritization problem, and for guiding real-life decisions to address this; drawing from the similarities, differences and complementarities between established health product development prioritization approaches. The focus here is not only on producing new information or knowledge about EID vaccine R&D investment priorities, but also about how to make optimal choices once information has become available. This requires the application of a variety of procedural, stakeholder engagement tools combined with rigorous analytical tools for problem structuring and valuation under conditions of uncertainty, resource constraints and heterogeneity of stakeholder perspectives.

1.2. Objectives

The overall objective of this thesis is to develop and apply a prioritization framework for supporting investments in EID vaccine development. This framework should be able to integrate models for addressing a set of interconnected problems of strategic objective setting, investment boundary setting, project and portfolio selection in the context of EID vaccine R&D. To achieve this objective, the thesis aims to: a) demonstrate how models can account for multiple criteria and formally incorporate stakeholder preferences in the face of decision uncertainty and evolving trade-offs; b) contribute to the evidence base about priorities in EID vaccine development through the application of the framework in an international, multi-stakeholder setting.

Specifically, four research objectives are explored in separate papers as follows:

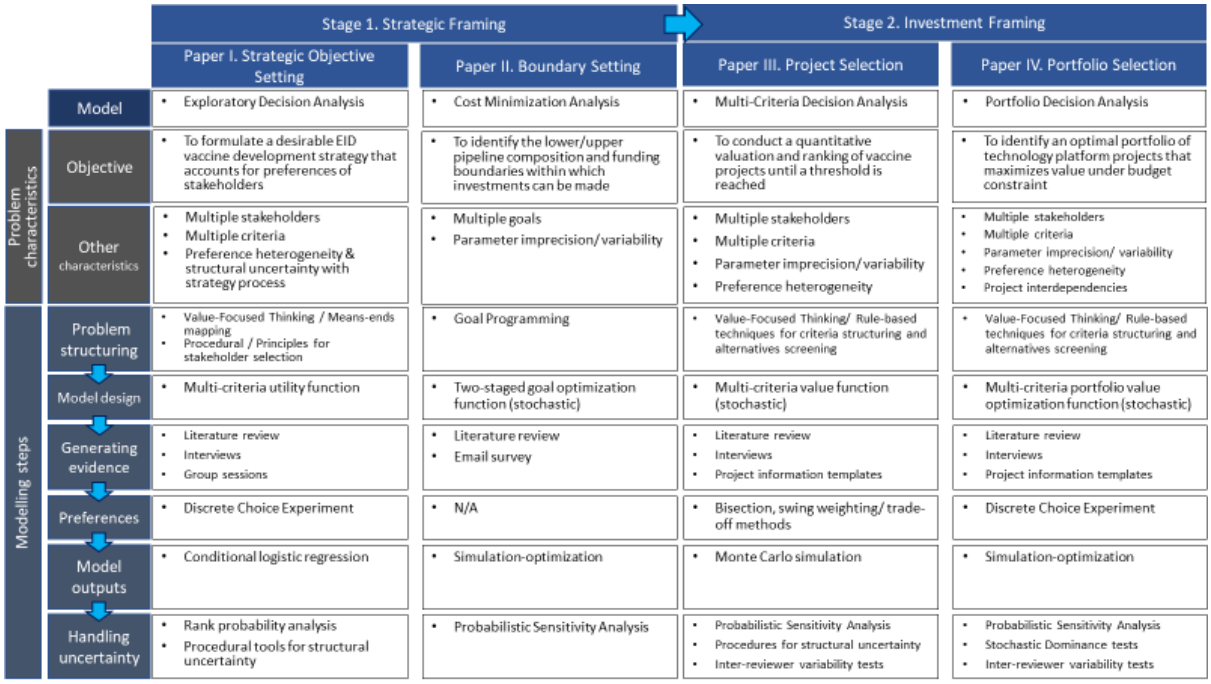
- **Paper I**: To identify strategic objectives and examine their relative importance for EID vaccine R&D among diverse stakeholders in an international coalition setting.
- **Paper II**: To estimate the minimum cost for achieving vaccine R&D preparedness targets against 11 priority EIDs.
- **Paper III**: To undertake a quantitative valuation for the ranking and selection of EID vaccine R&D projects.
- **Paper IV**: To undertake a quantitative valuation for the selection of a portfolio of rapid response technology platform projects to unexpectedly emerging infections.

To develop the framework, the thesis draws from normative and methodological perspectives in the Health Research Priority Setting (HRPS), Decision Analysis and Operations Research literature (see Chapter 2). A conceptual model is introduced, presenting the lifecycle of EID vaccine development and the characteristics of EID vaccine R&D decisions. A definitional frame is established, within which different prioritization typologies can be distinguished and prioritization methodologies can be reviewed. An appraisal of theoretical and empirical

approaches to health product development prioritization identifies the conditions under which it is appropriate to use different methods to support the prioritization of investments along the EID vaccine R&D continuum. These conditions inform the structuring of a general framework for addressing strategically interconnected prioritization problems in EID vaccine R&D.

Whereas the overall methodological approach to address these objectives is that of multi-criteria modelling, a variety of procedural and analytical techniques are employed to address the different problems considered in the framework (see Chapter 3). This is done in two stages. The first stage concerns the establishment of an overarching strategic prioritization frame, against which individual investment decision problems can be addressed at the second stage. Across the two stages, five characteristics help define the nature of prioritization problems that can emerge and the methods relevant to addressing these: stakeholders, alternatives, decision criteria, analytic objectives, uncertainties and interaction effects. With these characteristics in mind, six steps are then undertaken to develop an appropriate prioritization model for each problem: problem structuring; model formulation; selection of methods for generating factual information; selection of methods for generating preference information; selection of methods for model output computation; and selection of methods for handling uncertainty. Figure 1.1 summarizes the framework and the models employed within this to address the four research objectives of the thesis (see Chapter 3 for details on problem characteristics and methods employed).

Figure 1.1. Summary of prioritization modelling framework.



1.3. Structure of thesis

The remainder of the thesis is structured as follows. Chapter 2 presents the theoretical framework underlying the chosen methodologies, providing a justification for the process steps and analysis techniques employed in the thesis. Chapter 3 gives an overview of the

methodological approaches undertaken to address the EID vaccine R&D prioritization problem, from strategic objective and boundary setting, to R&D project and portfolio selection. Chapter 4 provides a summary of the results from the implementation of these methods across the two stages of the EID vaccine R&D prioritization problem (**Papers I-IV**). Chapter 5 provides a discussion of the main findings, methodological and practical contributions as well as limitations of the thesis. Chapter 6 summarizes the thesis's conclusions. **Papers I-IV** and their supplements are provided in full in the Appendix.

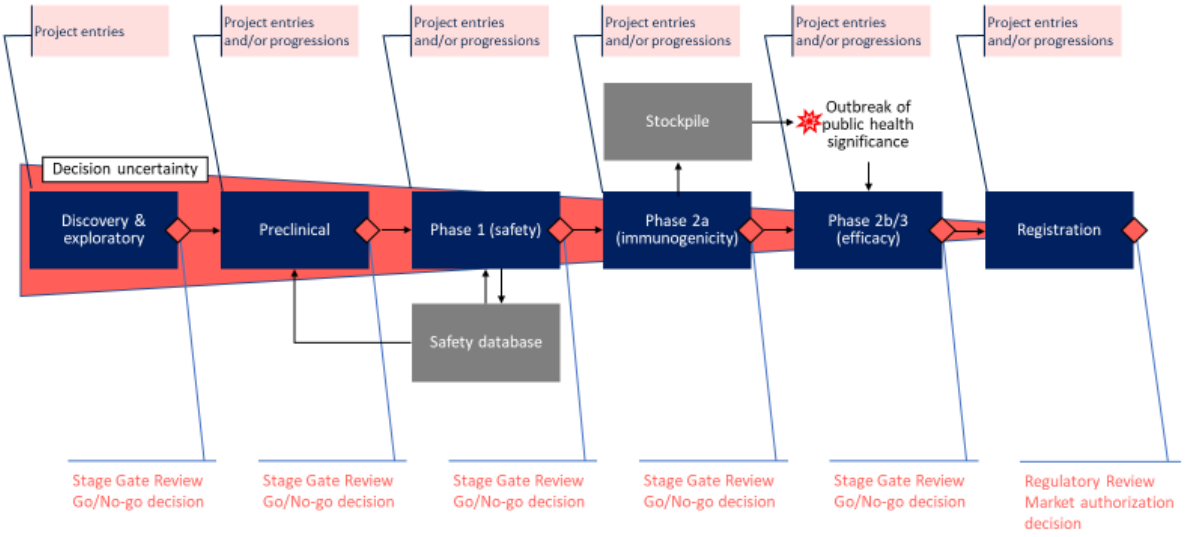
2. Theoretical Background & Framework

This chapter presents the theoretical background underlying the development of the prioritization framework and the structure of its application. To this end, a conceptual model is initially introduced presenting the lifecycle of EID vaccine development, followed by the establishment of a definitional frame within which different prioritization typologies can be distinguished. An overview is presented of methodological approaches that have been used or proposed for different health product development prioritization problems. Lessons are then drawn for the development of a framework to support the prioritization of investments in EID vaccine R&D. The chapter ends with a presentation of a general framework structure and considerations for bringing different analytical and procedural elements together to appropriately support the prioritization of investments in EID vaccine R&D.

2.1. The lifecycle of EID vaccine development

Although the reality of vaccine development can be complex, several authors have attempted to describe in simple terms the different phases in vaccine development and key characteristics (e.g. [8,12]). However, in order to determine what methods can appropriately support different steps of the EID vaccine R&D prioritization process, a further link needs to be established between development phases, types of decisions to be made and challenges facing these different decision points. Figure 2.1 provides a simplified view of this relationship along the path of EID vaccine development, from exploratory to different product access endpoints.

Figure 2.1. An illustration of phases and pathways and of decision points in EID vaccine development.



2.1.1. Phases & Pathways

Based on figure 2.1., there are several phases in the lifecycle of EID vaccine development. Typically, most EID vaccines can only be developed through four sequential phases in off-

epidemic conditions: discovery & exploratory for antigen selection; preclinical trials in animal models; Phase 1 safety trials in humans; Phase 2a safety and immunogenicity trials in humans. In off-epidemic conditions the incidence of EIDs is non-existent, low and/or sporadic. Therefore, Phase 2b/3 efficacy trials in humans are typically not possible to conduct, unless there is an outbreak that triggers an accumulation of cases to allow its launch. If a vaccine successfully advances through to end of Phase 2a clinical trials, clinical investigational vaccine material can be stockpiled, which can then be used in a Phase 2b/3 study just-in-case an outbreak occurs. However, there may be some EIDs – e.g. Chikungunya, Lassa – whose incidence is predictable enough so that Phase 2b/3 studies can be initiated and conducted in off-epidemic conditions, without the need for a major outbreak of international concern to occur.

Vaccine technology platforms can also be tested for their potential to enable just-in-time vaccine development in response to an unexpected epidemic infection emergency. Typically, once such platforms have been discovered and/or designed, these are tested in preclinical models and in Phase 1 safety trials in humans utilizing model pathogens, to demonstrate speed of vaccine development and production together with safety and immunogenicity enabling potential. In off-epidemic conditions, platforms can be tested across multiple pathogens, in order for databases on safety characteristics to be built, which can accelerate regulatory decisions for a just-in-time implementation of Phase 2a and Phase 2b/3 studies in response to an unexpected outbreak. Development of specific vaccines using these platforms can continue through Phase 2a trials in off-epidemic conditions. However, the rationale of the platform approach is essentially an alternative pathway to stockpile-based preparedness for Phase 2b/3 studies and is particularly relevant to new and unexpectedly emerging infections.

It is worth noting that the above development phases and pathways can be compressed in response to novel EID outbreaks, where no vaccine has previously been developed. This point is exemplified by the COVID-19 pandemic response, where a combination of clinical evidence on vaccine performance against related pathogens and the accumulation of evidence on platform performance against model pathogens allowed for an accelerated development of COVID-19 vaccines once the right antigen had been selected [18].

2.1.2. Decision points

Throughout the lifecycle of EID vaccine development new pipeline entry decisions need to be made. New vaccine or platform candidates can enter the development pipeline at any phase of development, depending on if they are available and if they are successfully evaluated and selected for entry, during what are typically known as project or portfolio selection decisions.

Once a project has entered the development pipeline, periodic decisions need to be made on whether to continue or to abandon a project, and/or how to prioritize it if a portfolio of projects has been established but not all projects can be afforded to advance due to budget or other constraints. These decisions usually occur at the end of each phase, during what are typically known as stage gates [47].

2.1.3. Decision challenges

Pipeline entry or stage gate criteria depend on the strategic priorities of those making the R&D investment decisions. Assuming a newly established, international multi-stakeholder

setting (such as in CEPI), a first challenge is to clarify what strategic objectives for vaccine development to pursue, given diverse opinions of stakeholders on the nature and relative importance of these (see section 2.2.). Second, because of the multi-staged nature of EID vaccine development, any framework developed for the evaluation and selection of new projects will require some consistency in its evaluation features with these objectives and with periodic updates needed to support stage gate decisions.

Third, whether investments will generate economic or societal benefit is subject to significant uncertainty, because of: not knowing if the product will protect against an unexpectedly emerging pathogen outbreak; and not knowing what the value of that protection will be – that is, how many people would be put at risk by the pathogen and what risk the pathogen would pose to them [20]. Whereas technical and operational uncertainties are likely to diminish as product candidates advance through development phases and new evidence becomes available [48], outcome uncertainties will most likely remain, unless the incidence of disease becomes predictable. For these reasons, no single standardized financial or health-economic value metric is likely to be able to measure the value of EID vaccine R&D investments. In absence of such commonly acceptable impact-based metrics, sources of value may need to be identified that incorporate stakeholder preferences to inform how such values should be traded off, if conflicting.

2.2. Prioritization as a frame

To fully appreciate the complexity facing efforts to prioritize investments in EID vaccine R&D, it is helpful to think of prioritization as a frame along the path of vaccine development. Keeney [49] has described a philosophical approach to defining decision problems as reasoning frames, mainly focusing on values for evaluating the actual or potential consequences of action and inaction of proposed alternatives and of decisions. Building on this framework, prioritization in this thesis can be treated as one type of such a decision frame, where the requirement is to choose a single alternative, or a subset of alternatives, from a larger set of defined alternatives. This requires several key distinctions to be made, based on which a number of relationships can be established between inter-connected prioritization frames. These are discussed below.

2.2.1. Distinctions

A first distinction should be made between setting priorities and prioritizing investments. Setting priorities is an activity that can be carried out by different stakeholders, with the resulting priorities used, or not used, by decision makers responsible for allocating resources. Priority setting approaches are typically applied in more strategic contexts and when linked to specific organizational environments they often take the form of strategic frameworks [50-53]. Here, investment alternatives are rarely defined at the start of the process, instead they are typically the outputs, or the resulting priorities, of the process. Investment prioritization suggests the allocation of resources and requires the engagement of stakeholders accountable for making investment decisions [54]. Most of the approaches proposed for prioritization in health product development are applied in (or developed for) institutional contexts where investment alternatives are already well defined at the start of the exercise and assume the presence of stakeholders with decision making authority. This distinction is made because the

two terms relate to two different types of problems that by Keeney's approach should be sequentially inter-connected within an integrating prioritization framework.

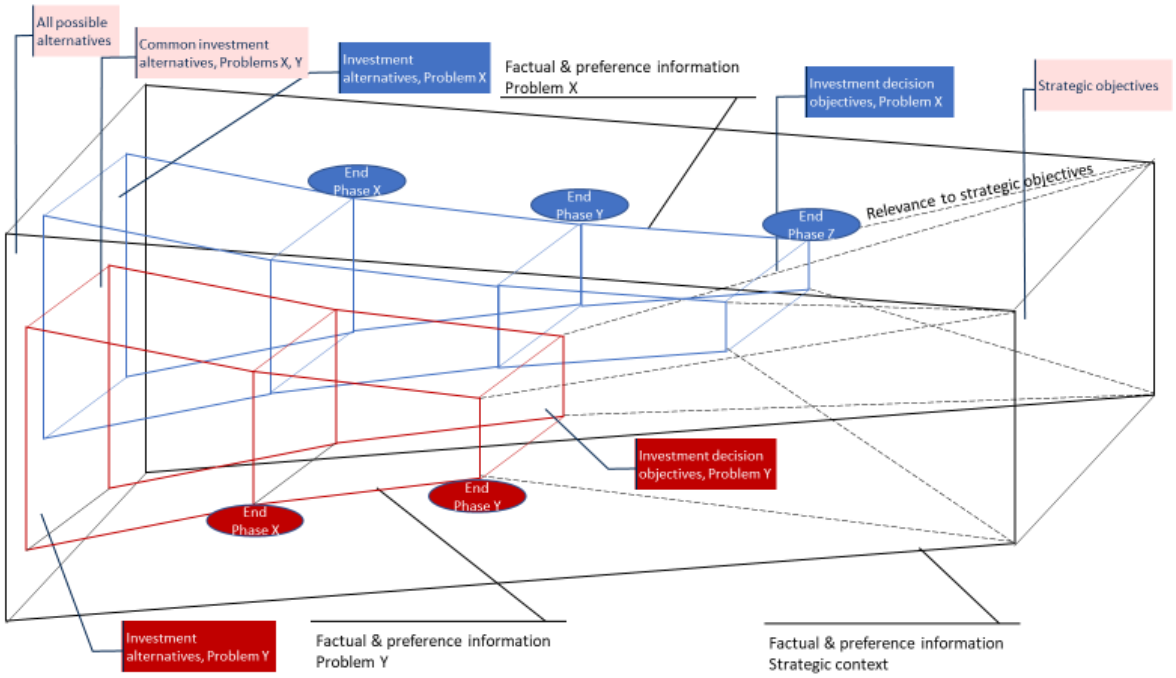
A second distinction must be made between valuation and prioritization. Whereas prioritization is about choosing a single alternative, or a subset of alternatives, from a larger set of defined alternatives, this can be contrasted with the typical situation of examining the value of a single alternative (e.g. through health technology assessments [48, 55]) to inform a go/no-go authorization decision, which is commonly observed for instance during stage gate reviews [47]). The distinction between valuation of single alternatives and choice between them is important, as choice often requires, in addition to the valuation of each alternative, the explicit consideration of value trade-offs between these, i.e. a systematic exploration of reasons why for example one alternative, with a given estimate of performance, should be selected over another alternative, with another performance estimate.

A third distinction should be made between different types of prioritization problems and objectives. On one hand, project selection is the process of arriving at an overall ordering between *independent* decision alternatives, whether that may be some form of binary selection, listing, ranking, clustering or sequencing (also known as scheduling) of preferred *versus* non-preferred alternatives. On the other hand, portfolio selection is the process of arriving at an overall ordering of subsets of *interdependent* alternatives out of a larger set. The solution to both project selection and portfolio selection problems is dependent on some form of valuation of individual decision alternatives, as discussed above. The ultimate prioritization objective may be similar between the two types of prioritization problems (i.e. an optimal selection of preferred alternatives in the form of a binary, list-, rank-, cluster-, or sequence- based ordering). However, it is the level of choice trade-offs that changes in the two problems, because of the way that the value of individual alternatives is realized in presence of interaction effects (e.g. shared resources, risk or value interdependencies, etc.). This distinction is important because the presence of interaction effects adds a significant layer of complexity in how portfolio selection problems should be structured to address their prioritization objectives. In absence of such interaction effects, portfolio selection problems are, in practice, nothing more than project selection problems which can be addressed in less elaborate ways. From an analytical standpoint, literature often unnecessarily classifies prioritization problems as portfolio selection problems, when these should really be treated as problems of project selection (for details see section 2.3.).

2.2.2. Relationships

Illustrating prioritization as a frame by drawing on the above distinctions can help visualize relationships between different types of specific, seemingly disconnected analytical problems vis-à-vis otherwise commonly shared, fundamental prioritization objectives. In doing so, a multiplicity of analytical methods can be introduced to support different types of prioritization problems that are strategically and/or sequentially interconnected. Figure 2.2 presents such a frame, spanning from priority setting to specific types of prioritization problems.

Figure 2.2. Framing strategically interconnected prioritization problems with flow of information indicated. An adaptation of the Keeney [49] Value-Focused Thinking framework.



Based on this figure, two stages can be distinguished. Per Keeney's classification [49], the broadest prioritization frame is the strategic decision frame where the decision maker's ultimate priorities are set, referred to as strategic objectives. Others refer to this as simply the strategy table [56], or within corporate management settings the strategic buckets approach [50]. These priorities provide an overarching context within which all other efforts can be realized that are associated with prioritizing specific investments.

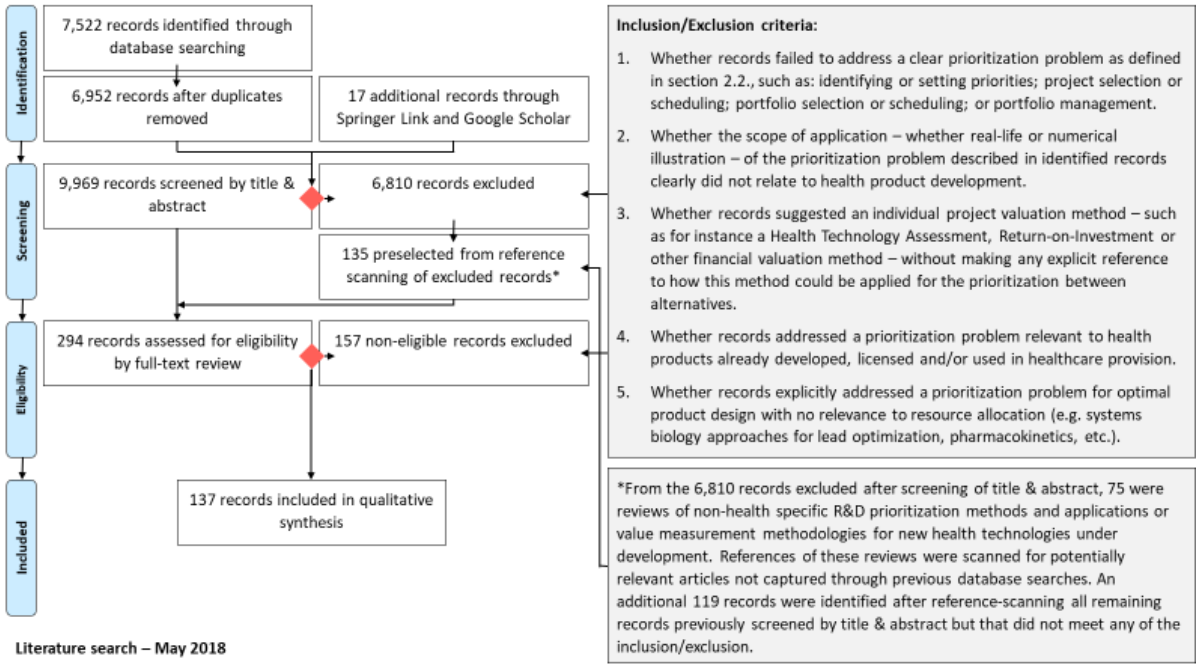
Specific investment decision frames distinguish those concerns relevant to specific prioritization problems from concerns relevant to all prioritization problems that may face the decision maker within the overarching strategic decision frame [49]. However, a key principle here is that anticipated outputs from specific prioritization problems must be clearly linked to the achievement of the decision maker's strategic objectives. This can be done by structuring the objectives for specific investment decisions around the achievement of previously defined strategic objectives.

2.3. Methods relevant to EID vaccine R&D prioritization

Considering the above definitions and distinctions, an attempt is made in this section to put relevant prioritization methods into perspective. The literature on research prioritization is large, yet a single framework for EID vaccine R&D prioritization is lacking and no targeted review of approaches for health product development has previously been provided. The purpose of this section is to give an overview of published methods for health product development prioritization, and to put these within context of the decisions and challenges laid out in sections 2.1 and 2.2. The focus here is on studies that identify priorities or offer insights into how investments can be prioritized in real-life settings or through numerical illustrations.

The literature assessed below arises from the mining of articles from various electronic databases (Pubmed, Embase, Web of Science, Scopus, ScienceDirect, Global Health (Ovid), Emerald Journals, Wiley Online), book chapters from SpringerLink and all types of publications from Google Scholar, using variants of the following search string: (health OR biomedical OR pharmaceutical OR biotechnology) AND ("research and development" OR "product development") AND ("priority setting" OR "project selection" OR "portfolio selection" OR "portfolio management" OR prioritization). Figure 2.3 summarizes this literature search process.

Figure 2.3. Summary of the literature search process.



Specifically, three sets of methods that emerge from this targeted literature search are explored for insights in how to prioritize EID development: Health Research Priority Setting (HRPS), Decision Analysis and Operations Research. Each of these poses different types of problem formulations and places a different emphasis on how analytical tools are employed *versus* on whether and how stakeholder engagement is handled. Whereas other bodies of literature are likely to offer further insights into criteria and valued goals as well as on stakeholder processes and analytic methods, these are assumed to be less meaningful in the context of this thesis, as they typically focus on different types of problems.

2.3.1. Health Research Priority Setting methods

Several attempts have been made to inform priorities about health product development over the past three decades. Often these studies are referred to as Health Research Priority Setting (HRPS) [57]. Whereas hundreds of HRPS studies have been conducted on a variety of health research topics as reviewed by several authors, e.g. [58-63], the number of HRPS studies dealing specifically with health product development priority setting is comparatively small (see Table 2.1. for an indicative list of studies). Some of these explicitly focus on vaccine development (e.g. see [28-44]), but most of them vary in scope, stakeholders, criteria and objectives.

Table 2.1. Examples of models for health product development priority setting.

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
Examples of normative & qualitative, procedural models						
[64]	Vaccine development priority setting / R&D candidates / Normative	Disease burden; Public perception of risks; Cost; Ability to integrate into vaccination programmes; Production bottlenecks; Intellectual property rights; Product liability	N/A	List of challenges / One-off	Qualitative synthesis of information	N/A
[65-69]	Product development priority setting for orphan, rare and other diseases / Diseases and R&D areas / Normative	Respect for autonomy; Non-maleficence; Beneficence; Justice or fairness Social responsibilities; Balance of public and expert input; Public-private cooperation	Industry; funders; subject-matter experts; institutional stakeholders; general public	List of challenges / One-off	Bioethics / Qualitative synthesis of information	- Workshop - Expert- and general public-focused deliberations
[70]	Antibiotic drug development priority setting / R&D areas / Normative	Immediate harm; Social value; Scientific unpredictability; Intergenerational justice; Higher bar for approval	N/A	List of challenges / One-off	Bioethics / Qualitative synthesis of information	N/A
[71,72]	Neglected Disease product development priority setting / Diseases / Real-life	Basic product characteristics of current tools (safety, effectiveness, affordability, ease of use); Geographical spread; Disease magnitude (based on incidence or prevalence); Disease severity (mortality, burden of disease/DALYs); New chemical entities marketed in last 25 years; Drugs under clinical development; Number of publications; Number of people working; Targeted initiatives	Subject-matter experts	List of recommendations / One-off	Qualitative synthesis of information	- Expert consultations
[73]	Diagnostic imaging technology and therapeutics device development priority setting / R&D areas / Real-life	Unmet need	Subject-matter experts	List of recommendations / One-off	- Qualitative synthesis of information	- Workshop
[74]	Vaccine development priority setting / R&D strategies / Real-life	Health outcome measures (e.g., incident cases or premature deaths averted or various health-adjusted life year options); Economic criteria (e.g., cost or efficiency measures); Deployment issues (e.g., cold chain requirement, dosages, fit with existing vaccine protocols); Other specialized interests (e.g., scientific feasibility, special sub-populations of interest, military personnel issues, foreign policy goals)	Subject-matter experts (National Vaccine Advisory Committee); federal agencies; domestic and international stakeholders; public representatives	List of recommendations / One-off	N/A	- Public meetings - Expert stakeholder meetings
[75]	Alzheimer's disease drug development priority setting / Treatment areas / Real-life	Unmet need	Policymakers, researchers, clinicians, advocacy and patient group experts	List of recommendations / One-off	- Qualitative synthesis of information	Conference calls over several months; Face-to-Face workshop
[76]	Medical product development priority setting / Thematic areas / Real-life	Tailor-made care; General improvement of therapy; Self-management; Early and correct diagnoses; Delay of the progression of the disease and/or recovery	Patients, patient representatives (informal carers) and non-patient representative experts (health professionals)	List of recommendations / One-off	Qualitative synthesis of information	Dialogue model: interviews and focus groups;

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
[77-81]	Malaria drug development priority setting / Thematic areas / Real-life	Importance to increasing productivity of drug discovery; Degree of unmet meet as perceived by stakeholders	Subject-matter experts	List of recommendations / One-off	Qualitative synthesis of information	- Workshops - Stakeholder decision forums
[82]	Respiratory syncytial virus (RSV) vaccine development priority setting / Thematic areas / Real-life	Unmet needs	Subject-matter experts	List of recommendations / One-off	Qualitative synthesis of information	- Expert Panel meeting - Working group discussions
[83]	Sexual and reproductive health Multi-purpose prevention technology priority setting / R&D candidates / Real-life	Target Product Profile parameters – Indications, Target Efficacy, Side Effects, Dosage Forms, Contraindications, Reversibility, Shelf Life, Storage Conditions. Cost of Goods; Cost of development to licensure; Time to regulatory licensure; Manufacturing and scalability; Intellectual property status; Product development organization; Product presentation/packaging; Potential for discreet use/concealability; Required level of provider support; Acceptability and adherence potential; Effects on lifestyle; Effects on sexual experience; Feasibility for delivery and access; Disposal requirements/waste material	Subject-matter experts	List of recommendations / One-off	Qualitative synthesis of information	- Document reviews - Expert consultations & Working Group proceedings - Workshop
[84]	Vaccine product development priority setting / R&D areas / Real-life	Unmet public health need; Likelihood of a product emerging from the pipeline and the extent of awareness, activity and investment in a given area; A clear role for WHO with perceived added value for engagement in the pathogen area.	Subject-matter experts	List of recommendations / Repeated	Qualitative synthesis of information	Expert Committee meeting
[85-86]	Health product development priority setting / R&D areas / Real-life	Potential for national competitive advantage	Subject-matter experts; representatives of business, government, and non-governmental sectors	List of recommendations / One-off	Foresight Analysis	- Document reviews - Expert panels - Delphi survey - Stakeholder consultations
Examples of scoring & multi-criteria models						
[87]	Medical device development priority setting / R&D candidates / Real-life	Development timeline; Strategic market penetration; Cost of goods sold; Product complexity; Next generation platform; Adequate resources available; Blockbuster product; Return on investment; Capital costs; Level of project risk	Subject-matter experts and decision makers (Internal)	Ranking / Repeated	- Scoring - Bartlett's and Levene's (F-Test) tests for equal variance, Analysis of means for variation across criteria	- Interviews - Surveys
[88-89]	Enteral nutrition and Probiotics product priority setting / Disease areas & Product characteristics / Real-life	Unmet need	Subject-matter experts; Patient representative experts	Clustered ranking / One-off	- Scoring (weighted) - Statistical tests for uncertainty	- Interviews - Surveys

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
[90]	Infectious disease product development priority setting / Disease areas / Real-life	Disease knowledge; Impact on animal health and welfare; Impact of public health; Impact of wider society; Impact on trade; Control tools	Subject-matter experts	Ranking / One-off	- Scoring (weighted)	Group discussions
[28-30]	Respiratory Syncytial Virus, Childhood pneumonia, meningitis and influenza product development priority setting / Vaccines, immunoprophylactics and immunotherapeutics / Real-life	Answerability; Cost of development; Cost of product; Cost of implementation; Efficacy and effectiveness; Deliverability; Affordability; Sustainability; Maximum potential impact on disease burden reduction; Acceptability to health workers; Acceptability to end users; Equity	Subject-matter experts	Ranking / One-off	- CHNRI methodology	- Document reviews - Expert Panel meeting
[91]	Infectious disease product development priority setting / Diseases / One-off	Disease risk index	Subject-matter experts; government / military stakeholders	Ranking / One-off	- Scoring (weighted) using AHP	- Expert consultations - Discussion panels
[92]	Medical product development priority setting / Technology areas; Development strategies within each technology area; Resource alternatives within each development strategy / One-off	Alternatives are the criteria	Subject-matter experts; Policy makers from government; Technology management experts from the health industries; Sectoral representatives	Ranking / One-off	- Scoring (weighted) using AHP - Inter-expert variability analysis (statistical) and algorithmic sensitivity analysis for uncertainty	Expert Panel meeting
[93]	EID product development priority setting / Diseases / One-off	Human transmission; Medical countermeasures; Severity of case fatality rate; Human-animal interface; Other disease factors; Public health context of affected area; Potential societal impacts; Evolutionary potential of pathogen	Subject-matter experts	Ranking / One-off	- Scoring (weighted) using AHP	- Delphi - Expert consultations - Moderated discussions
[94]	Maternal health product development priority setting / R&D candidates / One-off	Gap filling potential for health; Technology performance; Enabling factors (e.g. alignment with international guidelines, existing support and capabilities); Market considerations (e.g. time-to-market, investment needed); Considerations for introduction and scaling of technology	Subject-matter experts	Ranking / One-off	- Scoring (weighted) using MCDA - Maternal and Neonatal Directed Assessment of Technology model developed by assessing potential number of lives saved for each technology	- Expert consultations - Online survey
[31-40]	Vaccine development priority setting / Diseases and R&D candidates / Real-life and illustrative	29 in-built attributes, including: Health outcome measures (e.g., incident cases or premature deaths averted or various health-adjusted life year options); Economic criteria (e.g., cost-effectiveness or savings and efficiency measures); Deployment issues (e.g., cold chain requirement, dosages, fit with existing vaccine protocols); Other specialized interests (e.g., feasibility, risk of pandemic potential,	Subject-matter experts; Funders; Multiple sector stakeholders; Public representatives	Rankings and Lists of recommendations / One-off and Repeated	- Scoring (weighted) (SMART vaccines method) - Scenario-based analyses for uncertainty	- Public meetings - Expert and broader stakeholder meetings - Various stakeholder consultations

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
		workforce productivity gains, special sub-populations of interest, military personnel issues, foreign policy goals).			- Interpolation/ extrapolation techniques supported by sensitivity analysis on data effects to scores	
[95]	Vaccine product development priority setting / Disease areas & R&D candidates / Real-life	Severity of the disease target; Cost-effectiveness; High mortality; Incidence disease cases prevented per year; Fits immunizations schedule; Lack of availability of alternative public health measures; Serious pandemic potential; Targets a disease occurring primarily among infants and children; Likelihood of successful licensure in 10 years; QALYs gained or DALYs averted; Net workforce productivity gained; Target a disease occurring primarily among the socioeconomically disadvantaged; Interests of NGO and philanthropic organizations; Potential for eradication or elimination of the disease; Net direct savings of the vaccine use; Target a disease occurring primarily among the elderly; Interest for national security preparedness and response; Vaccines raises public awareness; One-time costs; Demonstrates new production platform	Subject-matter experts	Rankings and Lists of recommendations / One-off and Repeated	- Scoring (weighted) (SMART vaccines method)	Expert Panel Meeting
[96]	Vaccine product development priority setting / Disease areas & R&D candidates / Real-life	Cost-effectiveness (including cost-benefit and cost-utility analysis); Incidence disease cases prevented per year, particularly those with high severity of target disease (risk of morbidity and mortality); Serious pandemic potential with a high interest for national security, preparedness, and response; Lack of availability of alternative public health measures	Subject-matter experts	Rankings and Lists of recommendations / One-off and Repeated	- Scoring (weighted) (SMART vaccines method)	Expert Panel Meeting
Examples of health-economic and other evidence-based models						
[41-43]	Vaccine development priority setting / Diseases and R&D candidates / Real-life	Quantified and included in core model: Expected health benefits (reduction of morbidity and mortality); Expected net savings of health resources. Non-quantified and excluded from core model: Goals of agency and schedule for their achievement; Equity in distribution of benefits; Opportunity and need for agency to exert influence on development; Balance of projects; Potential for restoration of public confidence in immunization.	Subject-matter experts; government representative experts	Ranking / One-off	- Cost-Effectiveness Analysis - Rule-based techniques for problem structuring - Equivalence preference measurement techniques and Health Utilities Indices for estimation of health benefit preferences - Scenario-based sensitivity analyses for uncertainty	- Document reviews - Expert consultations - Surveys - Consensus decision forums
[97]	Osteoporosis and pressure ulcers product development priority	Expected net benefit; cost-effectiveness	N/A	Ranking / One-off	- Payback analysis	N/A

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
	setting / Diseases and clinical trial alternatives / Illustrative				- Value of Information analysis - Probabilistic sensitivity analysis and cost-effectiveness acceptability curves for uncertainty	
[98,99]	Disease product development priority setting / Disease areas / Real-life	Estimated European and global burdens of disease; Common risk factors amenable to pharmacological intervention that have an impact on many high-burden diseases; Prediction of disease burden trends, based on epidemiological and demographic changes in Europe and the world; Principle of "social solidarity" applied to diseases for which there are currently no market incentives to develop treatments	Subject-matter experts; industry and government representative experts	List of recommendations / One-off	Burden of Disease Analysis & consensus judgement on other clinical and ethical considerations	- Document reviews - Multiple types of consultations
[100]	TB drug regimen priority setting / product regiments / One-off	Primary: Reduce mortality over defined time horizon Secondary: Reduction in incidence; Reduction in total number of patient-months on treatment; Reduction in mortality in other epidemiologic settings; Reduction in mortality when regimen improvements enhanced or limited scaleup of the novel regimen	Subject-matter experts	Ranking / One-off	- Epidemiological modelling - Scenario-based sensitivity analysis for uncertainty	- Expert consultations
[44]	Measles vaccine development priority setting / R&D candidates / One-off	Incremental cost per DALY averted	Subject-matter experts	Ranking / One-off	- Cost-Effectiveness Analysis through epidemiological modelling and microcosting analysis - Scenario-based sensitivity analysis for uncertainty	- Literature review - Stakeholder consultations

A common goal of HRPS studies is to gain consensus about areas where increased research effort – including collaboration, coordination and investment – will have wide benefits to society [62]. Given HRPS approaches are predominantly practice-oriented, a unifying theory underlying them is lacking. These models generally draw from multiple theories including stakeholder theories (e.g. see [101]), theories of justice (e.g. see [102,103]), and utility theories for decision making (see section 2.3.2.).

As illustrated in Table 2.1., HRPS studies use a variety of stakeholder engagement tools and for the most part they focus on the procedural aspects of priority setting, which are generally ignored by more sophisticated analytical models (see section 2.3.2.). HRPS studies typically assume that much of the value from priority setting models derives from the process of using them rather than from their analytical outputs [104]. Consequently, equal or more emphasis is typically placed on processes of stakeholder engagement than on the theoretical justifications over the use of tools for quantifying and analytically comparing alternatives.

Defining characteristics

(1) Emphasizing process and principles of stakeholder engagement

HRPS studies treat priority setting as a complex and interactive process of engagement and coordination between multiple stakeholders. In doing so, these studies tell us that issues such as who should inform the priorities, how or when opinions should be incorporated and how priorities should be set in relation to social goals and needs, must play a central role. As highlighted by several HRPS studies in different ways, priority setting should be driven by explicit principles around the types and rationale for inclusion of different stakeholder perspectives. For instance, the participation of different types of stakeholders in the priority setting process is frequently highlighted as a requirement for consensus building and partnership orientation towards strategy and agenda setting against commonly accepted challenges (e.g. see [65-76, 85-86, 88-89, 98-99]).

Stakeholders typically concern technical subject-matter experts, as well as representatives of different sectors carrying funding, policy making, or R&D implementation authority. Through a variety of consultation tools, such as exploratory interviews, workshops and surveys, expert panel meetings, working groups and conferencing tools (see Table 2.1. for details), stakeholders are involved in several distinct steps, including: (1) identifying priority alternatives; (2) identifying criteria to assess alternatives; (3) providing opinions or assessments of alternatives; and (4) deriving priority recommendations. Some approaches suggest the additional use of expert advisory committee or project governance structures to ensure oversight or control of this stepwise deliberation process (e.g. see [41-43, 74, 77, 80, 84, 90]), which is also highlighted as good practice in recent HRPS reviews [62, 104].

The needs of additional special stakeholder groups, such as patients or end users, are also increasingly highlighted as an essential success factor in health product development priority setting, demonstrating how patient or user views can improve acceptability and societal relevance of priority setting outcomes [76, 88, 89].

Arguments for the participation of different stakeholder groups into the priority setting process have been made on the basis of ethical concerns. [65] and [66] highlight the importance of public input for improving the accountability of priority setting. [68] questions the justifiability of prioritizing product development for populations affected by rare diseases

against principles of fairness or equitability, societal relevance or need. [67] outline moral dilemmas arising from the prioritization of resources for product development against different types of diseases, revolving around rights and obligations to benefit populations *versus* advancing medical science. And [69] explore the relationship between priority setting and what values and procedural considerations should underpin global health research priority setting as a matter of justice.

(2) Acknowledging multiple criteria

HRPS studies typically express priority alternatives in terms of multiple criteria [57]. Consequently, these models are increasingly making use of Multi-Criteria Decision Analysis (MCDA) frameworks (see section 2.3.2 for a formal introduction). For instance, [31-40] have proposed a prioritization framework called SMART Vaccines to analytically support the ranking of vaccine R&D priorities, explicitly taking stakeholder preferences into account for eliciting priority trade-offs. Several other multi-criteria scoring frameworks have also been proposed for identifying priorities in different health product development domains (e.g. see [28-30, 87-94] in Table 2.1.). In doing so, these studies highlight four analytical steps, in addition to the stakeholder engagement steps previously discussed: (1) ensuring that the identified list of criteria is appropriately structured, complete and measurable; (2) defining a range of performance levels for each criterion; (3) eliciting stakeholder preferences to determine weights of relative importance between criteria; and (4) aggregating to generate an overall worth for each priority alternative in order to justify some sort of ranking.

Evidence-based or data driven models are also used to inform health product development priority setting without any explicit acknowledgement of multiple criteria trade-offs. [100] reports an epidemiology model for prioritizing TB drug regimens with different characteristics. [98-99] report a Burden of Disease Analysis for establishing new medicine priority lists. [44] demonstrate the feasibility of prospective cost-effectiveness modelling—combining infectious disease dynamic modelling with economic modelling— for informing decisions about vaccine innovation R&D. The US Institute of Medicine has published a series of reports on vaccine development priorities where variants of cost-effectiveness analysis play a central role [41-43]. As frequently argued by others [48, 55, 105, 106], health-economic modelling or any other method conforming to the principles of evidence-based medicine is generally good practice for measuring performance of decision alternatives in health, assuming data is available to support this. However, as insightful as such analyses may be, they say little on their own about whether the outcomes of their analyses are relevant, and to what degree, to stakeholders responsible for implementing their recommendations. To this purpose, some of the evidence-based HRPS approaches (e.g. [43, 98, 99]) report additional consensus judgement steps to their analyses for priorities to be determined. Others (e.g. [100]) simply acknowledge that real-world choices are seldom made based on evidence alone and without the consideration of preferences of those accountable for decision making.

(3) Identifying one-off priorities

Resulting priorities from HRPS studies often take the form of descriptive lists of recommendations or score-based rankings of alternatives (for details, see Table 2.1.). These recommendations are often one-off outputs targeted towards informing strategy or policy development and planning within a specific disease or product area, or across different thematic R&D areas. Outputs are mainly prescriptive in nature, in that the values they reflect

assume wider societal (or at least broader stakeholder) concerns. Despite being heavily practice-oriented, HRPS studies generally do not report whether or how the generated priorities had an impact on policy or practice [62, 97]. Without any apparent link to how recommendations have been followed up by specific actions (e.g. investment decisions or policy making initiatives) it is difficult to assess the practical validity of these models, in particular as they may relate to goals of those accountable for allocating resources.

2.3.2. Decision Analysis and Operations Research methods

Whereas HRPS methods place a strong emphasis on *procedural* aspects of stakeholder engagement to identify collective priorities for policy development and planning, there has been an interest in *analytical* methods to support investment decisions with relevance to health product development since the 1950s and 1960s [107-110]. Two main streams of research in this field derive from decision analysis and from operations research. Both place an emphasis on the development of models for the selection and management of R&D projects or R&D portfolios predominantly at the individual organization level. Although there is a substantial overlap between the two streams in terms of analysis techniques for valuing alternatives or dealing with uncertainty, each places a different emphasis on how and what types of prioritization outputs are derived.

2.3.2.1. Decision Analysis

Various decision analysis models have been used to support project selection, portfolio selection, and increasingly also priority setting in health product development. These methods vary in scope and offer a mix of illustrative and real-life applications (for details, see Table 2.2. for project selection and portfolio selection methods; Table 2.1. for priority setting methods).

Table 2.2. Examples of decision analytic models for health product development prioritization.

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
Examples of statistical decision rule & decision-tree models						
[111,112]	R&D project selection / Drug candidates / Illustrative	Profitability Index (Pearson)	N/A	Ranking / Repeated	- Statistical decision rules	N/A
[113]	R&D portfolio selection / Drug candidates / Illustrative	Probability-Cost-Profitability Index (stochastic Pearson index)	N/A	Optimal portfolio / Repeated	- Statistical decision rules	N/A
[114-117]	R&D project and portfolio selection (sequential) / Drug candidates / Illustrative	Profitability Index (Gittins)	N/A	Sequencing / Repeated	- Statistical decision rules	N/A
[118]	R&D project selection / Drug candidates / Illustrative	eNPV-to-Cost ratio (Pearson); max discounted eNPV per unit of discounted time (Gittins)	N/A	Ranking and Sequencing / Repeated	- Statistical decision rules - Recalculation of statistical indices at each decision point for uncertainty, as new information generated	N/A
[119-120]	R&D portfolio selection / Drug candidates / Real-life	Risk-adjusted rate of return	Individual company members of staff	Optimal portfolio / Repeated	- Statistical decision rules - Monte Carlo simulation - Mean-Variance and Mean-Gini analyses for uncertainty	- Online questionnaire - Stakeholder deliberations
[121]	R&D portfolio selection / Drug candidates / Real-life	Return on Investment (NPV-to-cost)	Individual company members of staff	Ranking / Repeated	- Decision tree analysis - Scenario-based sensitivity analysis for uncertainty	- Stepwise / multiple stakeholder meetings
[45]	R&D portfolio selection / Vaccine and drug candidates / Illustrative	Cost-to-PoS ratio	N/A	Optimal portfolio / Repeated	- Decision tree analysis - Scenario-based sensitivity analysis for uncertainty	N/A
[122]	R&D portfolio selection / Drug candidates / Illustrative	Expected NPV	Individual company members of staff	Optimal portfolio / Repeated	- Decision tree analysis - Monte Carlo simulation - Risk tolerance scenarios for uncertainty	- Expert panel assessments - Profiling decision makers using investment games, exercises, or by observing past decision behaviours

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
[123]	R&D projection selection / Central Nervous System disease drug candidates / Real-life	Real Options Value	Individual company members of staff	Ranking / repeated	- Real Options Analysis using decision trees - Simulation-based sensitivity analysis for uncertainty	- Interactive discussions
Examples of multi-criteria models						
[124,125]	R&D project selection / Oncology drug candidates / Real-life	Scientific data (PoS, Chemistry, Biology); Fit with available resources (work burden, commitment duration); compatibility with strategy and portfolio; Financial and business strategic fit (sales, licensing rights, market exclusivity	Individual company members of staff	Clustering / One-off	- AHP	- Expert consultations and meetings
[126]	R&D projection selection / Drug candidates / Real-life	Therapeutic need; Competitive position; Technical feasibility (Biological, Chemical, Clinical); General support; Product champion; Ancillary uses; Competences of existing staff; Research investment	Individual company members of staff	Ranking / One-off	- AHP - Bias ratings and re-scoring for uncertainty	- Expert consultations and meetings
[127-128]	R&D portfolio selection / Cardiovascular disease drug candidates / Real-life	Project level: Technical feasibility (time, risk); Product champion; Staff competence; Competitive position; Research investment; General support; Therapeutic need; Ancillary uses. Portfolio level: Balancing factors (probability-time curves)	Individual company members of staff	Optimal portfolio / Repeated	- AHP	- Group discussions - Expert consultations - Decision conferencing
[129]	R&D project selection / Device technology areas / Real-life	Marketability; Technology applicability; Public benefits	Subject-matter experts	Ranking / One-off	- AHP	- Stakeholder consultations - Workshop - Evaluation committee deliberations
[130]	R&D project selection / Medical devices / Real-life	Multiple regulatory compliance criteria; Time to market; Multiple economic and business performance criteria	Subject-matter experts	Ranking / One-off	- Multicriteria Hierarchical Model (AHP)	- Interviews - Consultations
[107]	R&D project and portfolio selection / Drug candidates / Illustrative	Project level: Market potential; Technical feasibility; Competition in research; policy restrictions and resource constraints. Portfolio level: diversification based on risk	N/A	Optimal portfolio / Repeated	- Expected Rate of Return Analysis (partial MCDA)	N/A
[131]	R&D portfolio selection / Drug research areas and candidates / Illustrative	Portfolio aggregate: Composite risk-adjusted rate of return Research areas: Innovativeness of products out of such an area: Expected sales within the target market; Resources required; Scientific risk; Environmental risk / acceptance; Time to registration of the first product out of the area. Candidates: Innovativeness of that particular compound; Expected sales and profit for a product with the given properties; Chances of the compound to pass all the	Individual company members of staff	Optimal portfolio / Repeated	- Goal Programming	- Expert Panel assessments

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
		hurdles to reach the market; Time to register for that compound; Interest of the marketing people; Technical problems; Scientific judgement. Portfolio level: Risk-adjusted sales; Capacity constraints; Balancing factors (New chemical structure > me too; Patentable >non-patentable).				
[54]	R&D portfolio selection / Health product development candidates / Real-life	NPV (financial value); Medical Need (extent to which the project will meet unmet medical need); Business Impact (protecting the existing business); Future Value (contribution to evolution to a specialty pharmaceutical company); Probability of Success (probability that the benefits will be realized)	Individual company members of staff	Optimal portfolio / Repeated	- Benefit-Cost Analysis (MCDA) Scenario-based sensitivity analysis for uncertainty	- Decision conferencing
[132]	R&D portfolio selection / Robotic innovations for minimal invasive surgery / Real-life	Project level: QALY gains for patients; Economic benefits to healthcare; Fit with company expertise and resources; Market size; Market competitiveness Portfolio level: Budget constraints; Project synergies in benefits, risks and costs	Individual company members of staff	Optimal portfolio / One-off	- Benefit-Cost Analysis using MACBETH model (MCDA)	- Expert consultations
[133,134]	R&D portfolio selection / Oncology and other drug candidates / Illustrative and Real-life	Project level: Medical need, Novelty, Reward / Commercial success, Strategic fit, Market presence / Access, Speed of development Portfolio level: R&D phase balance	Individual company members of staff	Optimal portfolio / Repeated	- Multi-objective decision analysis (Value Focused Thinking, Decision Trees) - Simulation scenario-based sensitivity analysis for uncertainty	- Expert consultations - Decision conferencing
[135]	R&D project selection / Type 2 Diabetes Mellitus Biomarker Technology candidates / Real-life	Commercial headroom (Reduction in downstream healthcare costs, Added quality-adjusted survival, Cost of intervention); Barriers to realize potential (Feasibility of treat-all-option, Performance of competitors, Ease of implementation)	Research institute members of staff	Ranking / One-off	- Scoring matrix (Health-economic modelling and MCDA) - Rank acceptability matrix and simulation-based sensitivity analysis for uncertainty	- Brainstorm sessions - Group discussions
Examples of other health-economic & practitioner-based decision-analytic models						
[136]	R&D project selection / Health product development candidates / Illustrative	Expected Net Benefit of Research	N/A	Ranking / Repeated	- Value of Information Analysis - Confidence indices for uncertainty	N/A
[137]	R&D project selection / Cancer drug clinical trial designs / Real-life	Expected treatment effect; Incremental QALYs; Incremental healthcare costs	Subject-matter experts	Ranking / One-off	- Value of Information Analysis using Monte Carlo simulation	- Stakeholder consultations

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
					- Simulation-based sensitivity analysis for uncertainty	- Expert Committee meetings
[138]	R&D project selection / Drug candidates / Illustrative	Anticipated clinical profile of new drug (efficacy and effectiveness scenarios); Anticipated health outcomes QALYs using e.g. SF-36 or EuroQol; Cost (medical mostly)	Subject-matter experts	Binary choice / Repeated	- Cost-Effectiveness Analysis - Simple sensitivity analysis (one-way, two-way, three-way), threshold analysis, analysis of extremes and probabilistic sensitivity analysis for uncertainty	- Stakeholder consultations - Surveys
[139]	R&D project selection / Regenerative medicine technologies / Illustrative	incremental cost-effectiveness ratio (incremental cost-to-incremental benefits (QALYs))	N/A	Binary choice / Repeated	- Headroom analysis	N/A
[140]	R&D project selection / Pharmacogenomic testing technologies / Illustrative	Medical and/or service outcomes; Cost of care	N/A	Binary choice or ranking or clustering / Repeated	- Various cost-effectiveness and decision analysis models	N/A
[141]	R&D portfolio selection / Health product development / Illustrative	DALYs averted-to-Profitability Index matrix	N/A	Optimal portfolio / One-off	- Social and Business Return on Investment Analysis (Health Economic modelling)	N/A
[142,143]	R&D project selection / Drug clinical trial designs / Illustrative and real-life	Likelihood drug effect within statistically significant range; Time savings; Cost savings	Subject-matter experts	Optimal trial design / One-off	- Clinical trial simulation - Probabilistic Sensitivity Analysis for uncertainty	- Stakeholder consultations
[144]	R&D portfolio selection / Drug candidates / Illustrative	Project level: Potential value (commercial benefit; medical benefit to customers, physicians and patients); Cost; Development timeline; PoS; Strategic fit; Organizational ability, capability, expertise, and resources. Portfolio level: Balance (between long term and short term strategic business needs; low/high risk; long/short time to fruition; low/high payoffs; territory-specific vs. global strategic business needs); Diversity (between: therapeutic areas; disease states; platforms; early vs. late stage projects).	N/A	Balanced portfolio / Repeated	- Qualitative clustering - eNPV analysis - statistical decision rules / profitability indices - Multi-criteria decision analysis - Scenario-based sensitivity analysis for uncertainty	N/A
[145]	R&D portfolio selection / Drug candidates / Illustrative	eNPV; 'fitness' to risk score	Individual company members of staff	Optimal portfolio / Repeated	- preference adjusted eNPV	N/A

Reference	Problem context / Alternatives / Application Type	Criteria	Stakeholders	Objective / Anticipated output	Analytical tools	Procedural tools
					analysis (Portfolio Decision Analysis)	
[146]	R&D project and portfolio selection / Drug discovery candidates / Real-life	Project level: Feasibility (PoS); Maturity; Product characteristics; Product potential; Project risk (relation of maturity to feasibility) Portfolio level: Balance; Portfolio potential	Individual company members of staff	Ranking and clustering / Repeated	- risk-adjusted scoring (Criteria based scoring model (3D analysis); Expert black box scoring model) - Risk analysis for uncertainty	- Expert panel assessments and meetings - Surveys
[147]	R&D portfolio selection / Molecular amplification diagnostic technologies / Real-life	Excess equilibrium relative return (%)	Individual company members of staff	Ranking / One-off	- Black-Litterman model	- Consensus consultations

A common goal of decision analysis methods is to provide insight into the value of decision alternatives, based on which rational resource allocation choices can be made. Decision analysis typically assumes rational, utility-maximizing agents that want to make optimal and coherent choices [148-150]. Traditional utility theory [151-152] and multi-attribute utility theory [153] postulate axioms that describe such choices, including completeness, transitivity, continuity and independence (see [154] for detailed definitions). Drawing from such theories, decision models adopt a much more stringent, normative perspective in comparison to HRPS approaches, although many practitioners utilize them in a constructive spirit [149].

To serve its purpose, decision analysis conventionally distinguishes between probabilities and consequences (or outcomes) of alternatives. These are then combined in a structured way, e.g. through statistical decision rules [111-120] or through decision tree models (see for instance [45, 121-123]) to derive an estimate of expected value for each alternative considered.

Where there is more than one valued consequence in the prioritization problem, an extension of conventional decision analysis can be used, briefly introduced in section 2.3.1. as MCDA and formally introduced in [153]. In addition to allowing for the combination of the expected values for each consequence into a composite measure of overall expected value, MCDA further distinguishes between expected levels of achievement of the different consequences and preference trade-offs between these (typically referred to as weights) (e.g. see [54, 124-135]). However, probabilities in MCDA models are often treated as separate criteria in practice. This is the case for instance in partial MCDA models [155], where the aggregation of information on criteria is not required into a single expression of value (e.g. in qualitative models to support deliberative processes as commonly observed in HRPS studies). This is also typically the case in simplified multi-attribute rating (SMART) methodologies [156], which are increasingly adopted by HRPS studies [28-40], where the structuring of the criteria (e.g. distinguishing between probabilities and consequences) and the incorporation of weights (e.g. by simplified rank ordering techniques) are somewhat more arbitrary.

Defining characteristics

(1) Accommodating criteria relevant to decision maker needs

Similarly to HRPS studies, decision models typically assume that the criteria employed for the comparison of alternatives should reflect essential stakeholder concerns. However, decision models implicitly or explicitly place limits on who the relevant stakeholders should be, distinguishing between stakeholders that provide inputs for the valuation of alternatives, including preferences, and stakeholders that are responsible for making decisions. Consequently, the focus in these models is mainly on criteria that reflect specific decision needs, with less emphasis given on wider societal concerns of stakeholder groups that are either not directly held accountable or without the necessary subject-matter expertise.

In commercial settings, the consequences of each alternative within conventional decision analysis models are typically measured in economic terms, such as net present value (NPV) [121], augmented NPV, or Real Options Value [123]. NPV-to-risk ratios [121], or NPV-to-cost or equivalent risk-adjusted profitability indices [114-120] are typically employed as overall metrics for the selection of alternatives, although deciding on which one of these to

use will often depend on the nature of the project selection problem in hand (e.g. one of parallel *versus* sequential selection over time [118]. In non-commercial settings, other prioritization criteria have also been proposed, such as Value of Information [136,137], cost-effectiveness [138-140], and other pharmacoeconomic metrics [142-144]. Where multiple criteria are explicitly considered, consequences typically include a combination of economic and non-economic criteria [54, 124-135], depending on the commercial or non-commercial nature of the decision maker's concerns. Table 2.2. provides examples of the types of criteria decision models applied in different types of health product development prioritization contexts.

By assuming relevance of single criteria of economic or other expected value, conventional decision models expend their efforts on illustrating how the computational methods work, ignoring the question of whether such criteria are sufficient to support resource allocation decisions. This is in contrast with MCDA models, which generally treat the identification of relevant criteria as a critical first step of structuring prioritization problems. This is an approach familiar to HRPS studies, with literature reviews and stakeholder consultation tools generally employed to map all relevant criteria. However, MCDA models are generally more stringent in their application of rules, based on which criteria can be constructed. Such rules can include for instance checks on completeness, non-redundancy, non-overlap, and preference independence between the criteria [149]. These are examples of rationality axioms stemming directly from decision theoretical foundations underlying decision models [154]. Practically, the application of such rules suggests that long lists of potential criteria can be logically reduced into smaller lists of criteria at the end of the identification process, facilitating more meaningful choice trade-offs to be made [106].

(2) Structuring criteria in analytically meaningful ways

Once relevant criteria have been appropriately identified, decision models can contribute to structuring these in analytically meaningful ways, because of rules they typically impose, such as distinguishing between sources of value (consequences) and sources of risk (probabilities). In single criterion models, where statistical decision rules or conventional decision trees are applied, a prominent and specific role is typically placed in measures of project feasibility or PoS, cost, and time-to-completion, treated as adjustment factors to expectations of economic or non-economic returns. This enables decision makers to transparently capture the uncertainties and risks as well as the incremental rate of return from investments in health product development [121].

In MCDA models an extension of the decision tree logic applies, whereby value trees [153] or analytical hierarchies [157] are used to cluster consequences into higher-level and/or lower-level criteria. This can be achieved with the help of a variety of problem structuring techniques, either top-down – e.g. Value Focused Thinking [49] to distinguish between ends (higher-level) and means (lower-level) criteria – or bottom up – e.g. Alternatives Focused Thinking [158] to distinguish criteria that characterize (already established) alternatives, then grouping these into higher-level criteria. Similar rules and techniques can also be applied in partial MCDA models, where the aggregation of information on criteria into a single source of value is otherwise not demanded [155].

The employment of such problem structuring rules allows decision models to make the characteristics of prioritization problems salient [123]. In doing so, decision models can help

decision makers think through carefully and understand the fundamental drivers of value, based on which decision trade-offs would need to be made. However, most applications of decision models in health product development prioritization focus on projects as their unit of analysis and therefore rarely deal explicitly with issues of interdependencies in risk or value between alternatives. For instance, decision models set up to support portfolio selection problems have recognized the importance of balancing aspects on portfolio value, such as diversity between technologies, risk or value profiles of projects (e.g. see [127, 128, 131, 135]). However, with the exception of a handful of studies (e.g. see [54, 107, 132, 145]), such interaction effects are not typically included explicitly in these models, resulting in analytically incomplete solutions.

(3) Distinguishing between measures of factual *versus* preference information

To populate their models, decision analysis approaches typically distinguish between factual information to measure performance of alternatives against single or multiple criteria of concern, and preference information to make the value judgements of decision makers explicit. In doing so, decision models have long highlighted that analyses which ignore or suppress preference data tend to miss what is really important when making decisions [126]. This argument is especially pertinent when it is unclear whether some alternatives outperform others on the basis of factual information alone and where resources might be limited to select all [135]. In such situations, a distinction between performance measurement and preference modelling can assist in formalizing the relationship between evidence on performance and decision makers' preference structures [106, 155]. This way decision makers can systematically investigate their own preferences and compare them transparently with the factual information in hand.

Performance measurement

Decision models can typically combine different types of performance measures, whether these refer to quantitative or qualitative scales. The scale required for measuring the performance of an alternative against a given criterion will depend on how the criterion is defined, what data is available and how the decision maker intends to use it. For instance, economic valuation techniques are most common where economic criteria are being considered and forecasts of anticipated revenues can realistically be made. However, the relevance of such performance measures is limited in non-commercial settings such as EID vaccine development.

Health economic measures, such as cost-effectiveness, Value of Information and other pharmacoeconomic indices may also be relevant where health outcomes under resource constraints are explicitly considered. Evidence suggests that the estimation of health economic outcomes is becoming more and more desirable in health technology assessments in general [48, 55, 138, 159], largely relying on modelling assumptions for new technologies in earlier phases of development (e.g. see [138]). Such measures typically require strict assumptions about how new product candidates would perform in specific clinical settings and simpler expert-based scoring alternatives have been proposed to reflect the uncertainties and lack of data at early phases of health product development [135]. Use of health economic measures will also depend on decision maker capacities and preferences for their implementation. For instance, they may be more applicable in settings where their predicted

outcomes, despite their uncertainties, are considered meaningful enough to inform repeated decisions along the lifecycle of product development.

Preference measurement

When it comes to preference information, common ways to express this is through single- or multi- criteria utility indices and rules that account for stakeholder values in assessments of performance of alternatives against criteria. These can typically be referred to as *within*- and *between*- criteria weights. Within-criterion weights can be viewed as performance adjustment factors that capture the strength of preferences for different levels of performance on a single criterion. In models where criteria performances are measured in different scales, these weights allow for performance estimates against each criterion to be translated into a common scale of relative desirability. Between-criteria weights can be viewed as additional adjustment factors to the relative desirability of alternatives, capturing the relative importance between criteria along a common scale of value. Rules can also be applied to reflect preferences about minimum or maximum levels of performance of alternatives, in the form of thresholds or constraints, or to capture preferences about the sequence in which investment in different alternatives can be realized. Table 2.3. summarizes examples of methods that have previously been used to elicit weights in the health product development prioritization literature.

Table 2.3. Examples of weighting techniques to incorporate preferences into health product prioritization models.

Weighting method	Within-criterion elicitation task	Between-criteria elicitation task	Elicitation tools	References
Examples from health-economic models				
Time trade-off method	Alternatives are compared pairwise to identify the point of indifference of duration between health states.	N/A	- Questionnaires	[139]
Preference equivalence measurement technique	State how many units in each morbidity category would be considered to carry the same disutility as one death	State how many units in each morbidity category would be considered to carry the same disutility as one death	- Questionnaire	[41, 42]
Multi-attribute utility indices (e.g. SF-36, EuroQol, Health utilities index)	State preference for different levels of health states relative to full health or death	State preference for different levels of health states relative to full health or death	- Surveys	[43, 138]
Examples from multi-criteria models				
Point allocation	Points are allocated to alternatives in proportion to their relative importance on a criterion	Allocation of points between criteria in proportion to their relative importance	- Online surveys - Expert panels / moderated group discussions	[88-90, 92, 94]
Analytic Hierarchy Process (AHP)	- Assess alternatives on each criterion and their "intensity of importance" relative to each other on a pre-defined ratio scale.	- Pairwise comparisons of the "intensity of importance" between criteria on a pre-defined ratio scale	- Decision conferencing & workshops / moderated discussion panels - 'Do-It-Yourself' (DIY) scoresheet templates	[91, 93, 124-130]
Rank order centroid weights / scales	Importance of alternatives on each criterion is considered on a scale (slide bars)	Rank order of criteria	- Use of software tool (SMART vaccines)	[32-40]
Swing weighting	Determine relative importance of changes in performance within a criterion through pairwise comparisons of alternatives	Determine relative importance of changes in performance between criteria through pairwise comparisons of alternatives	- Decision conferencing	[54, 128]
Stochastic multicriteria acceptability analysis	Linear re-scaling of performance measurements to 0-1 interval (normalization)	Pairwise winning indices	- Scenario assumptions based on group discussions	[135]

Weighting method	Within-criterion elicitation task	Between-criteria elicitation task	Elicitation tools	References
Rule-based	N/A	Eliminate criterion if not preferentially independent / overlapping with others	- Scoring questionnaire - Expert panel meeting	[28-30]
Examples from other decision-analytic and operations research models				
Fuzzy constraint satisfaction degree	Determine grade of possibility that constraint value will be realized in a given range of constraint values	N/A	Unspecified / Illustrative	[160]
Sequence priority indices (e.g. Reward/Risk priority rules)	Index that quantifies the perception the decision makers have about the relative importance of projects due to their possible interactions. E.g. use reward/risk ratios of projects to prioritize activities in non-increasing order, to resolve resource conflicts in the list schedule scheme. In TOPSIS, the selected alternative should have the shortest distance from the negative ideal solution in geometrical sense.	N/A	Unspecified / Illustrative	[131, 161-164]
Black-Litterman model	Specify risk-aversion coefficient based on an intuitive confidence scale	N/A	- Consensus consultations	[147]
Threshold ratio	Determine the minimum acceptable expected reward-to-expected cost ratio	N/A	Unspecified / Illustrative	[118]
Certainty equivalence / Risk tolerance	Utility function is adjusted by risk tolerance factor, specified for instance through profiling decision makers using investment games, exercises, or by observing past decision behaviours		- Expert judgement through interactive discussion - Retrospective analysis of past decisions	[122, 123]

(4) Identifying sources and demonstrating impact of uncertainty

Decision analysis models have dealt with uncertainty in health product development prioritization problems in variable ways (see Table 2.2.). Typically, these models associate uncertainty with notions of project risk and PoS. (e.g. see [41-43, 91, 111-114, 116, 118, 145]). Some models treat risk as a distinct criterion within multi-criteria measures of value (e.g. see [32-40, 54, 124-128, 131, 135]). Other models make an explicit distinction between PoS and risk as an additional measure of variance around the expected values of alternatives considered (e.g. see [107, 123, 136, 143]).

A significant number of decision analysis approaches to health product development prioritization have attempted to capture the impact of *imprecise or incomplete model information* on the variability of analytical outcomes through: data interpolation/ extrapolation techniques followed by scenario-based sensitivity analyses (e.g. see [32-40]); recalculation of statistical decision indices at each decision point [118]; assigning ranges to preference parameters and actively tracking deviations from statistical means [93]; modelling the evolution of cost, PoS and value through development phases as stochastic processes [113]; deterministic sensitivity [44, 54, 93] or simulation-based sensitivity analyses under different scenarios [123, 135, 137, 138, 143].

A handful of studies have reported sensitivity analysis through scenarios as a useful tool for checking for *heterogeneity* of stakeholder opinions on value drivers and its impact on analytical outcomes, such as the stability or efficiency of portfolio value [54, 121, 132].

The quality of the evidence, in particular the *reliability* of preference information, has been checked in several studies in different ways, including through: consistency ratio rules in AHP models [91, 124-129]; direct bias rating and re-scoring [126]; use of confidence indices on expert judgements [136]; inter-expert variability and algorithmic sensitivity analysis [92].

Structural uncertainty is also acknowledged in a handful of studies, in the form of disagreement with the model structure, which is dealt with through criteria structuring or weighting method modifications in subsequent exercises (e.g. see [127] *versus* [128]; or [54]).

2.3.2.2. Operations Research

A large variety of operations research models has been proposed to support problems of portfolio selection [160, 165-187], scheduling [161, 188-192], or their combination [162-164, 193-210] in health product development. These methods are quantitative in nature and mathematically sophisticated. Their applications are mostly illustrative (see Table 2.4.), demonstrating nonetheless how health product development processes could be mathematically modelled and/or engineered *in-silico* to support planning and management of investments within individual organization settings (see examples in Table 2.4.).

Table 2.4. Examples of Operations Research models for health product development prioritization.

References	Problem context / Decision Variables / Application Type	Typical objectives (criteria)	Typical constraints / Interaction characteristics	Typical parameters / Evidence-base	Typical optimization/ programming methods	Typical computational search algorithms	Typical uncertainty analysis techniques
Examples of Operations Research models for portfolio selection							
[165]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize probability of registering at least one candidate Maximize expected profit; Maximize expected productivity	- Budget constraints	Project costs, PoS, revenues	Linear programming	Simplex algorithm	N/A
[166]	Optimal R&D portfolio and manufacturing strategy selection / Drug candidates / Illustrative	Maximize eNPV	- Probability thresholds on NPV (below x and worst possible NPV) - Sales / marketing constraints	- Project costs, PoS, development timelines, commercial characteristic (demand forecast, price, marketing expenses, etc.) - Manufacturing costs and capacity requirement - Accounting structure of company	Two-stage stochastic programming	Hierarchical procedure	Scenarios
[167]	Optimal R&D portfolio selection / Drug candidates and manufacturing sites / Illustrative	Maximize NPV	Technical capacity, time and revenue constraints	Product features, Manufacturing capacity features, trading structure	Mixed integer linear programming	MILP algorithm	N/A
[168]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize risk-adjusted return (profitability index and internal rate of return)	- Budget constraint	- R&D project PoS, cost, return	Stochastic non-linear optimization	Branch and bound	Mean of variance analyses (Mean-Variance; Mean-Gini)
[169-172]	Optimal R&D portfolio selection / Drug and Monoclonal antibody candidates / Illustrative and Real-life	Maximize eNPV, minimize variance of NPV	- Budget constraint	- R&D project cost, development timelines, PoS, TPP characteristics, returns - Portfolio risk criteria (variance measures) - Activity durations, resources - Time discounting factors	Efficient frontier optimization	Simulation algorithms	- Simulation scenario-based sensitivity analysis for uncertainty - Probabilistic sensitivity analysis
[173]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize eNPV, Maximize probability NPV>threshold	- Budget, risk constraints	- R&D project cost, development timelines, PoS, returns	Simulation-optimization / Multi-stage stochastic mixed integer programming	Genetic / Evolutionary algorithm	- Mean-variance, Value at Risk, simulation-based scenario analysis
[174-178]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize Real Options Value	- Budget constraints - Precedence constraints	- R&D project future value, cost, development timelines - Precedence effects - Time discounting factors	Simulation-optimization / Multi-stage stochastic mixed integer linear programming	'OptFolio' (stochastic programming based algorithm)	- Simulation scenario-based sensitivity analysis

References	Problem context / Decision Variables / Application Type	Typical objectives (criteria)	Typical constraints / Interaction characteristics	Typical parameters / Evidence-base	Typical optimization/ programming methods	Typical computational search algorithms	Typical uncertainty analysis techniques
							- Gini minimization analysis
[160]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize Real Options Value	- Budget - Human resources - Budget by strategic goal (to deal with balance) - technical interdependencies between projects	- R&D project future value, cost, development timelines, contributions to strategy - Time discounting factors	Fuzzy zero-one integer programming	Newton-Raphson algorithm	Fuzzy sets, Possibilistic scenario analysis
[179]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize expected Real Options Value (RoV – investment cost)	- Budget - Resources Balance (min/max spend between strategic goals)	- Project timelines, costs, resources available (budget, staff), volatility - Time discounting factors	Robust 0-1 integer programming	Bertsimas & Sim algorithm for robust optimization	- Optimization using worst case values using 'budget of uncertainty' approach
[180]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize expected Real Options Value	- Budget constraint - Technology interrelations	- Project cost, development timeline, market volatility, current and real options value - Time discounting factors	Robust mixed integer programming	Robust combinatorial optimization algorithm	- Optimization using worst case values
[181]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize worst-case NPV	- Budget constraint	- Project cost, development timelines - Cashflow parameters	Robust mixed integer programming	Robust ranking heuristic; Greedy multiple-knapsack heuristic	- Optimization using worst case values - Scenarios
[182]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize expected Real Options Value	- Budget constraint	- Project market value and annual volatility, PoS, cost, development timelines - Time discounting factors	Multi-period stochastic optimization / Mixed integer linear programming	Simultaneous backward reduction algorithm	Scenarios
[183, 184]	Optimal R&D portfolio selection / Drug candidates / Illustrative	Maximize value (composite score)	- Resource constraints	- Multiple value criteria - Process / resource intensities - Project duration and cost	Mixed integer linear programming	Knapsack algorithms	Scenarios
[185]	Optimal R&D portfolio selection (sequential) / Drug candidates / Illustrative	Minimize queue length	- Queue sizes - Time sequencing interrelations	Project durations, capacities, PoS	Sequential programming	Simulation algorithm	Scenario-based sensitivity analysis for uncertainty
[186, 187]	Optimal R&D portfolio selection (sequential) / Drug candidates / Illustrative	Maximize expected reward; Maximize Profitability Index; Maximize Internal Rate of Return	- Budget and resource constraints - Precedence relations	- R&D PoS, costs, timelines, NPV - Discounting factors	Stochastic Markov modelling / Dynamic integer programming	Newton-Raphson algorithm	Stochastic modelling
Examples of Operations Research models for project and portfolio scheduling							

References	Problem context / Decision Variables / Application Type	Typical objectives (criteria)	Typical constraints / Interaction characteristics	Typical parameters / Evidence-base	Typical optimization/ programming methods	Typical computational search algorithms	Typical uncertainty analysis techniques
[188, 189]	Optimal R&D project and portfolio scheduling / R&D activities / Illustrative	Maximize eNPV	- Task precedence constraints - Task completion timeline constraints - Resource constraints	- Task costs, PoS, completion timelines - Project revenue - Time discounting factors	Deterministic and stochastic optimization / Mixed Integer Programming	Cutting plane algorithm	Stochastic modelling, Probabilistic Scenario analysis
[190]	Optimal R&D project scheduling / R&D activities / Illustrative	Maximize NPV	- Cost, resource, time sequencing and precedence constraints	- Activity durations, cost, PoS, resource requirements - Discounting factors	Mixed integer linear programming	Heuristic decomposition algorithm	Scenarios
[191, 192]	Optimal R&D project scheduling / R&D activities / Illustrative	Minimize cost-to-go value (expected cost – profit)	- Probabilistic correlations between uncertain parameters	- project future costs, rewards - R&D activity durations, PoS, cost, resource requirement - Time discounting factors	Simulation-based optimization / Stochastic Markov Chain modelling / Approximate dynamic programming	Dynamic Programming algorithm in a heuristically defined state space; Q-learning algorithm	Simulation scenario - based analysis
[161]	Optimal R&D project scheduling / R&D activities / Illustrative	Minimize cost of schedule	- Resource, task precedence constraints - Resource interrelations	- Activity durations, resource requirement - Discounting factors	Time indexed integer programming	Lagrangian decomposition heuristic	Scenarios
Examples of Operations Research models for simultaneous portfolio selection and scheduling							
[162-164, 193-201]	Simultaneous optimal R&D portfolio selection & scheduling / Drug or Monoclonal antibody candidates and R&D activities / Illustrative	Maximize eNPV	- Risk constraint (probability NPV<risk tolerance threshold) - Average Time to Market / Expected Makespan (Average Time to Market<acceptable time to product launch threshold) - Resource and budget constraints - Resource, cost, return, and technical interdependencies / activity precedence	- R&D project cost, development timelines, PoS, returns - Activity durations, resources - Time discounting factors	Combinatorial, simulation-optimization / Multi-stage stochastic mixed integer programming	Genetic / Evolutionary algorithms	Stochastic modelling, parameter and value probability thresholds, Probabilistic scenario analysis
[202-206]	Simultaneous optimal R&D portfolio selection & scheduling / Drug candidates and R&D activities / Illustrative	Maximize eNPV	- Risk constraint (probability NPV<risk tolerance threshold) - Task precedence constraints - Task completion timeline constraints - Resource constraints	- Task costs, PoS, completion timelines - Project revenue - Time discounting factors	Stochastic optimization / Multi-stage mixed Integer Programming	Branch-and-cut algorithm	Stochastic modelling, Probabilistic Scenario analysis, Value at Risk, Conditional Value at Risk
[207]	Optimal R&D portfolio selection & scheduling / Drug or Monoclonal antibody candidates and R&D activities / Illustrative	Maximize robust NPV	- Budget constraint - Precedence relations / timing dependencies	- R&D project cost, development timelines, PoS, returns, resources - Time discounting factors	Robust optimization programming	Bertsimas & Sim algorithm for robust optimization	- Optimization using worst case values using ‘budget of uncertainty’ approach

References	Problem context / Decision Variables / Application Type	Typical objectives (criteria)	Typical constraints / Interaction characteristics	Typical parameters / Evidence-base	Typical optimization/ programming methods	Typical computational search algorithms	Typical uncertainty analysis techniques
[208, 209]	Optimal R&D portfolio selection & scheduling / Drug Phase 3 trials and schedules / Illustrative	Maximize eNPV	- Budget constraint	- Drug trial costs, expected revenues, PoS, sequencing and scheduling requirements - Time discounting factors	Stochastic Integer Programming	Decision trees; knapsack algorithm	Simulation scenario-based sensitivity analysis, Value at Risk analysis / Probabilistic Sensitivity Analysis
[210]	Optimal R&D portfolio selection & scheduling / Drug candidates and R&D activities / Real-life	Maximize weighted work performed within a given time window	- Precedence relations - Activity deadline, resource, execution constraints	- Project value, timeline, work content - Activity duration, resource requirements, work content, capacity requirement - Capacity of resources	Multi-mode 0-1 integer programming	Sequential and concurrent project selection and scheduling heuristics	Variance analysis

A common goal of operations research methods in health product development prioritization is to identify the best possible composition and/or sequencing of a subset of decision alternatives (e.g. R&D candidates) out of a larger set, based on which optimal resource allocation choices can be made. The underlying theory behind these models is that of optimization. Optimization theory is interdisciplinary in its foundations, drawing from mathematical theories of constrained optimization [211-214], financial portfolio optimization [215-217] and process systems engineering [218-220].

To achieve their purpose, operations research models employ mathematical programming techniques that structure the problem of prioritization as one of optimizing (maximizing or minimizing) an objective function (i.e. a quantifiable aggregate measure of interest) subject to a set of constraints (e.g. budget or other resource limitations). They generally disregard procedural aspects of stakeholder engagement common in HRPS and decision analysis approaches. Instead, they place emphasis on how computational procedures can efficiently search for solutions in problems that are large and complex enough that would be difficult for decision makers to uncover by simply rank-ordering individual decision alternatives. They do so through use of computational search algorithms (for examples see in Table 2.4.) to identify the best combinations of decision alternatives (optimal solutions) out of all possible combinations of these (the feasible search space). In doing so, they typically assume, and explicitly address, interactions between decision alternatives (e.g. technical risk, cost or value interdependencies between R&D candidates). Consequently, they transform choices between individual decision alternatives into choices between their combinations (e.g. R&D candidate portfolios).

Defining characteristics

(1) Distinguishing between objectives, decision variables, parameters and constraints

An operations research model may seek to optimize single or multiple objectives, with the composition and/or sequencing of projects in an optimal portfolio likely to change depending on the objective(s) adopted. Models emphasizing a single objective typically measure this in terms of maximizing a total reward, such as for instance expected NPV [162-164, 166, 167, 169-173, 182, 188-190, 202-206, 208, 209] or robust NPV [181, 207], Real Options Value [160, 174-180], profitability or other metrics of returns [165, 168, 186, 187], or in terms of minimizing a total expected cost [161, 185, 191, 192]. Few optimization models explicitly construct multi-criteria objective functions in health product development prioritization problems (e.g. [183, 184, 210]. More commonly such models place emphasis on optimizing an overall quantitative measure of return, while minimizing others – such as risk criteria for portfolio selection (e.g. see [160, 162-164, 166, 179, 193-201]), or time and workload capacity criteria for scheduling (e.g. see [200-206, 210]) – in the form of constraints.

To solve its objective function, an operations research model typically distinguishes between decision variables, parameters, and constraints. Decision variables are mathematical representations of the decision alternatives in the model, whose selection determines the value of the objective function. In health product development prioritization problems, decision variables typically take a binary form, i.e. alternatives are either chosen or not in a portfolio (although continuous decision variables can also typically be observed in scheduling problems).

Constraints are the boundaries that define the size and shape of the feasible space of optimization solutions. They can take many forms and can apply to different model components – from decision variables (e.g. limiting them to integer forms or placing limits on how many can be selected), to model parameters or to the overall objective function (e.g. as lower or upper limits of value). The most common example of a constraint to the overall objective function is a budget constraint. Other constraints may relate to: limits on technical or human resource capacity and workload, timelines and sequencing of activities (e.g. relevant in scheduling problems); level of risk (e.g. to minimize chances of portfolio losses); or volume of projects by type (e.g. to ensure balanced portfolios between disease, technology, or research area).

For their parameters operations research models typically rely on measures of value generated by other quantitative (e.g. financial or health economic) models. An appropriate programming function is then applied, depending on the nature of the decision variables, parameters, and constraints of the problem, which identifies the optimal solution through the operation of a suitable optimization algorithm (for examples see Table 2.4.).

(2) Modelling uncertainty

Operations research models emphasize that making health product development portfolio decisions is challenging because of multiple uncertainties inherent in the R&D process. Consequently, many of these models typically argue that any attempts at optimal portfolio decision making must begin by characterizing all uncertainties associated with parameters of development and manufacturing activities, costs and economic or non-economic returns. Merely distinguishing between probabilities and outcomes in these models is often not sufficient. Through the employment of a variety of analytical techniques, uncertainties around key parameters are specified endogenously, and risk criteria are added for the assessment of robustness of optimal solutions.

Key parameters, such as project and/or activity costs, durations, or PoS are typically modelled as stochastic (e.g. [162-164, 168, 182, 191-206, 208, 209]), fuzzy [160], or robust (e.g. [180, 181, 207]), defined as random variables with probability distributions (if stochastic or fuzzy) or with worst-case realizations given some uncertainty ranges (if robust). Where such parameters are not defined as uncertain (e.g. [167, 174, 183, 184, 188]), the need to re-design or test the sensitivity of the models to account for parameter uncertainties is often explicitly acknowledged.

The consideration of parameter uncertainties allows operations research models to introduce measures of uncertainty that capture variance of R&D portfolio outcomes. These measures are then typically used to test for dominance or robustness of portfolio solutions that optimize a specified objective. Standard portfolio theory [215, 217] suggests that an optimal portfolio solution is also stochastically dominant if it simultaneously satisfies two criteria: a) its expected value being greater than or equal to other portfolio alternatives of a given variance; and b) its variance being smaller than or equal to other portfolio alternatives of a given expected value. Although variants of these conditions have been introduced over time (e.g. see [168]), operations research models typically apply some measure of portfolio risk to validate the optimality of their recommended solutions. Various risk criteria have been proposed in this body of literature such as: Value at Risk or Conditional Value at Risk (e.g. see [205]), fuzzy value [160], reward/loss ratios (e.g. see [163, 164, 195, 197], or value

probability thresholds (e.g. see [162-164, 193-201]), variance of portfolio value distribution (e.g. see [170, 174, 178, 180]), semivariance below or above portfolio value thresholds (e.g. see [170]), or covariance of portfolio value, cumulative probability distribution of portfolio value and Gini criteria (e.g. see [168]).

These models then typically go about generating uncertain parameter estimates and solving portfolio prioritization problems satisfying risk criteria by using a variety of optimization algorithms, such as genetic or evolutionary (e.g. see [193-201]), fuzzy optimization [160], or robust optimization (e.g. see [207]) algorithms (for details, see Table 2.4.). Whereas choice of uncertainty analysis technique appears to be dependent on how parameters have previously been defined, the common rationale is to accommodate every possible solution to a problem giving confidence to the identification of optimal as well as robust solutions.

(3) Accommodating portfolio-level effects

As illustrated so far, operations research models highlight that prioritizing health product development portfolios involves a series of trade-offs between optimizing economic or non-economic returns and handling portfolio risk. A final and critical aspect of such trade-offs is how to maintain diversity in the mix of R&D candidates for given levels of available resources.

Diversity considerations are important because of cost, risk, or value interdependencies between projects whose presence can have an impact on the overall risk or value of the portfolio, with implications on the optimality of resource allocation decisions. To ensure that portfolio diversity is captured in operations research models, a balance criterion, portfolio-level preference factor or constraint is typically introduced, for instance by: structuring R&D portfolios by disease area, platform technology type, or early *versus* late phase of development of projects considered (e.g. see [164, 178]), imposing a limit on the allocation of resources between project types by strategic goal (e.g. see [160, 179]), restricting resource allocation between R&D activities because of resource dependencies (e.g. see 160-164, 193-201]), or placing a limit on the variation around an R&D portfolio's expected value (e.g. see [162-164, 193-206]). Where the scheduling of projects or activities in a portfolio are of interest, additional sequential portfolio entry rules can be imposed, through use of precedence constraints (e.g. see 161, 188-207]) or priority indices elicited directly from the decision makers (e.g. see [160-164] in Table 2.3. of the previous section). Correlated measurements of PoS have also been proposed to capture the impact of technical success or failure interdependencies between projects on the success of portfolio outcomes (e.g. see [175]), however such dependencies are not as commonly acknowledged in practice [110].

2.4. Towards a framework for EID vaccine R&D prioritization

A review of the literature on health product development prioritization highlights a multiplicity of normative views, process and analysis tools to support a variety of problems, namely: priority setting, project and portfolio selection. Sections 2.1 and 2.2 address the complex structure of EID vaccine development and the notion of prioritization as a series of interconnected decision frames, providing a basis for distinguishing between different health product development prioritization approaches in section 2.3. A review of this literature demonstrates how the practice of prioritization can benefit from theoretical foundations,

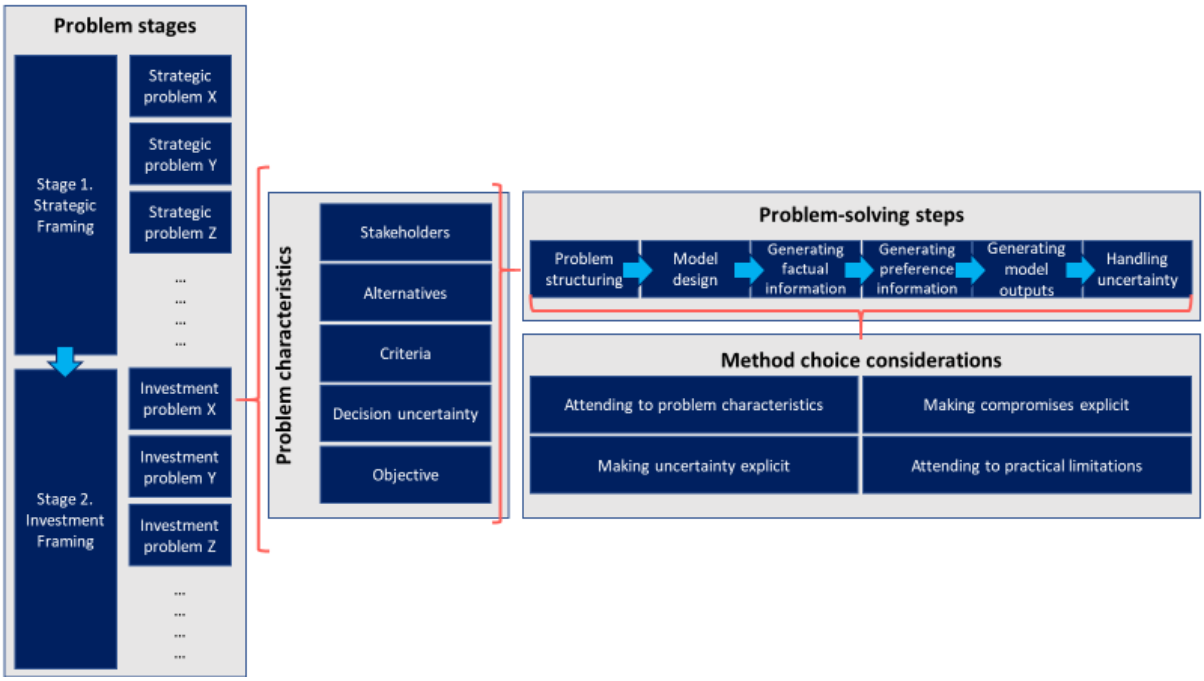
particularly as these emerge from ethical theories, utility and portfolio optimization theories of decision making.

Throughout this review, the approaches of HRPS, decision analysis, and operations research illustrates similarities, differences and complementarities for how to tackle prioritization problems. It is these shared features as well as insights from the differences between approaches which, in my view, can facilitate the selection of appropriate methodologies for EID vaccine development prioritization, without attempting to impose strict normative judgements on some approaches being more useful over others. Given the practical necessity for bringing key elements of these approaches closer together to structure and implement a framework for prioritizing investments in EID vaccine development, this section presents a general structure of such a framework and offers some general considerations on choice of methods.

2.4.1. A general framework structure

The general structure of a framework to address sequential and inter-connected prioritization problems in EID vaccine development is laid out in figure 2.4.

Figure 2.4. A general framework for addressing sequential and inter-connected prioritization problems in EID vaccine development.



Based on this figure, four building blocks can be distinguished: problem stages, problem characteristics, problem-solving steps, and method choice considerations.

(1) Stages – Stages relate to the sequencing of different types of interconnected prioritization problems. As explained in section 2.2., two main stages can be distinguished: (1) setting the strategic prioritization frame; and (2) setting specific investment prioritization frames. In order to meaningfully contribute towards the achievement of fundamentally desired goals, specific investment decisions need to be framed in ways that clearly link their outcomes to the achievement of the decision maker's strategic objectives.

(2) Characteristics - Within this staged frame, each prioritization problem is determined by its problem characteristics. Stakeholders, alternatives, decision criteria and objectives, and decision uncertainty provide the problem context. Properties of alternatives (e.g. interaction characteristics) and of criteria (e.g. quantitative or qualitative measures), preferences of stakeholders as well as model use expectations (e.g. intended use in repeated problems throughout the lifecycle of vaccine development) help specify the prioritization modelling objective.

(3) Steps - In order to transition from problem setting to achievement of the prioritization objective, a prioritization problem can typically be broken down into the following steps: (1) identifying and structuring problem characteristics; (2) building the prioritization model; (3) collecting factual and preference information; (4) running model findings and uncertainty analysis ; (5) generating recommendations.

(4) Considerations - Different procedural and analytical tools will lend themselves to use in different, yet complementary ways within this framework structure. In general, the methods required will depend on how the problem characteristics are specified, the degree to which it is desired for compromises between alternatives to become explicit, the need to model uncertainties and how much attention is given to practical limitations.

2.4.2. General considerations

(1) Attending to problem characteristics

The first consideration and a central theme in common between approaches is that of structuring complex prioritization problems in terms of alternatives and criteria. This structuring can be handled in different ways. HRPS approaches emphasize ethical principles for the participation and role of different stakeholders in the priority setting process. Procedural tools attending to different stakeholder needs can be helpful at early stages of problem specification, for purposes of exploring stakeholder values, identifying alternatives and generating the context for more detailed assessments of alternatives in relation to social goals and needs.

Decision analysis approaches stress the importance of some form of discipline in the identification of alternatives and criteria by ensuring that these are consistent with certain logical rules (see section 2.3.2. on rationality axioms). The application of these rules allows the characteristics of prioritization problems to become salient. Therefore, some type of formal analysis (e.g. construction of value trees) can be beneficial as part of the problem structuring process, reducing ambiguities around problem characteristics' definitions.

Operations research approaches separate criteria between goals and constraints. Such approaches to problem structuring are helpful when trade-offs between individual alternatives cannot be easily expressed, for instance in portfolio decision contexts, where individual alternatives' worth cannot be distinguished without accounting for interactions with other alternatives.

(2) Making compromises explicit

A second consideration as well as common theme between HRPS, decision analysis and operations research approaches, is how to accept compromises that are required when distinguishing between preferred and non-preferred solutions. In HRPS studies, compromise

is typically the result of complex and interactive processes of stakeholder engagement, where preferred solutions emerge and evolve as part of deliberative processes. Stakeholder interaction models can be beneficial to making compromises explicit by testing the practical utility, validity and uptake of model findings throughout the entire prioritization process.

In decision analysis approaches, compromise surfaces through the explicit analysis of choice trade-offs, with methods expending significant effort in eliciting measures of preference between alternatives. Where multiple criteria are considered, decision analysis approaches also encourage explicit statements of – and offer rigorous tools to elicit – acceptable trade-offs between criteria. Although no golden rule exists for choice of preference elicitation method [106, 155, 156, 221-225], swing weighting, choice methods, bisection and difference methods carry specific properties that may bring decision-making in practice closer to the normative ideal of coherent choices [106]. Specifically, by capturing the rate at which changes within or between criteria compensate one another, these methods serve as scaling constants that can discriminate between alternatives in a consistent manner as changes in performance occur. Consequently, these methods can offer greater precision in preference orderings if that is desired. Where choices are not easy to make for every single combination of alternatives for which consequences could be established (e.g. in portfolio selection problems), choice methods [226, 227] may be preferable to use, to maximize the likelihood of capturing the true decision maker preferences on the basis of choices that can actually be observed. These methods draw from random utility theory [228-230], which is consistent with traditional utility theory axioms.

AHP, direct rating or other interactive methods may be sufficient to generate a crude ordering of priority alternatives in instances where the required degree of precision in valuing alternatives is generally low; reflecting the imprecise way alternatives are defined (e.g. broad R&D thematic areas), or the limited availability of factual information to assess performance. However, compliance of such methods with decision theoretical axioms is not always preserved, which may lead to undesirable consequences. For instance, transitivity of preference ordering - i.e. if A is preferred to B and B preferred to C, then A should be preferred to C) - does not apply in AHP methods [231, 232], making them vulnerable to changes in the ordering between existing alternatives when new alternatives are introduced [106, 149, 233]. Practically this may not be much of a concern in one-off priority identification problems using stakeholder judgements with very limited or no other factual data [93, 110]. However, such an implication may be undesirable when consistency in preference orderings is required during repeated decision processes throughout the lifecycle of health product development.

In operations research models, acceptance of a compromise is essentially the imposition of limits to what constitutes an optimal solution, either because of some constraint (such as budget) or portfolio-level concern (such as a diversity criterion). In such problem structures, compromise considerations are elevated to the portfolio level, with optimization models highlighting how portfolio-level criteria such as portfolio risk or balance factors can be incorporated in constrained environments for acceptable compromises to be set.

(3) Integrating uncertainty

Uncertainty is a major issue in EID vaccine development and a common issue generally in models and decisions. Explicitly incorporating uncertainty into prioritization models is

therefore good practice. Understanding what type of uncertainty is relevant in a problem is necessary for incorporating the right types of uncertainty analysis techniques into the model structure.

HRPS studies generally acknowledge uncertainties implicitly or try to resolve them through interactive stakeholder consultation processes (e.g. consensus decision-making). Overall, this is not a very helpful approach in problems characterized by large uncertainties in inputs (e.g. PoS characteristics of vaccine candidates), preferences (e.g. diverse perspectives by multiple stakeholders) or outcomes (e.g. ability of vaccine candidates to offer sufficient protection once successfully developed). Even though these uncertainties are expected to diminish as vaccine candidates advance through development (see section 2.1.), the explicit modelling of uncertainty early on (e.g. during the selection of preclinical vaccine candidate projects or portfolios) is important for ensuring sound progress monitoring and consistency in periodic updates of decisions (e.g. during key stage gates or when new projects enter the portfolio).

Different types of uncertainty are both acknowledged and explicitly dealt with in both decision models and operations research approaches to health product development prioritization problems. Decision models highlight the importance of considering the impact of parameter uncertainty, preference heterogeneity, quality of evidence and structural uncertainty on model outcomes. Operations research models emphasize the need to characterize all uncertainties associated with parameters of vaccine development endogenously in prioritization models, with additional risk criteria considered explicitly for the assessment of robustness of optimal solutions.

Choice of uncertainty analysis techniques to deal with these uncertainties will depend on how the prioritization problem has been structured. At least some sort of scenario-based deterministic sensitivity analysis would always be desired, even with the simplest sets of model data. More complex analyses, e.g. stochastic sensitivity analyses in simulation frameworks, could accommodate every possible solution to a problem, however complex the different scenarios may be, thus giving the analysis a more realistic flavour [234] and creating a greater degree of confidence that priorities were set in the most effective way. However, such techniques cannot be used unless criteria and/or model parameters have previously been stochastically defined.

Performance or preference variability tests will be relevant in group decision contexts comprising multiple and diverse subject-matter experts and decision-making stakeholders. The active tracking of variations and updates in performance and preference parameters are important in repeated decision contexts. In such contexts, structural uncertainty assessments, and respective model updates, should be anticipated, with continued corrective actions based on new information ensuring the success of R&D investment decisions through the lifecycle of health product development [118, 234].

(4) Attending to practicalities

It is often argued that the subject of how to prioritize efforts in health product development, or decision analysis and optimization modelling more broadly, has limited significance unless it is applied, and that practical aspects should play a key role in choice of method [110, 149].

Within the HRPS literature, several authors highlight that stakeholder engagement methods with multiple steps can be resource intensive and that different types of stakeholders often

struggle to conceptualize problem characteristics or make compromises on resulting priorities [57, 62, 63, 75, 76, 88, 89, 104]. Such observations are echoed in decision analysis applications, though special emphasis is given here to the trade-offs required between modelling *versus* attention to social processes (e.g. see [54, 124-128]). Decision models can be time and resource intensive to build and populate with all relevant data inputs, particularly if performance measures are dependent on complex quantitative models. Even in absence of such complexities, preference elicitation tools can feel tedious, requiring time and resources to implement. Some methods, e.g. swing weighting techniques, typically require workshop settings, which may sound unrealistic in remote settings. Stated choice methods can be easier and quicker to implement remotely – e.g. health utility trade-ff surveys [41-43, 138, 139] – but the repetitive nature of choice questions can cause fatigue and inconsistencies in responses, if surveys are not appropriately designed [235, 236].

Cognitive burden may be less of a concern where stakeholders are smaller groups of invested experts who are familiar and have experience with the subject matter [106]. But the uncertainty associated with differences in preferences of different stakeholders, even within smaller groups, may require random sampling strategies, multiple workshops or surveys [237, 238], at the cost of complicating model interactions with stakeholders.

Model complexity has also been a major obstacle for practical uptake of operations research models. Impractical data requirements and abstruse mathematics [110], distancing model predictions from decision maker perceptions [54, 127, 239, 240], and failure to incorporate high-level strategic needs [110] are some of the key reasons highlighted in the literature for a growing disuse of mathematical programming by practitioners since the 1970s [110, 126, 128, 241]. Such criticisms are frequently echoed by practitioners of health R&D portfolio management. Practitioner-based approaches to portfolio management largely acknowledge key aspects such as constraints, interdependencies, and balancing factors, however placing emphasis on visual tools (e.g. bubble diagrams, charts and checklists) (e.g. [50, 51, 53, 144, 146, 172, 242]) and/or social processes (e.g. [171, 243, 244]) to help address portfolio prioritization problems. Whereas such perspectives provide digestible insights into problem objectives, they do not necessarily provide any answers, which optimization models attempt to do [110, 243].

Remarkable advances in computer technology since the 1990s have facilitated the development of powerful computational algorithms, capable of handling large volumes of data and conducting complex computational tasks [239], including the handling of extreme uncertainty and complex interactions [245-247]. The literature reviewed in this chapter suggests that optimization models are both easier and more accessible to use today than earlier models. Whether such complexity should be a ‘price that stakeholders pay’ is likely to depend on the specific problem needs and stakeholders’ commitment to make use of models that are as sophisticated as such needs dictate.

Clearly, practical issues and challenges need to be acknowledged, and dealt with, if any framework is to effectively inform the practice of prioritization in a real-world setting. However, well designed models that offer logical and structured approaches to prioritization needs can be useful throughout the lifecycle of a product’s development. Whereas practical challenges may be difficult to resolve in one-off prioritization problems, many of these should eventually be possible to resolve in repeated contexts.

3. Materials and methods

The previous chapter presented a general framework for addressing strategically interconnected prioritization problems and reviewed methodologies that can potentially support different steps of the EID vaccine R&D prioritization process. In coherence with that framework structure, the current chapter gives an overview of the methodological approaches undertaken to address the EID vaccine R&D prioritization problem, from strategic objective and boundary setting, to R&D project and portfolio selection. The chapter begins with a brief overview of the overall study design across problem stages. It continues with a presentation of data types and sources. The chapter ends with an overview of methods utilized for data collection and analysis, including descriptions of how these methods work in general and how they were employed specifically in the thesis.

3.1. Overall study design

Figure 3.1. frames the overall EID vaccine R&D prioritization problem this thesis was tasked to address. Based on this figure, two stages and four specific problems can be distinguished. Problem characteristics are summarized as they were specified during respective problem structuring steps.

Figure 3.1. Characteristics of the EID vaccine R&D prioritization problem

		Stakeholders	Alternatives	Criteria	Objective	Uncertainties & interactions
Stage 1. Strategic Framing	Paper I. Strategic Objective Setting	• >100 representatives from governments, multilaterals, civil society, industry, academics, non-profits	• Strategy formulations (=combinations of importance levels of different strategic objectives)	• 1. Improve preparedness • 2. Improve response speed • 3. Improve market predictability • 4. Improve equity	• Formulate a desirable strategy that accounts for preferences of multiple stakeholders	• Preference heterogeneity • Structural uncertainty associated with the strategic objective setting process
	Paper II. Boundary Setting	• 64 vaccine development organizations	• Pipelines (=combinations of #vaccine candidates per phase of development)	• Goal 1: Maximum #vaccine candidates per R&D phase • Goal 2: Maximum funding for successful development	• Identify the lower/upper pipeline composition and funding boundaries within which investments can be made	• Imprecision/ variability of PoS, cost and R&D outcome parameters (stochastically defined)
Stage 2. Investment Framing	Paper III. Project Selection	• 44 expert reviewers • 29 SAC members (decision makers)	• 18 vaccine projects against Lassa, MERS, Nipah • Cost per project: $22-68m • Timeline per project: 4-6 yrs	• 1.Likelihood of generating a suitable vaccine for Lassa/ MERS/ Nipah • 2. Likelihood technology will be suitable for vaccine development against new pathogens	• Conduct a quantitative valuation and ranking of projects until a threshold is reached	• Imprecision/ variability of performance parameters (stochastically defined) • Preference heterogeneity (preference estimates stochastically defined)
	Paper IV. Portfolio Selection	• 27 expert reviewers • 29 SAC members (decision makers)	• 16 vaccine technology platform projects • Cost per project: $6-65m • Timeline per project: 3 yrs	• Probability at least one project successfully developed per platform type (x5) against unexpected/ new pathogens	• Identify an optimal portfolio of projects that maximizes value under budget constraint	• Imprecision/ variability of performance parameters (stochastically defined) • Preference heterogeneity (preference estimates stochastically defined) • Interdependencies in cumulative value of projects because of diversity preferences

The goal at the strategic framing stage was to set the strategic objectives and boundaries within which subsequent R&D investments could be achieved by a newly established entity operating in the EID vaccine development space. There were two parts to the attainment of this goal. The first was to formulate a desirable strategy that accounted for the preferences of the multiple stakeholders involved (**Paper I**). This necessitated the identification, structuring, and exploration of the relative importance of multiple and potentially conflicting objectives. The second was to estimate the maximum required pipeline composition and cost for

achieving key strategic objective targets (**Paper II**), which could guide the setting of boundaries within which subsequent R&D investment decisions could be made.

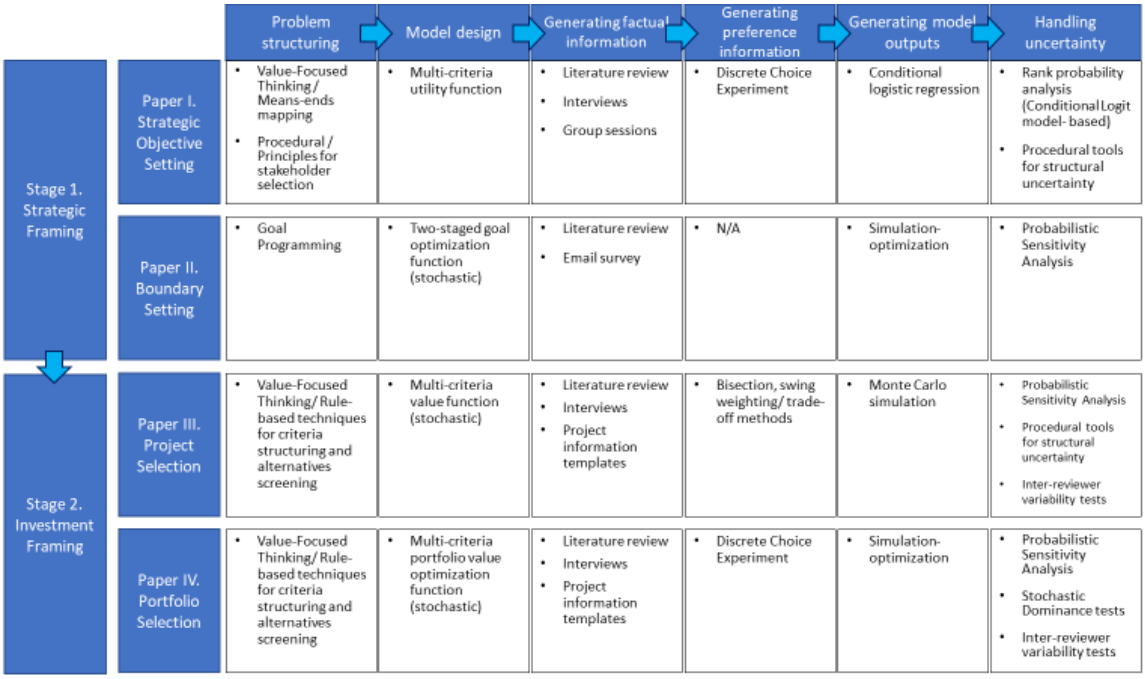
Broad ethical questions and moral dilemmas as to whether investing in EID vaccine development should be justifiable were assumed as already resolved and were therefore not explicitly addressed during the strategic framing stage. However, ethical principles for stakeholder selection and engagement were assumed important and therefore needed to be accounted for (**Paper I**). Multiple sources of uncertainties were assumed, including: heterogeneity of stakeholder perspectives and structural uncertainties associated with strategy design (**Paper I**); uncertainties in the availability of vaccine candidates, the PoS in their development and cost requirements for achieving key strategic objective targets (**Paper II**).

The goal at the investment framing stage was to undertake a quantitative evaluation and selection of projects considered in two separate investment opportunities, which were of interest to decision makers. There were two parts to the achievement of this goal. The first was to value and rank EID vaccine R&D projects against multiple criteria and to select as many of them as possible until a threshold was reached (**Paper III**). The second was to identify an optimal portfolio of platform technology investments that would maximize portfolio value under a budget constraint (**Paper IV**).

Multiple sources of uncertainties were assumed in both investment problems, including on performance estimates and stakeholder preferences (**Papers III-IV**). Interdependencies were assumed in the cumulative value of vaccine technology platforms (**Paper IV**) because of diversity effects – a preference placed on the mix of platform types included in the portfolio. It was also assumed that time would affect value, however only vaccine projects (**Paper III**) had variable timelines for development. Development timelines were the same for all platform projects (**Paper IV**).

Figure 3.2. summarizes the methods used to address the overall EID vaccine R&D prioritization problems. Based on this figure, a series of problem structuring, multi-criteria modelling, factual and preference data generation, computational and uncertainty analysis steps were employed to address the four specific problems. A variety of data sources and tools were employed to support different steps, which are presented in more detail in the following sections.

Figure 3.2.: Methodological steps and tools undertaken to address the EID vaccine R&D prioritization problem.



3.2. Data types and sources

Data was drawn from a total of over 700 literature references, 71 sets of project information documents, and 294 stakeholder responses to support different steps across the two stages of the prioritization problem (for details, see **Papers I-IV**). Stakeholders included representatives of governments, multilateral government institutions, non-profit institutions, academic institutions, industry, as well as independent experts.

In this thesis, two types of data can be distinguished: factual and preference information. Factual information was collected for two purposes: (1) problem structuring (**Papers I-IV**); and (2) performance measurement of investment alternatives (**Papers III-IV**). Preference information was collected both for problem structuring purposes and for preference modelling to inform overall assessments of value and ordering between alternatives, across the different stages of the prioritization problem (**Papers I, III, IV**).

3.2.1. Factual information

Factual information that was relevant for problem structuring included three sets of evidence. First was evidence on needs and potential objectives, types of actors, functions and models of coordination for EID vaccine R&D partnerships. This information served as prompts for representation of important aspects of the problem during initial stakeholder consultations, consequently providing a basis for the identification of strategic objectives under the strategic framing stage (**Paper I**).

Second was evidence on EID vaccine R&D pipeline characteristics, such as types and numbers of vaccine candidates available per phase of development; cost and PoS data associated with these. This data served as input to the estimation of optimal pipeline structures and costs for generating at least one successfully developed vaccine per priority EID under the strategic framing stage (**Paper II**).

Third was evidence on potential factors informing the performance of specific investment alternatives. This information was used to generate long lists of criteria that were potentially relevant to project and portfolio selection decisions under the investment framing stage (**Papers III and IV**).

Factual information on investment alternatives (**Papers III-IV**) included various aspects of: organizational competency, experience & track-record of vaccine development; technical feasibility and manufacturing scalability & speed characteristics; vaccine product profile and technology platform profile characteristics; time-to-completion and cost of development information (for details see methods sections of **Papers III-IV**). This information served as a baseline for estimating performance of investment alternatives against various criteria of interest, relevant to the respective problem settings (**Papers III-IV**).

3.2.2. Preference information

Preference information that was relevant for problem structuring included perspectives on strategic principles and objectives within a Value-Focused Thinking framework (**Paper I**), as well as views on value criteria to support decisions on R&D investments (**Papers III-IV**). This information built on the factual information prompts for identifying strategic objectives (**Paper I**) and contributed to the literature review of criteria with potential relevance for evaluating investment alternatives (**Papers III-IV**).

Once prioritization models were specified, preference information was elicited for assessing the relative importance between criteria in these models (see section 3.3.3.2. and methods sections of **Papers I, III, IV**).

3.3. Methods

As highlighted in Chapter 2, methods for data generation and analysis are dependent on, but also contribute to how prioritization problem characteristics are defined. This section provides an overview of the techniques employed to support the various steps across the prioritization problem stages, as they relate to problem structuring, model specification, generating factual and preference information, deriving model outputs and dealing with uncertainty.

3.3.1. Identifying and structuring problem characteristics

Structuring complex prioritization problems requires the consideration of stakeholders, alternatives and criteria, as previously discussed (see chapter 2). The thesis employed both procedural and analytical tools to identify and structure these characteristics.

3.3.1.1. Procedural tools

Procedural tools for problem structuring relate to rules for stakeholder selection and participation. As highlighted in chapter 2, different stakeholder concerns can be informative at early stages of complex prioritization problems, for purposes of exploring fundamental values and setting the context for subsequent assessments of alternatives in relation to strategic objectives.

Drawing on principles of fairness and accountability in stakeholder participation, stakeholders responsible for strategic objective setting (**Paper I**) were selected based on subject-matter expertise, sectoral and geographical representation. Stakeholders responsible for reporting pipeline and cost information (**Paper II**) were selected based on prior evidence

from the literature on developing EID vaccines. Under the investment framing stage, two types of stakeholders were distinguished: those responsible for making decisions, and those responsible for assessing performance of investment alternatives. Stakeholders accountable for decision making were already set at the start of this stage of the problem, their selection been driven by similar criteria as those applied for stakeholder selection under the strategic framing stage (**Paper I**). Stakeholders responsible for assessing performance of investment alternatives (**Papers III-IV**) were selected through open competitive processes based on demonstrable experience – including years of work experience – in different aspects of vaccine development, and no conflicts of interest.

3.3.1.2. Analytical tools

The overarching analytical approach embedded in all problem structuring efforts in the thesis is that of Value Focused Thinking (VFT). Assuming relevant stakeholders have been identified, VFT sets the foundations on which different analytical techniques can be employed to help define and structure alternatives and criteria across the prioritization problem's stages.

Value Focused Thinking (VFT)

VFT is a systematic approach to identifying what fundamentally matters to stakeholders during the structuring of decision problems. VFT distinguishes between two types of criteria: (1) fundamental criteria, which characterize the essential reasons or endpoints for a given decision, and (2) means criteria, which enable the achievement of fundamental criteria [49]. In doing so, VFT requires for the criteria to be separated between fundamental consequences and factors contributing to the realization of these consequences, imposing this way a structure whereby unambiguous trade-offs between fundamental sources of stakeholder value can be made. For these reasons VFT is considered an essential element of structuring decision problems and value frameworks in general [149].

VFT typically starts with an idea generation exercise through stakeholder consultations. It then develops a representation of the generated concepts into categories associated with means and ends objectives. The structure that emerges is then examined for coherence of alternatives and criteria considered, according to some rationality assumptions (see chapter 2).

Multiple techniques can be employed to operationalize the VFT framework, depending on how well alternatives and criteria are defined at the start of the problem structuring process. In this thesis, VFT was applied at all stages of the prioritization problem, albeit in somewhat different ways. Specifically, three types of problem structuring techniques were distinguished that built on VFT principles: means-ends mapping, goal programming and rule-based techniques.

Means-ends mapping

In ill-defined problems, such as strategic decision problems in newly established organizational settings (**Paper I**), alternatives are neither obvious nor easy to generate. In addition, following on a description of the problem through stakeholder consultations and literature prompts (see section 3.3.3.1.), a wealth of concepts is typically generated, not all of which can be classified as fundamental objectives. In such settings, VFT can ensure that objectives and alternatives are coherently specified through use of means-ends mapping.

Means-ends mapping starts by separating the various concepts and establishing relationships between them by examining the reasons for each, and, where possible, their implications. It then establishes a network of means–ends argument chains within and between distinct reasoning clusters. These clusters move from the specification of problems to the conceptualization of benefits anticipated by alternative solutions, including reasons why these are likely to be important. In doing so, this process allows for the elimination of redundancies of previously reported concepts and checks for consistency between stakeholder perspectives. A qualitative assessment of alternatives' characteristics can then be conducted within the structure of this map. This allows for a transition to a simplified multicriteria model structure, where criteria can be qualitatively defined.

Means-ends mapping was employed in the strategic objective setting problem (**Paper I**) for the specification of a hierarchy of means–ends objectives, distinguishing between preferentially independent ends objectives.

Goal programming

The goal programming approach to problem structuring (and to MCDA more broadly) can be viewed as an operational implementation of the satisficing rule [149]. Satisficing places emphasis on achieving satisfactory levels of achievement on each criterion, with attention shifting to other criteria once this is achieved [248]. Satisficing levels are usually specified as measurable goals to be achieved and the problem can be typically formulated within the context of mathematical programming to approach these goals [249-251]. Here, each criterion needs to be associated with a quantitative measurement scale. It is possible that stakeholder values are not explicitly expressed, as these are typically implied in terms of goals, defined in terms of minimum or maximum levels of performance.

The problem can be constructed by optimizing each goal in turn (e.g. if a goal is to maximize some value, the criterion will be described in a minimizing sense, and *vice versa*). Once the level of satisficing on one criterion has been reached, the problem focuses on optimizing the next goal, and so on. It is anticipated that different goals considered are conflicting and that the optimization of one goal will therefore be constrained within a decision space bounded by the satisficing levels associated with a previous goal.

Where goal programming is treated as a problem structuring technique, it can help in background screening of alternatives, generating shortlists of alternatives for more detailed evaluations, or introducing boundaries on future evaluations and decisions [149]. Stakeholder interactions are typically assumed to have already generated a number of quantifiable goals as part of a preceding process, for instance through VFT [49, 252].

Goal programming was used as part of problem structuring during the strategic framing stage (**Paper II**). The first goal was to generate a maximum number of projects anticipated for the successful development of at least one vaccine candidate against each priority EID (the criterion expressed in a minimizing sense). The second goal was to estimate the maximum cost ceiling (expressed again in a minimizing sense) for the successful development of a vaccine per EID, without the pipeline exceeding the total number of projects identified as necessary during the optimization of the first goal. These goals were set as a direct outcome from the strategic objective setting process (**Paper I**), where target values of stakeholders had previously been explored. The direct output was a specification of lower/upper pipeline and

funding boundaries within which desired objectives could feasibly be attained in subsequent investment decision problems.

Rule-based techniques

Where alternatives are known and the overarching strategic frame (e.g. objectives, boundaries) has been set, simpler rule-based techniques can be employed within a VFT framework to ensure that: (1) criteria of interest (and strategic relevance) are coherently specified; and (2) alternatives are screened out if they do not comply with some minimum specifications.

Criteria screening rules typically relate to the adherence of certain analytical principles when structuring these in a multicriteria model – such as completeness, non-redundancy, non-overlap and preferential independence (see Chapter 2). During the structuring of both project and portfolio selection problems (**Papers III-IV**), stakeholders were asked to determine: whether all factors relevant to strategic or specific investment decisions had been captured by the previously formulated criteria; the relationship between the criteria, and whether any of the criteria should be removed or re-grouped if overlapping, or irrelevant. The application of these rules led to a narrowing down of long lists of criteria initially considered and informed their combination into value functions (see section 3.3.2.).

Screening rules for alternatives relate to: a) the adherence of analytical principles when structuring a model; b) the compliance of certain minimum specifications when assessing early in the process as to whether alternatives should be further evaluated by the model. In terms of analytical principles – e.g. completeness, transitivity and independence of choices (see Chapter 2), perhaps the most relevant one to check for at this step is that of independence. The presence of interactions between alternatives (e.g. because of risk, cost or value interdependencies between R&D candidates) will dictate whether they should be modelled as independent choices or subsets of interdependent choices.

In terms of non-compliance to minimum specifications, three rules can typically be considered. First, if any alternative is "dominated", i.e. performs worse than all others on all criteria, it can be excluded from further consideration. Second, if there is a minimum level of performance on any criterion that an alternative does not meet, and criteria are assumed preferentially independent, this alternative can potentially be excluded. Third, in conjunction with the second rule, an alternative does not have to be excluded if it performs below the minimum requirement on a criterion but compensates by an exceptional performance on other criteria of interest.

The application of these screening rules led to the specification of the EID vaccine R&D investment problem as one of project selection (**Paper III**). Given interaction effects identified during stakeholder consultations, the vaccine technology platform problem was specified as one of portfolio selection (**Paper IV**) (see section 3.1.). Moreover, the application of rules around non-compliance led to the elimination of 15 alternatives in the project selection problem (**Paper III**) and 16 alternatives in the portfolio selection problem (**Paper IV**), before a full-scale evaluation of the remaining alternatives was conducted by the models in these decision problems.

3.3.2. Specifying models

Once problem characteristics have been identified and structured, these can be expressed more formally in specific model structures. Given that multiple criteria, multiple stakeholders and uncertainty are essential characteristics of the EID vaccine R&D prioritization problem (see section 3.1.), models can be expressed in formats that explicitly account for these features.

Where multiple criteria are essential features of the problem and preferences are made explicit, additive value functions can be specified, given that criteria have been structured in a way that satisfies properties of independence. In their simplest form, such functions can be expressed as per equation (1).

$$V(i) = \sum_{j=1}^{n} w_j v_j(i) \qquad (1)$$

Where:

$V(i)$ *= overall value of alternative* i

$v_j(i)$ *= partial value of alternative* a *on criterion* j

w_j *= preference coefficient reflecting relative importance of criterion* j

Where quantitative performance data is not available on criteria and the overall value of an alternative is based simply on some estimate of desirability directly elicited from stakeholders, equation (1) can be rewritten as $\sum_{j=1}^{n} u_j(i)$, where $u_j(i)$ is the preference (or utility) of alternative a on criterion j. v_j can be typically viewed as a combination of a performance estimate and a within-criterion weight. Where within- and between-criteria are elicited simultaneously (e.g. through stated choice methods such as a DCE), w_j can be viewed as a combined partial value and relative importance coefficient, with v_j representing just the performance measurement function on criterion j. How specific components of such models – e.g. as they relate to performance or preference coefficients – are integrated into a value aggregation function will depend on methods used to generate such estimates (e.g. see section 3.3.3.2.).

Where quantitative goals are essential characteristics of the problem, their satisficing can be expressed in an optimizing (i.e., maximizing or minimizing) sense. For instance, assume a two-criterion problem. For a criterion j, a^j is denoted as the feasible solution that maximizes $v_j(a)$ over the decision space. Let $v_j(a^j)$ be the optimal performance for this criterion and $v_{jk}(a^k)$ the performance for criterion j when criterion k is being optimized. In its simplest, linear form [149, 253, 254], a goal programming function would first optimize $\sum_{j=1}^{m} v_j x_j$ to obtain $v_j(a^j)$. It would then optimize $\sum_{k=1}^{n} v_{jk} x_k$ subject to $v_{jk}(a^k) \leq or \geq v_j(a^j)$. Here, x_0 denote the decision variables that need to be selected subject to the relevant constraints.

Value aggregation can also be expressed in a multiplicative form, assuming preferences are perceived in ratio scale terms (e.g. one alternative is preferred twice as much as another) [149]. Where uncertainty in outcomes is a feature of the problem, multiplicative combinations are required between criteria representing consequences and criteria representing probabilities of these consequences occurring (see chapter 2). Depending on

assumptions around preference structures, value aggregation in presence of uncertainty can take a multiplicative or additive combination form [153].

Based on the objectives emerging from the means-ends mapping exercise as relevant to the assessment of alternative strategy formulations (**Paper I**), the most desirable strategy formulation was identified as the one with the highest sum of utilities associated with different levels of importance per strategic objective across all objectives considered. Sources of utility were additively expressed, so that each objective could be represented by a preference coefficient accounting for that objective's marginal utility, as levels of importance per objective were assigned a binary code 1 if the level was present and 0 if it was not in a given strategy formulation. Typically, the lowest attribute level in such a model serves as a reference point and always gets the binary code 0 [255, 256].

A goal programming function was specified for deriving a maximum feasible number of projects for successfully developing at least one vaccine per EID (goal 1), followed by the estimation of a maximum desirable cost to attain this goal (goal 2) (**Paper II**). A stepwise optimisation model was built that included uncertainty. Under goal 1, the sum of the product of the number of projects and PoS was optimized as projects (their integers) transitioned between phases of development. Under goal 2, an uncertain cost parameter was added to the sum of products function, with goal 1 outputs now operating as constraints.

Based on the factors emerging from the problem structuring step as relevant to the assessment of alternatives in the project selection problem (**Paper III**), a multi-criteria utility function was specified that accounted for: (1) multiplicative relationships between criteria to ensure the additive and preferential independence of consequences in a multiplicative-additive model formulation; (2) partial value and relative value (weight) coefficients (see section 3.3.3.2.) to adjust expected consequences for preferences of stakeholders; and (3) a time preference that operated as a discount factor on the overall utility function. Given the anticipated uncertainty in performance estimates and heterogeneity in stakeholder preferences, all performance and preference coefficients were stochastically modelled (for details see methods section of **Paper III**).

Following on the problem structuring procedures in the portfolio selection problem (**Paper IV**) value interdependencies emerged as critical in the assessment of technology platform projects. Therefore, a multi-criteria portfolio value function was specified that accounted for: (1) multiplicative relationships between project-level criteria that operated as PoS factors in the model; (2) portfolio-level preference coefficients that acted as value of diversity factors on projects falling under different portfolio criteria (i.e. platform types) in the model. As per the project selection problem, uncertainty in performance and preference estimates was integrated through the stochastic modelling of these parameters (for details see methods section of **Paper IV**).

3.3.3. Generating information

Once a model structure and alternatives for prioritization have been identified, the next step is to generate the information required by the model. As highlighted in section 3.2., two types of information can be distinguished: factual and preference information. A combination of procedural and analytical tools was employed for generating this information.

3.3.3.1. Procedural tools

Various procedural tools were employed to collect factual and preference information in the thesis, including literature reviews, semi-structured interviews and group discussion sessions (teleconferences, email exchanges and face-to-face meetings), online surveys and other information templates. These tools are classified as procedural in this context because they do not presuppose any contingent propositions on their own [257]) but can be rather viewed as operational implementations of the propositions underlying the models they support (e.g. see section 3.3.3.2. on use of surveys within preference elicitation models).

Literature reviews

Literature reviews were employed to identify needs and potential objectives for EID vaccine R&D partnership building (**Paper I**), to identify EID vaccine candidates and PoS estimates relevant to vaccine development (**Paper II**), and to generate long lists of potential performance factors and value criteria for decision making (**Papers III-IV**). In all reviews, tailored search terms were developed, multiple databases were mined, reference lists of identified sources were scanned, at least two researchers were tasked with collating the evidence and multiple stakeholders were approached to confirm or to add to literature findings, in line with good practice for completeness and quality assurance [258-260].

These reviews were helpful in different ways. The identified needs and potential objectives for EID vaccine R&D partnership building (**Paper I**) facilitated ideation fluency in stakeholder consultations, steering discussions towards critical issues previously raised in the literature that would have likely been omitted without any relevant literature prompts. The mapping of EID vaccine R&D pipeline and PoS information (**Paper II**) enabled the estimation of realistic pipeline structures and costs adjusted for PoS in developing EID vaccines. The identification of potential performance factors and value criteria (**Papers III-IV**) prompted stakeholder discussions on these and helped mitigate potential risks such as oversimplified problem representations or omissions of important concerns [261].

Semi-structured interviews & group discussion sessions

Semi-structured interviews and group discussions were employed to identify strategic objectives (**Paper I**), performance factors and value criteria (**Papers III-IV**) of interest to stakeholders engaged in the prioritization process. Questions included in the questionnaires were crafted based on recommended problem structuring techniques in the decision analysis literature [149, 261-264]. Questions revolved generally around the identification of sources of value and the specification of reasons as to why these should be deemed important. Questions were purposefully repetitive to allow for implicit values to become more explicit statements of objectives and, in a way, to also test for stakeholder response consistency in a qualitative manner.

One-on-one interviews were followed by group discussion sessions in the form of teleconferences, email exchanges and face-to-face meetings to ensure completeness of problem representations (**Papers I, III, IV**), or to update initial performance assessments (**Paper IV**). In the latter case, stakeholders were asked to discuss the technical merits of project alternatives in diverse subject-matter expert group sessions. Experts were given the opportunity to revise their individual assessments, if needed, without obtaining access on

quantitative assessments provided by other stakeholders. This was to avoid anchoring biases while minimizing overconfidence errors [261].

Online surveys and other information templates

Two types of survey and other information templates tools were employed to collect factual and preference information across the stages of the prioritization problem. In terms of factual information, EID vaccine R&D pipeline and cost information (**Paper II**) was generated through a structured data collection survey, administered via email. Here, product developers were asked to confirm the status of the vaccines identified previously by the literature review as well as to clarify development costs for developing these vaccines. EID vaccine project (**Paper III**) and vaccine technology platform project (**Paper IV**) information was provided by product developers through the online submission of multi-page project description and budget documents in response to the launch of competitive Calls for Proposals. Stakeholders reviewing the performance of alternatives in the project selection (**Paper III**) and portfolio selection problem (**Paper IV**) were given templates for submission of quantitative assessments and qualitative justifications of their assessments. Guidelines for conducting assessments were provided through instruction manuals, email and teleconference- based clarifications, throughout the performance assessment processes.

Structured surveys were developed to elicit preferences that could be translated into appropriate weighting factors for the estimation of overall values of alternatives considered during the strategic framing (**Paper I**) and the investment framing stage (**Papers III-IV**). The design of the preference elicitation survey templates was conditional on the choice of preference elicitation method (see section 3.3.3.2.).

Regardless of purpose, all survey and information template tools were pilot tested for content, structure, format and functionality with several colleagues of the investment entity internally, then piloted with select respondents externally, prior to their formal launch, in line with good practice [265, 266]. Upon submissions of information templates, at least two colleagues checked for completeness of the submitted information. In the case of the pipeline and cost information survey (**Paper II**), further clarifications were provided in response to specific questions over missing or unclear information submissions, via email and phone. Formal eligibility screening procedures were undertaken in the cases of EID vaccine project (**Paper III**) and vaccine technology platform project submissions (**Paper IV**), which CEPI management was responsible for.

3.3.3.2. Preference elicitation techniques

Two types of preference elicitation techniques were employed in the thesis: stated choice (**Papers I and IV**) and stated preference methods (**Paper III**). As alluded to in chapter 2, these methods share common properties that make them compatible with multi-attribute utility theory axioms and multi-criteria model specifications. However, they differ in how they elicit preferences and consequently how they translate these into trade-off coefficients in value functions.

Discrete Choice Experiment (DCE) methods

A DCE was employed to elicit preferences for strategic objectives (**Paper I**) and for vaccine technology platform types (**Paper IV**). This is a stated choice method for decomposing stakeholder preferences for alternatives into separate preferences for alternatives'

characteristics (the attributes) [226, 267]. The analysis of choices can then be used to generate a utility function describing how variation in attributes (the explanatory variables) contributes to the preference for an alternative (the dependent variable).

General overview

Given several attributes have been identified as relevant for describing the worth of an alternative, alternatives can be modelled as positions (the levels) occupied on the different attributes describing them within a choice experiment. For each set (typically a pair) of some hypothetical alternatives (the choice set), a choice is made between alternatives occupying varying levels on each attribute. In undertaking this choice task, stakeholders compare both the level of one alternative against levels of other alternatives occupied on each attribute, and the level of one attribute against levels of other attributes occupied by each alternative. In doing so, stakeholders express their preferences for alternatives as an outcome of the simultaneous consideration of both types of trade-offs, as ultimately reflected by their statement of choice in a given choice task.

This choice task is repeated multiple times, i.e. the experiment requires stakeholders to repeat their choice between alternatives through multiple choice set iterations, each time changing the levels that alternatives occupy on each attribute. The total possible number of choice tasks in an experiment will depend on the total possible combinations between the number of attributes describing an alternative, the number of levels an alternative can occupy on each attribute and the number of alternatives comprising the choice set in each choice task. For instance, in presence of five attributes, each with three levels, 81 unique choice tasks would need to be undertaken, if each task required a choice out of a set of three unique combinations of attribute levels (i.e. unique alternatives).

In practice, having to choose from all possible combinations of attribute levels is too tedious of an exercise for stakeholders to engage in. Therefore, preferences of only a fraction of all possible alternatives are typically considered in a choice experiment design. Such a fraction of alternatives can meaningfully support the elicitation of preferences in a choice experiment if several *ex-ante* and *ex-post* properties are met (i.e. conditions before and after the launch of the DCE). *Ex-ante* properties typically concern [268=271]: (1) whether there is a similarity in frequency of occurrence of levels of attributes across all choice tasks of the experiment (known as the property of balance); (2) whether the attributes are uncorrelated, and therefore statistically independent of each other (known as the property of orthogonality); and (3) whether each attribute's levels are different across all alternatives within each choice set (known as the property of minimum overlap). The degree of balance can be tested by counting and comparing for equality between the total number of occurrences of each attribute level across all choice tasks in the fractional experiment design. The degree of orthogonality can be tested by computing pairwise correlations between attributes and their levels considered in the selected fractional design. The degree of overlap can be tested by counting the frequency that an attribute level repeats itself in each choice set. Whether a fraction of all possible alternatives can adequately help capture preferences for alternatives in an experiment will depend on the degree to which the two properties of balance and orthogonality are satisfied and the degree to which overlap is minimized. Typically, there will be a trade-off between the degrees to which these properties can be attained in a fractional design. Therefore, the extent to which a fractional design can efficiently capture preferences

for alternatives in an experiment will depend on whether the combined attainment of these properties can be maximized (commonly measured by what is known as the D-efficiency statistic) [271].

Ex-post properties typically concern [270, 272]: (1) whether a dominant alternative was correctly chosen when compared with dominated alternatives in a choice set (known as the dominance test); and (2) whether an alternative was consistently chosen out of a set of alternatives when the same choice task was repeated in the experiment. Both dominance and consistency tests are typically incorporated as additional choice tasks in the experiment, intended to help clarify to what extent stakeholders appropriately attend to the choice tasks. Whereas *ex-ante* properties must be accounted for before the DCE is launched, *ex-post* properties can only be assessed after DCE responses have been obtained, and thus serve as assurance about the quality of preference information collected.

Once a fractional design has been selected, the DCE can be conducted in different ways, e.g. through an online or postal survey, face-to-face structured interviews, etc., depending on the cognitive capacity of DCE respondents, their geographical disbursement, access to postal or internet services, etc. [269]. Some general considerations about designing survey-based data collection tools have already been described in section 3.3.3.1. Some additional considerations when administering a DCE include: the number of stakeholders participating in the experiment; the bias potentially caused by the order in which the choice sets occur or the attributes are described; and the cognitive fatigue anticipated when the volume of choice tasks a stakeholder is required to address is high [270, 272]. Depending on the number of attributes, number of levels on each attribute, and number of alternatives comprising a choice set in each choice task, the number of participating stakeholders required to generate statistically significant results may be forbiddingly high. Various minimum sample size calculation rules can be employed [273] to ensure that the number of stakeholders participating in a DCE is sufficient. Contingent on such calculations, multiple survey versions can be administered, dividing the total number of choice tasks between them, and/or changing the order in which choice sets occur or attributes are described.

Once DCE response data has been obtained, analysis of choices typically involves a probabilistic model of choice between alternatives, related through a logistic regression to the levels of achievement of individual attributes. Common utility estimation models are the Conditional Logit or Multinomial Logit models, although many other choice model specifications exist (e.g. Multinomial Probit, Nested Multinomial Logit, etc.) depending on whether dependent variables are polychotomous, whether alternatives are correlated, etc. [269, 271].

Overview of application in thesis

A DCE was first employed for the estimation of an overall probability of attractiveness associated with alternative strategic objective formulations (**Paper I**). Strategy alternatives were defined as positions (or levels) of importance on each strategic objective (the attributes) considered in the model. A fractional design of 18 choice tasks was selected that maximized D-efficiency out of a total of 1,000 design alternatives considered. The experiment was administered via an online survey in two versions of 9 choice tasks each, with stakeholder respondents, ordering of attributes and of tasks randomly selected within each individual survey. Internal consistency tests (through a dominance and a repeat choice task) were

included in all survey templates. A dummy-coded, linear, conditional logistic regression was applied (see section 3.3.4.1.) to assess the contribution of strategic objectives' importance on preference for strategy alternatives.

Second, a DCE was employed for the estimation of preference weights on types of vaccine technology platforms considered in the portfolio selection problem (**Paper IV**). Portfolio alternatives were defined as probability levels of successfully developing at least one platform project on each platform type (the attributes). A fractional design of 32 choice tasks was selected that maximized D-efficiency out of a total of 1,000 design alternatives considered. Similarly to Paper I, the experiment was administered via an online survey in two versions of 18 choice tasks each, with stakeholder respondents, ordering of attributes and of tasks altered within each individual survey. A dominance and a repeat choice task were incorporated in surveys to test for consistency of responses. A conditional logistic regression was applied (see equation (4) in **Paper IV**) to assess the contribution of changes in the probability of generating at least one project for each platform type to a portfolio choice being preferred. Results of this model were used to estimate preference functions for the different platform types (see equation (5) in **Paper IV**).

Bisection method

The bisection method [156] was employed to elicit within-criterion weights (or partial values) for criteria of interest to decision makers in the project selection problem (**Paper III**). This is a compositional preference elicitation method in that it involves eliciting partial values for criteria separately from between-criteria weighting [106]. This contrasts with DCE methods described previously, which require the simultaneous consideration of within- and between-criteria trade-offs when making choices between alternatives. The bisection method searches for a value midpoint on a predefined criterion performance range, which can then be used to generate a partial value function describing how changes in performance of an alternative on a given criterion contribute to the preference for an alternative.

General overview

To begin with, the bisection method requires that the performance on a criterion is specified within a range that corresponds to an interval scale of value, with endpoints of this scale defined and the scale's direction monotonically increasing or decreasing over the performance range. The method then initiates a procedure of identifying a point within the performance range that is midway, in value terms, between the two endpoints of the scale. It does so by modelling alternatives as changes in performance corresponding to different segments of the value scale within an iterative, pairwise choice procedure.

In the first iteration, a midpoint distinguishes between alternatives that splits the value scale into two equal segments. If performance changes describing alternative A are considered indifferent to performance changes describing alternative B, the procedure typically stops there. I.e., the partial value function is considered linear in that the same rate of preference applies over performance changes along the range. If alternative A or B is chosen (i.e. a performance change describing one alternative represents a greater change in preference than the other alternative), a new pairwise choice is made in a second iteration. Here, a value midpoint distinguishes between alternatives A and B which corresponds to half the performance range associated with the alternative selected during the previous iteration. This

pairwise choice procedure is repeated several times, i.e. the method requires stakeholders to update their choice between alternatives in multiple pairwise comparisons (assuming no indifference between alternatives has been selected). Each time, alternatives can be distinguished by a reference point equal to half the performance range associated with the alternative selected in the previous iteration.

There is no golden rule on up to how many iterations should be run. Partly this should depend on the nature of the performance range and how operationally meaningful different segments of this range are, the smaller they become. In practice, it is commonly accepted [149], and empirically tested [274, 275] that five iterations should be sufficient to enable the elicitation of a partial value function.

Once a recursive pairwise choice procedure has been designed (e.g. in the form of a decision tree), the bisection method can be administered in various ways, e.g. face-to-face consultations or through surveys online. Similar considerations apply here as with administering DCEs (see above) and as with survey- based data collection tools in general, if administered this way (see section 3.3.3.1.).

Once pairwise choices have been made, analysis of choices typically involves a partial value function. Such a function can be defined as a linear expression in which the criterion is weighted by a partial value coefficient to account for the criterion's marginal value. For each segment of the interval scale that is distinguished by a midpoint, it is usual to specify the partial value coefficient in terms of a ratio of the value over the performance range corresponding to that segment.

Overview of application in thesis

The bisection method was employed for the estimation of partial values on criteria of interest to decision makers in the project selection problem (**Paper III**), via an online survey (24 respondents). Stakeholders answered up to six pairwise choice questions that iteratively approached the value mid-point on each criterion, using a decision-tree logic (see appendix of **Paper III**). For each stakeholder, the pairwise choice questions identified a point within the performance range that was midway, in value terms, between the two endpoints of the value scale. Based on this, a partial value function was defined to account for each criterion's value over its performance range (for details, see methods section and appendix of **Paper III**).

Swing weighting and trade-off methods

A combination of swing weighting [149] and trade-off methods [153] was employed to elicit between-criteria weights for criteria of interest to decision makers in the project selection problem (**Paper III**). As with the bisection method, these techniques are compositional preference elicitation methods in that they involve eliciting criteria weights separately from (and typically after the elicitation of) partial values. Swing weights are used to reflect the relative importance of criteria in multi-criteria value functions, capturing both the ordering between criteria and the extent to which the measurement scale adopted discriminates between alternatives [149]. The trade-off method can help assign values to criteria along this scale, once an ordinal ranking of swings has been established.

General overview

Swing weighting begins by rank ordering the criteria. This is typically done by considering the swing from the worst value to the best value on each criterion. The criterion whose swing is perceived to give the greatest increase in overall value of an alternative is assumed to have the highest preference. This process is repeated on the remaining criteria, each time identifying a criterion with the highest preference out of the remaining set, until an ordinal ranking of criteria has been determined.

Once criteria have been ranked based on the above procedure, a value is assigned to the highest ranked criterion, against which stakeholders are required to assess the relative value of a swing from worst to best on the remaining criteria. Whereas there may be many ways of doing this e.g. from qualitative rating to point allocation [149, 276], the trade-off method can be useful when the total number of criteria is small and numerical precision is desired. This method begins by considering two hypothetical alternatives against two criteria only (considering all other criteria equal, if more than two criteria are relevant to the problem). An iterative, pairwise choice procedure is then conducted to identify an indifference point for which both alternatives are equally preferred. It does so by modelling alternatives as pairs of criteria that differ by some value.

Similar to the bisection method, trade-off methods for elicitation of swing weights can be administered in various ways and similar considerations apply around design of choice tools (see section 3.3.3.1.).

Once pairwise choices have been made, analysis of these typically involves a multi-criteria value function (see section 3.3.2.). Such a function can generally be defined as a linear expression in which each criterion's partial value is weighted by a scaling constant to account for the relative value of changes in that criterion's performance. It is common to derive these scaling factors through marginal rate of substitution techniques [153]. Once these have been computed, weights can be normalized to sum to 1, 100, or other scale of interest, allowing this way the interpretation of each weight as a share of the total importance weight in the overall value function [149].

Overview of application in thesis

Swing weights were elicited for criteria of interest to decision makers in the project selection problem (**Paper III**) via an online survey (24 respondents), using the trade-off method. Given two criteria of interest, one of these was assumed to be more important based on stakeholder perceptions, at the start of the elicitation exercise.

An iterative pairwise comparison (up to six questions) was used (see decision-tree logic in appendix of **Paper III**). This helped identify an indifference point within the performance range of the highest ranked criterion, for which a swing from worst performance to this point would be equally preferred to a swing from worst to best on the lowest ranked criterion. Based on this, a relative value coefficient was estimated for the criteria per unit changes in performance. This coefficient was then used to estimate the relative values of the swings in performance of criteria associated with the indifference point so that they sum to 1 (for details see appendix of **Paper III**).

A similar approach to trade-off weighting was undertaken to elicit a time preference, which was integrated through a time discounting function as a scaling factor on the overall value function (for details see methods section and appendix of **Paper III**).

3.3.4. Generating model outputs

Analytical outputs can be generated once models have been specified and factual and preference information has been obtained. Given the general EID vaccine R&D prioritization problem uncertainties (section 3.1.) and the way decision problems were structured (section 3.3.1) and modelled (section 3.3.2), three output generation techniques can be distinguished: preference modelling through conditional logistic regression; Monte Carlo simulation; and Simulation-Optimization.

3.3.4.1. Conditional logistic regression

In absence of quantitative data on the performance of alternatives against criteria of interest (**Paper I**), a direct elicitation of utility scores can be employed, given crude estimates of the comparative desirability of alternatives are deemed sufficient. Section 3.3.2. describes such a function specified for measuring the desirability of alternative strategy formulations. Section 3.3.3.2. describes how preference coefficients were elicited using a DCE to be incorporated into a conditional logistic regression for assessing the contribution of strategic objectives' importance on preference for strategy alternatives.

In its simplest form, a conditional logistic regression model calculates the probability of an alternative being selected, based on which a likelihood function can be maximized to generate utility coefficients associated with different levels of the attributes considered. In this model, a dichotomous dependent variable indicates the choice, which is a linear expression of explanatory variables (the attributes). In this expression, each attribute level is weighted by a coefficient to account for the marginal utility associated with differences in attribute levels between the choices being analysed. A relative probability of an alternative being chosen compared with other alternatives can then be estimated by calculating the ratio of the alternative's utility against the utility of all alternatives being evaluated.

In this thesis (**Paper I**), the strategy formulation that maximized utility was deemed the most preferred strategy, contingent on the overall statistical significance of the attributes considered in a conditional logit model. The overall attractiveness of this strategy was compared with alternative strategies probabilistically. This was done in pairwise comparisons between the preferred strategy and all alternative strategy formulations. For each pairwise comparison, a relative probability of attractiveness was estimated as the ratio of the expected utility of each alternative strategy formulation to the sum of this expected utility and the expected utility of the most preferred strategy (for details see **Paper I**).

3.3.4.2. Monte Carlo simulation

Where quantitative data was made available (**Papers II, III, IV**), both performance and preference estimates on alternatives were generated using Monte Carlo simulation. Monte Carlo simulation is a random sampling technique for transforming input and output parameters of a given value model into probability distributions, if such parameters have previously been stochastically defined [277]. Given ranges of estimates have been assigned to model parameters with known or assumed distributions, these parameters can be modelled as statistically independent trials within a simulation experiment. For each parameter, an estimate is randomly selected from a predefined distribution and parameter estimates are then

combined to generate outcomes as prescribed by their underlying value models. This process is repeated multiple times, i.e. the experiment runs the value model through multiple trial iterations (typically several thousand times). The total number of occurrences of different parameter estimates across all iterations allows the estimation of a range of these estimates and their associated likelihood of occurrence. In doing so, random sampling helps calculate the mean and variance in the estimate of a given parameter, as well as the probability that different estimates are likely to occur within that range.

Simulation was first employed for the estimation of EID vaccine R&D pipeline outcomes and associated costs (**Paper II**). As explained in section 3.1., cost and PoS parameters were stochastically defined. To move from single vaccine candidate costs to costs accounting for PoS, the simulation drew cost and PoS estimates from their respective distributions 10,000 times, allowing each time for the sum of the product between the number of vaccine candidates, PoS and cost per candidate to be calculated as vaccine candidates (their integers) advanced through development phases. This allowed the calculation of likely pipeline outcomes given the number of vaccine candidates made available and the estimation of the mean and variance of PoS-adjusted costs expected for the attainment of these outcomes.

Second, simulation was employed for the generation of analytical outputs in the project selection (**Paper III**) and the portfolio selection problem (**Paper IV**). In both problems, given uncertainties in project assessments and heterogeneous stakeholder preferences (see section 3.1.), model parameters were subject to significant variations and were therefore stochastically defined. Consequently, it was possible for each iteration to randomly select one reviewer, and randomly select a performance estimate from their performance distribution. At the same time, each iteration randomly drew the preferences of a single stakeholder's distributions. The mean and variance of model parameters was estimated when analysing estimates across all simulation iterations.

3.3.4.3. Simulation-optimization

As discussed in the previous chapter, optimization techniques are suitable for addressing prioritization problems when these need to be satisfied in a maximizing or minimizing sense, in presence of constraints and/or additional portfolio effects (e.g. diversity considerations, etc.). In presence of multiple sources of extreme uncertainty or interdependencies between alternatives, optimization problems can become increasingly complex either due to the irregular structure of the search space or because the search becomes computationally intractable [278]. Genetic or evolutionary programming can help address problems of such complexity, where deterministic solutions (i.e. single point estimates representing global optimum solutions without uncertainty) are not possible to obtain [278, 279].

An evolutionary algorithm will generate candidate solutions to some problem via random selection and evolution of solutions to near-optimal solutions through a series of fitness-based evolutionary steps. This type of algorithm typically operates within a Monte Carlo simulation framework. The algorithm starts by randomly drawing from a population of candidate solutions. As it assigns a set of values for the decision variables (e.g. makes a binary selection, where these are specified in integer form), a simulation of several thousand iterations is conducted to optimize the constrained objective function that is dependent on parameter uncertainties. The model uses these outputs to decide what set of values it should try next for the decision variables, aiming for better optima in relation to a current solution. A

new simulation is conducted with the algorithm adapting its search through random changes to the composition of the previous solutions, i.e. selecting the "fittest" and eliminating the "least fit" candidate solutions. This process is repeated until: (1) the maximum computation time allowed has been reached; (2) the number of 'fitness' iterations allowed has been reached; (3) the maximum time allowed for fitness iterations to take place without improving on the current solutions has been reached; (4) and a minimization of differences between new *versus* previous near-optimal solutions has been achieved (known as convergence). In practice, evolutionary programming software will typically pause when conditions 1-3 are reached, asking the user if he or she would like to continue the search. The software will stop the search when condition 4 is satisfied.

Once the algorithmic search has converged to an optimal solution, the analysis of model inputs and outputs can be conducted probabilistically, i.e. their mean and variance can be estimated by analysing estimates across all simulation iterations.

Simulation-optimization was employed for the estimation of minimum EID vaccine R&D pipeline costs (**Paper II**) and for the identification of optimal vaccine technology platform portfolios (**Paper IV**). In both cases, an evolutionary algorithm iteratively searched for optimal solutions through a fitness function on candidate solutions, until convergence was achieved. In both cases, given multiple, stochastically independent parameter uncertainties, a chance constraint was introduced against which a percentile of values for the objective function could be optimized, rather than the objective function's expected value (for details see methods sections of **Papers III-IV**).

3.3.5. Dealing with uncertainty

Given that the systematic examination of uncertainty is generally a hallmark of good practice [280], various procedural and analytical techniques were undertaken to test the impact of uncertainty on model structures and outputs in the thesis.

3.3.5.1. Procedural tools

Dozens of teleconferences, email exchanges, face-to-face meetings and formal decision-making forums were employed throughout the implementation of the multi-staged EID vaccine R&D prioritization process. Collectively, these procedures helped reduce the structural uncertainty as well as improve the quality of evidence in the various models. Specifically, they allowed for decision makers and broader sets of stakeholders to: validate the definitions and structure of strategic objectives (**Paper I**); approve the final lists of criteria and their measurement specifications in the project selection (**Paper III**) and portfolio selection (**Paper IV**) problems; update performance assessments and thus improve the quality of evidence (**Paper IV**); and highlight reasons for divergence (where that emerged) between analytical outputs and actual decisions (e.g. see **Paper III**). The latter triggered the explicit consideration of interaction effects in subsequent prioritization problems (e.g. see **Paper IV**).

3.3.5.2. Analytical techniques

Deterministic sensitivity analyses

The uncertainty of model outcomes in the project selection (**Paper III**) and portfolio selection (**Paper IV**) problems was large, as reflected by both the large variances around investment alternatives' values and by the substantial overlap between their confidence

intervals. To test the contribution of performance *versus* preference estimates to variability of outcomes in the models, analyses in both problems were re-run by re-specifying preference parameters deterministically (their mean values). In both problems, these scenarios demonstrated that less than 10% of the variation in model outcomes could be explained by variations in preferences. Stakeholders were comfortable with the preference estimate distributions without a need to further explore the impact of structural uncertainty through different weighting methods.

Variability checks

In absence of economic or health-economic data, project selection (**Paper III**) and portfolio selection (**Paper IV**) problems relied solely on expert opinions for the estimation of performance measures of alternatives against criteria of interest. Given that over 90% of the observed variation in model outcomes was due to variations in performance assessments, the variability in stakeholder assessments was thoroughly examined for each criterion based on the average difference of individual reviewers' estimates from the average estimate across all reviewers (for details see methods sections and appendices of **Papers III-IV**). In both problems inter-reviewer agreement levels were satisfactory, with differences reflecting genuine differences of expert opinion.

Stochastic Dominance tests

According to portfolio theoretic assumptions (see chapter 2), stochastic dominance of portfolios can be tested through variations of mean-variance statistics. Essentially, a risk criterion is introduced, operating as a constraint in a portfolio value optimization function. A portfolio can be deemed optimal only when its value is equal or higher whilst its risk is equal or smaller in comparison to alternative portfolios.

The mean, variance, semivariance, absolute deviation, and the mean-Gini statistic were estimated for each alternative in the portfolio selection problem (**Paper IV**). This allowed for different types of stochastic dominance tests and an assessment of risk-efficiency of the identified optimization solution (for details see methods section and appendix of **Paper IV**).

Probabilistic Sensitivity Analysis (PSA)

Variations of Probabilistic Sensitivity Analysis (PSA) were conducted to test for the impact of model input imprecisions to the robustness of model outcomes in **Papers II-IV**. PSA, which operates within a Monte Carlo simulation framework, determines the likelihood that different outputs will occur by simulating the consequences of random drawings from probability distributions characterizing uncertain parameters in a model. In doing so, PSA can both help identify the most likely sources of substantial variation in model outputs and validate (or invalidate) these outputs.

PSA was used to identify the probabilities associated with different pipeline and cost outcomes in the EID vaccine R&D cost minimization study (**Paper II**), which helped examine the degree of correlation between the variance in outcomes and the uncertain parameters of the model.

Comparison of projects within each iteration of the simulation conducted in the project selection problem (**Paper III**) generated a ranking of projects, which, when analysed across all iterations, allowed the estimation of the rank probability of a project.

Pairwise comparisons between the optimal portfolio and alternative portfolios under the budget constraint generated a ranking in each iteration of a simulation in the portfolio selection problem (**Paper IV**). The probability that the optimal portfolio would outrank each of these alternatives was then estimated based on the frequency of pairwise rankings, across all simulation iterations. The composition of portfolio alternatives was also examined, based on the frequency of different projects being included across clusters of these, grouped from lower to higher probability ranges of being outranked by the optimal portfolio. This allowed for the identification of projects having the most significant impact on variation of portfolio value, with implications on the optimal portfolio's robustness.

4. Summary of results

Previous chapters presented how a prioritization framework was developed and its methods structured to address a set of interconnected problems of strategic objective setting, investment boundary setting, project and portfolio selection in the context of EID vaccine R&D. The practical necessity of establishing a new multi-stakeholder entity for investing in EID vaccine development creates an opportunity for assessing whether this framework can help stakeholders make informed, real-life decisions and how prioritization models' supportive function can evolve. The current chapter provides a summary of the evidence emerging from the implementation of the framework across the two stages of the EID vaccine R&D prioritization problem. In doing so, the chapter also illustrates how the prioritization models informed decisions in face of decision uncertainty and how they were adapted in light of learning outcomes and evolving trade-offs from their application.

4.1. Stage 1. Strategic framing

4.1.1. Strategic objective setting (Paper I)

A VFT process and an analysis of stakeholder preferences elicited through a DCE identified four strategic objectives for EID vaccine development in the context of CEPI:

- Strategic objective 1: Improve R&D preparedness, through the development of vaccines to the latest R&D stage possible, complemented by other translational R&D milestones and regulatory innovations.
- Strategic objective 2: Improve the speed of R&D response, through the availability of manufacturing capacity on demand, clinical infrastructure to test vaccine candidates, and rapid-response vaccine platform technologies for EIDs.
- Strategic objective 3: Improve market predictability, through the generation of positive externalities to businesses and to the public, the minimization of disruptions to other business or public health work, and the availability of incentives for vaccine developer engagement in EID vaccine R&D.
- Strategic objective 4: Improve equity, through the availability of vaccines to priority populations, the strengthening of low- and middle-income country (LMIC) capacity, and the promotion of shared responsibility in financing across geographical regions.

Through their preferences stated in the choice model, stakeholders expressed the desire for a strategy that prioritizes preparedness and market predictability objectives, if some importance is also placed on equity and response speed objectives (see Figure 4 in **Paper I**). Practically, this meant that priority should be given to EID vaccine development through clinical safety and immunogenicity studies in humans (phase 2a), complemented by enabling and regulatory science innovations and incentives for developers to minimize losses from their engagement. Priority should also be given to developing rapid response technology platforms, or to ensuring the availability of manufacturing capacity, or to strengthening clinical testing infrastructure. Finally, at least one of the following should be prioritized under the equity objective: measures for securing vaccine access to priority populations, improving vaccine development capacities in affected regions, or promoting the sharing of financing responsibilities across regions.

The outputs of this exercise served as the basis for the specification of goals for estimating optimal pipeline and funding boundaries (**Paper II**), within which subsequent investment decisions could be made. Moreover, prioritization models were possible to develop to support investments in priority EID vaccine development (**Paper III**) and vaccine technology platforms (**Paper IV**), aligned with the investment entity's strategic objectives identified and structured through this process.

4.1.2. Investment boundary setting (Paper II)

A combination of literature review- and survey- based approaches identified a pipeline of 224 vaccine candidates from preclinical through to phase 2 for 11 priority EIDs (see Table 4 in **Paper II**). As the first goal was to identify a maximum number of projects for successfully developing at least one vaccine candidate against each priority EID, the simulation-optimization model identified different minimum pipeline structures per disease. 7 EIDs—Zika, Ebola, Chikungunya, Rift Valley Fever, MERS, Marburg, and Lassa—had sufficient vaccine pipelines for investments to generate successful phase 2a outcomes, irrespective of PoS assumptions. The following upper boundaries on project numbers for future investment were therefore possible to set, contingent on PoS assumptions: 4 to 10 projects for Chikungunya; 5 to 9 projects for Zika; 7 to 15 projects for Rift Valley Fever; 7 to 16 projects for MERS; 9 to 18 projects for Marburg; and 11 to 21 projects for Lassa. An Ebola vaccine had already been successfully advanced through phase 2 and was therefore excluded from further analysis. Under a high PoS scenario, an upper boundary of 11 projects could also be set for Nipah. However, the successful progression of a vaccine through to end of phase 2a would be unlikely under a low PoS scenario, given the available candidates for the disease. Vaccine pipelines for Crimean Congo haemorrhagic fever, severe acute respiratory syndrome, and severe fever with thrombocytopenia syndrome comprised too few candidates for any phase 2a outcomes to be predicted through investments in these, even under a more optimistic PoS.

Setting these outcomes as pipeline constraints under the second goal of the model, it was possible to estimate the maximum investment ceiling for the successful development of a vaccine per EID: $112-150M ($34-289M range) for Chikungunya; $149-158M ($45-357M range) for Zika; $224-244M ($61-570M range) for Rift Valley Fever; $244-245M ($71-543M range) for MERS; $274-358M ($86-792M range) for Marburg; and $319-469M ($99M-1.1B range) for Lassa. Under an optimistic PoS scenario, the investment ceiling for Nipah was estimated at $469M ($99M-1.1B range). The non-attainment of the model's first goal for the remaining EIDs—Crimean Congo haemorrhagic fever, severe acute respiratory syndrome, and severe fever with thrombocytopenia syndrome—meant that cost estimates for these diseases were conditional on 18-47 new vaccine candidates becoming available at the preclinical phase (see Table 5 in **Paper II**).

The two goals of the simulation-optimization model were set as an outcome of the strategic objective setting exercise (**Paper I**) and the quantification of the preparedness objective as reflected in CEPI's business plan [281]. Given the uncertainties associated with PoS, costs and characteristics of product developers (for details see methods section and appendix of **Paper II**), the two-staged stochastic formulation of the model was able to identify optimal performance levels for each goal; albeit with wide ranges around the expected pipeline and cost estimates under each scenario considered in the model.

The outputs associated with attaining the two goals of the simulation-optimization model informed decisions in different ways. First, it was possible to identify those disease areas where vaccine development investments would have a greater chance of satisfying the organization's strategic objective targets – Lassa, MERS, Nipah, Rift Valley Fever, Chikungunya. CEPI is currently funding vaccine development against all these pathogens. Second, within each disease area it was possible to identify a pipeline and funding ceiling that could serve as a constraint in subsequent investment decisions (e.g. see **Papers III-IV**).

4.2. Stage 2. Investment framing

4.2.1. Vaccine R&D project selection (Paper III)

In order to support the attainment of strategic objective 1 (see **Paper I**), a MCDA was employed to value, rank and inform the selection of vaccine candidate projects that could improve: a) the likelihood of generating vaccines relevant for use in response to CEPI's initial priority EIDs – Lassa, MERS, and Nipah (denoted as *O1*); b) the likelihood that the technology platforms supporting these vaccines would be suitable for use in vaccine development against newly or unexpectedly emerging EIDs (denoted as *O2*).

Out of an initial list of 33 projects that expressed interest in a Call for Proposals, use of eligibility criteria and of rule-based techniques (see chapter 3) narrowed down this list to 18 projects (7 for Lassa; 7 for MERS; 4 for Nipah) selected by CEPI for an extended review. Eligibility criteria reflected principles around equitable access, cost coverage and risk sharing that had been identified as operational boundaries under the strategic objective setting process (**Paper I**). For the evaluation of the 18 projects, it was assumed that no more than 6 projects should be funded per EID, based on optimistic estimates of Phase 1 candidates required for at least one candidate to advance through to end of phase 2a (**Paper II**). This assumption was supported by an expectation that projects selected for funding would be ready to start Phase 1 development by the time of project launch. It was further assumed that no more than $300M out of $700M initial capital should be allocated to selected projects, based on organizational budgeting that reflected the relative importance of strategic objective 1 during the strategic objective setting process (**Paper I**). This assumption was further supported by optimistic estimates of funding needed to advance at least one candidate to advance through to end of phase 2a for each of these diseases (**Paper II**). With these assumptions in mind, a ceiling of 14 projects was set as an upper constraint in the selection of vaccine candidate projects.

Stakeholder consultations identified five criteria as relevant to the evaluation of projects against *O1* and *O2*: C1. Applicant Competency, C2. Technical Feasibility, C3. Manufacturing scalability & speed, C4. Use potential for target pathogens, C5. Use potential for new pathogens. Expert assessments of projects on these performance criteria suggested a substantial overlap in the confidence intervals around most projects' aggregate performance on *O1* and *O2* (see Table 2 in **Paper III**).

Stakeholders suggested different value to outcomes *O1* and *O2* generated by different projects, a non-linearity in preferences for these outcomes, and a preference for faster development timelines (see Table 3 in **Paper III**). Specifically, stakeholders attached more value to the likelihood of projects generating vaccines relevant for use in response to each of the three target pathogens – Lassa, MERS, and Nipah – than to the likelihood that the technology platforms supporting these vaccines would be suitable for use in vaccine

development against newly emerging infections. Their preferences also implied increasing marginal returns to improvements in outcomes *O1* and *O2* generated by different projects. Moreover, the discount rate on overall project value was high, reflecting stakeholders' preference for shorter timeframes within which projects could be completed.

The aggregation of value accounting for variations in performance and preference estimates resulted in a ranking of projects by value and cost-to-value that could not easily distinguish projects due to overlapping confidence intervals around these estimates. A probabilistic ranking analysis within a Monte Carlo simulation generated clear project rankings through the consideration of top 14 rank likelihoods by value *versus* cost-to-value, despite the large uncertainty in criteria performance and stakeholder preferences (see Figure 3 of **Paper III**). These findings deviated from real-life decisions mainly because of technology platform considerations. This practically meant that two projects were recommended by decision-makers that limited platform diversity into the investment though increasing the number of projects for Nipah, despite their modest value across outcomes considered in the model. Consequently, two projects were excluded that the MCDA had positioned in the top 14 by value and by cost-to-value rank likelihoods.

These findings differentiated vaccine candidate alternatives in face of significant outcomes uncertainty, informing deliberative stakeholder processes of decision-making. However, the divergence in decisions and model outputs pointed to criteria that more explicitly capture distributional considerations – i.e., what is an acceptable spread of investment across vaccine projects employing different platforms to achieve target outcomes. These considerations were explicitly accounted for when structuring prioritization models in subsequent investment decision contexts (e.g. see **Paper IV**).

4.2.2. Technology platform R&D portfolio selection (Paper IV)

In order to support the attainment of strategic objective 2 (see **Paper I**), a Portfolio Decision Analysis (PDA) was employed to support the selection of a technology platform portfolio that could maximize the likelihood of accelerated vaccine development in response to outbreaks of new infections.

As in the vaccine R&D project selection problem, equitable access, cost coverage and risk sharing principles – identified as operational boundaries under the strategic objective setting process (**Paper I**) – were translated into eligibility criteria. Use of these and of rule-based techniques (see chapter 3) narrowed down an initial list of 38 projects to 16 projects – 4 RNA projects; 4 Viral Vector projects; 3 DNA projects; 3 Protein projects; 2 gene-encoded mAb projects – selected by CEPI for an extended review.

Anchored on learnings from the vaccine R&D project selection problem (**Paper III**) and on new stakeholder consultations, the goal was to select a portfolio that maximized the likelihood of accelerated vaccine development for newly emerging infections, accounting for: uncertainty in project evaluation; and formally incorporating stakeholder preferences, including on platform diversity. It was further assumed that no more than $140M should be allocated to the selected portfolio, based on organizational budgeting that reflected the relative importance of the strategic objective 2 during the strategic objective setting process (**Paper I**).

Stakeholder consultations identified seven factors influencing platform project PoS: C1. Applicant competency; C2. Project feasibility; C3. Clinical benefit; C4. Safety potential; C5. Manufacturing scalability & speed; C6. Operational suitability; C7. Operational sustainability. Expert assessments of projects on these factors suggested a wide range of platform project PoS estimates, but also a significant overlap between these (see Figures 2a-c in **Paper IV**).

Stakeholders suggested different preference to the probability of each platform type generating at least one successful rapid response platform project, and a non-linearity for preferences in this probability (see Table 4 in **Paper IV**). Specifically, stakeholders attached more value to the probability of at least one successfully developed project on RNA and on Viral Vector platforms than on DNA, Protein or gene-encoded mAb platforms. Stakeholders also suggested consistently decreasing returns to investing in increasing the probability of at least one successful project of a single platform type. For instance, stakeholders preferred an improvement of 0% to 30% in this probability for RNA platforms to the same gain in this probability for Viral Vector or other platforms. However, once exceeding 30%, the incremental return on this probability for RNA became less, justifying diversifying the portfolio into other platform types (for details, see section 3.2 in **Paper IV**).

The aggregation of portfolio value accounting for PoS uncertainty and platform preference trade-offs resulted in a marginally superior optimality frontier by value-to-budget in a simulation-optimization model than in a simpler alternative – the frontier that would have been generated if projects were ranked by expected PoS-to-Cost, then incrementally added to the portfolio without accounting for whether the resulting portfolios would maximize portfolio value under different budget constraints. More specifically, the optimal portfolio generated by this model under the $140M constraint – composed of the two best performing projects under each of the platform types RNA, Viral Vector, and Protein – was also the recommended portfolio by decision-makers to CEPI. However, the portfolio that CEPI finally approved excluded 1 Viral Vector and 1 Protein project from this portfolio, following on further due diligence of the recommended projects by internal CEPI expert teams.

Although the CEPI approved portfolio was also positioned on the optimal value-to-budget frontier (see figure 4a in **Paper IV**), various means of variance analyses suggested that the optimal portfolio was stochastically dominant to this portfolio as well as all other portfolios under the $140M constraint (see figures 5 and 6 in **Paper IV**). A probabilistic sensitivity analysis confirmed the optimality of the model solution, but also indicated high sensitivity to the downside risk of two out of the six projects comprising this portfolio (see figures 7a,b in **Paper IV**); which were eventually not approved for funding by CEPI. This raised questions about the robustness of the PDA solution relative to CEPI's formal attitude to portfolio risk.

Whereas it was not within the PDA's scope to support due diligence of recommended projects and CEPI's follow-up decisions, the probabilistic sensitivity analysis pointed to the importance of further due diligence on highly risky projects before actual investments were initiated. Importantly, this finding speaks to the need of making preferences explicit about levels of acceptable risk in portfolios as well as in projects, in face of substantial outcomes uncertainty and portfolio interaction effects. This could include, for instance, data on how decision makers trade-off increasing expected portfolio value and increasing variance around this value, and data on the acceptable level of outranking probability. Practically, this finding

also points to the importance of learning loops through experience-based feedback resulting in periodic updates of previous investment decisions, as more information emerges about project strengths and risks.

5. Discussion

5.1. Key findings

This PhD thesis reported the development and application of an integrated prioritization modelling framework for addressing a series of strategically interconnected decision problems in EID vaccine development. There are three key sets of findings that can be drawn from the thesis. First, it is possible to develop a coherent framework to inform the appropriate design of prioritization models that address related decision problems within a common strategic frame. The framework presented in this thesis demonstrates how prioritization modelling can benefit from theoretical foundations, particularly as these emerge from utility and portfolio optimization theories of decision making. In doing so, the framework highlights the need for adaptability of prioritization models to changing problem characteristics, while compliance is maintained with procedural and axiomatic principles around stakeholder engagement, problem structuring and model specification within an overarching strategic frame. Moreover, it does this through the integration of various normative and methodological perspectives to health product development prioritization, without attempting to impose strict normative judgements on some methods being more useful over others.

Second, it is possible to employ such a framework to generate evidence to inform EID vaccine R&D priorities and investment decisions through the systematic combination and adaptation of procedural and rigorous analytic tools. In terms of setting the strategic frame, it was possible for values to be structured – despite the multiple stakeholders and their diverse perspectives – and some quantitative thinking about trade-offs to bring strategic decisions stemming from CEPI's social bargaining processes closer to actual commitments for action (**Paper I**). The outputs of the VFT process and choice model were endorsed as part of CEPI's business plan and new investment opportunities were launched, aligned with these outputs; their budgets reflecting the relative importance of strategic objectives in the DCE. Building on the outcome of the strategic objective setting exercise, it was possible to generate EID vaccine development cost estimates by combining pipeline and cost information in a simulation-optimisation model, demonstrating investment boundaries in face of cost and PoS uncertainties (**Paper II**). These outputs informed the prioritization of pathogens against which subsequent investments would be made; with more funding allocated to date to Lassa, MERS, and Nipah, and some funding allocated to Rift Valley Fever and Chikungunya [19].

In terms of making investment decisions, it was possible to anchor a MCDA on objectives and boundaries set in the strategic frame and use this to support the prioritization of vaccine R&D investments in face of project performance uncertainty and variance in stakeholder preferences (**Paper III**). The use of a Monte Carlo Simulation reflected the uncertainty in rank probabilities that distinguished Lassa, MERS and Nipah vaccine projects, and that were broadly consistent with actual decisions. Learnings from deviations between model outputs and decisions due to structural limitations of the MCDA allowed for a PDA to more accurately reflect decision-maker preferences to fund a diverse portfolio of platform projects for newly emerging infections (**Paper IV**). Whereas a probabilistic sensitivity analysis on these outputs raised questions about the robustness of the PDA solution, final decisions validated these concerns, following on further due diligence on projects.

Third, the results of the application of these models suggest new evidence on EID vaccine development objectives, costs, risks and preferences. In terms of objectives, preparedness emerged as the highest priority, but it would be more desirable if advanced in parallel with market predictability, response and equity objectives. The average cost of successful EID vaccine development through end of phase 2a was estimated at up to $319–469M ($137M–$1·1BN range, contingent on PoS assumptions), requiring investment in 11 to 21 preclinical candidates to account for risks of project failure. However, investment is likely to be two to three times lower for pathogens with more vaccine candidates at advanced development stages – e.g. Chikungunya, Zika, Rift Valley Fever, MERS, Marburg.

The average PoS of EID vaccines through end of phase 2a was estimated at 33% (14-66% range) – as demonstrated by expert assessments on a number of Lassa, MERS and Nipah vaccines (see Table 2 of **Paper III**) – falling well within the min-max range of published benchmarks for vaccine candidates entering clinical development (see Table 1 of **Paper II**). When investing in vaccines, there is more value to this likelihood than to the likelihood that the technology platforms supporting these vaccines will be suitable for vaccine development against newly emerging infections.

Rapid response platform project PoS through end of phase 1 is low but also varies according to the platform type on which projects are being developed: <1-36% for Viral Vectors; <1-26% for Protein; <1-23% for RNA; <1-12% for DNA; <1-7% for gene-encoded mAb. There is more value to investing in RNA and Viral Vector platforms for rapid response to newly emerging infections than to DNA, Protein or gene-encoded mAbs. However, a diversified investment approach across multiple platforms is seen as justified in face of substantial platform PoS uncertainty and diminishing returns in investing in projects of a single platform type.

5.2. What is known on the topic and what this thesis adds

Prior to the formation of CEPI, the evidence on EID vaccine development priorities and investments had been scarce (for details, see discussion sections in **Papers I-IV**). This included evidence gaps both on investment alternatives, their expected costs and performance, and on values regarding strategic priorities and investment trade-offs. However, new evidence from the world's experience with COVID-19 is gradually emerging, as this relates to EID vaccine development priorities and strategies including on vaccine access [27, 282-285], pipelines and costs [7, 286-288], timelines and success rates of R&D efforts [289]. In addition, the literature on methods to support broader health product development prioritization problems is large, indicating an increasing use of multi-criteria models across diverse application domains (see Chapter 2 for a detailed review). Collectively, this evidence base highlights the importance of appropriate problem structuring and the consideration of preferences, uncertainty and practical constraints when designing prioritization models within dynamically evolving contexts.

With methodological insights and evidence gaps from the literature in mind, two sets of contributions can be drawn from the thesis around evidence and the experience using

methods to elicit this in order to support EID vaccine R&D priorities and investment decisions.

5.2.1. Evidence contributions

In terms of strategic objectives, the thesis clearly highlights the relative importance of preparedness and that this cannot be disassociated from adequate attention also to market predictability, response speed and equity objectives. The relevance and impact of this strategic framing has become apparent by the world's positioning and accelerated vaccine development efforts in response to the COVID-19 pandemic [18, 27].

Second, the research presented in this thesis provides new cost estimates for EID vaccine development (for a summary, see section 5.1; for details, see **Paper II**). The scale of vaccine R&D pipeline structures and associated investment needs has not been made explicit before. The cost estimates reported in **Paper II** highlight how significant the pipeline gaps and funding challenge are for optimizing EID vaccine R&D preparedness. This analysis identifies several disease areas for which the upstream vaccine R&D pipeline today is insufficient and highlights the need for entry of new vaccine candidates into preclinical development if the chances of minimum vaccine R&D preparedness targets are to be improved.

Third, the thesis suggests new PoS estimates for EID vaccines (**Paper III**) and technology platforms (**Paper IV**), where such estimates had previously been absent from the literature (for a summary, see section 5.1). In doing so, the thesis identifies and quantifies specific aspects of PoS, as these relate to technical and operational feasibility of projects, offering specific definitions for vaccine and platform PoS assessments that are largely omitted from the literature.

5.2.2. Methodological contributions

The thesis highlights modalities and merits of different procedural and analytical techniques employed to support the EID vaccine R&D prioritization problem, as its characteristics evolved across stages. Specifically, five sets of reflections can be drawn that provide grounds for the assessment of appropriateness of methods to support prioritization efforts within an integrated framework.

(1) Adaptability of problem structuring techniques to changing problem characteristics

Choice of problem structuring techniques within strategically interconnected problems will depend not only on problem characteristics (e.g. stakeholders, alternatives, criteria) but also on how these characteristics evolve across stages of the problem. For instance, procedural tools accounting for principles on stakeholder selection and participation will be important in early stages of ill-defined problems. Their application may be less critical once such principles (and stakeholders) have been rooted into the operational procedures of the investment entity.

Goal programming can help specify the boundaries of investment opportunities within which strategic objectives can be operationalized. However, it is only likely going to be a useful problem structuring technique if the goals adequately translate previously identified objectives into some quantitative target measures.

Assuming stakeholders have been identified, analytical techniques for problem structuring will vary depending on whether alternatives and fundamental values have already been

defined. Means-ends mapping is a useful operational implementation of VFT in strategic decision contexts where neither alternatives or values are established, albeit time consuming, cognitively cumbersome and visually complex. Where alternatives and fundamental values have been specified, simpler rule-based techniques for criteria structuring and screening of alternatives can be applied, assuming some form of discipline is desired that adheres to rational decision-making.

(2) Overall compliance with theoretical assumptions

Where multiple criteria characterize the prioritization problem, a MCDA model specification will be appropriate as it encourages compromises to be made explicit whilst offering a rational structure for doing so. As highlighted in chapter 2, value-based MCDA models will be more appropriate where rational preferences are assumed and where decisions are marginal, demanding precision and consistency of preference orderings in repeated decision settings. Specifically, if preferential independence between criteria is satisfied, value-based MCDA models can take the additive form (see section 3.3.2.). With these assumptions and properties in mind, models representing the strategic objective setting (**Paper I**), project selection (**Paper III**) and portfolio selection (**Paper IV**) problems were possible to build through an appropriate structuring of criteria in line with the additive multi-criteria value paradigm.

It should be noted that although a member of the value-based paradigm [149, 290], AHP will be challenging to apply, even though it is often used in health product development prioritization problems in practice (see chapter 2). AHP was intentionally not considered in the framework for two reasons. First, it has the potential of violating the rule of transitivity in preference orderings, or what in social choice theory is called the independence of irrelevant alternatives [291-293]. Given a set of criteria has been established, preference orderings in an AHP model are not built on the relative worth of changes between levels of performance on criteria but on the relative worth of alternatives on these. A weight in AHP is therefore causally related to the total set of alternatives being considered on each criterion. Consequently, inconsistencies in preference orderings (i.e. violations of the transitivity rule) are likely as alternatives come in or out of the decision space, inducing rank reversals between alternatives remaining in the decision set. Theoretically, this should not be much of a concern in one-off problems but poses challenges in repeated problem contexts where alternatives move in and out of the investment space on an ongoing basis, such as in EID vaccine development.

Second, the use of ratio scales for stating preferences in AHP is problematic as it assumes the existence of a natural reference point against which comparisons can be made (e.g. a natural zero when measuring mass or length) [149]. This suggests an absolute order in the strength of preferences (e.g. alternative A preferred x times as much as alternative B). Such preference structures are rarely the case in decision problems where reference points are strongly influenced by their framing [294] and marginally related [236].

(3) Flexibility in value model formulations

Within the additive multi-criteria value paradigm, model variations will depend on the nature of the alternatives (e.g. interactions necessitating portfolio- level re-formulations of

alternatives), and scales used to define criteria (e.g. quantitative and continuous *versus* qualitative or discrete).

In the strategic objective setting problem (**Paper I**), alternatives were combinations of strategic objectives' characteristics that were only qualitatively defined. In absence of continuously scaled definitions on criteria, models making use of partial values and scaling factors were not possible to use. Conditional logistic regression based on a DCE was deemed appropriate as the model allows for criteria to be measured on an arbitrary scale and represented by a limited number of discrete levels (e.g. low, medium, high degree of some criterion's attainment) [256].

Where alternatives were well defined and independent as well as described by quantitative measures of performance against criteria on continuous scales (**Paper III**), an additive multi-attribute value function was possible for ranking alternatives until a given constraint was exhausted. Where alternatives were characterized by interdependencies and thus the decision space exponentially increased (**Paper IV**), a multi-attribute value optimization function was deemed more appropriate for identifying an optimal subset of alternatives, given some constraints.

(4) Consistency of preference elicitation methods

Stated preference and stated choice methods employed in this thesis share common properties [235, 236, 295], which are useful when precision is desired to discriminate between alternatives. However, they go about eliciting preferences in different ways, with analytical and practical implications.

First, they elicit within- criterion and between- criteria weights differently (see section 3.3.3.2.), resulting in either single preference coefficients, or both partial value and relative value coefficients within a value function. In a DCE, trade-offs between criteria and between levels of performance within criteria are made simultaneously through the comparison of whole alternatives. Assuming stakeholders think rationally about the criteria and that there are enough levels in a model, the resulting preference coefficients should both display interval properties and serve as scaling constants [235, 236, 272]. In stated preference methods, partial values are typically estimated separately (e.g. via the bisection method) from the elicitation of relative values (e.g. via swing weighting and/or trade-off methods). Partial value functions naturally generate interval scales and relative values are typically interpreted as scaling constants in a value model.

Second, methods pose variable levels of cognitive and practical demands on stakeholders. Questioning procedures in DCEs are typically less demanding or time-consuming, partly because choosing between alternatives is more intuitive than having to describe a partial value function [236, 256]. However, the sample of stakeholders in relation to the number of criteria and levels considered in a model will largely determine the suitability of these methods in practice [273]. Because of the stepwise nature of stated preference methods, questioning procedures become increasingly demanding the more criteria are being considered, especially if stakeholders are geographically disbursed, necessitating questions to be administered online. Where choices for which numerical consequences could be established may not be easily obtained (e.g. in portfolio selection problems), the cognitive demands imposed on stakeholders will substantially increase. Stated preference elicitation

approaches may not be desirable from a practical point of view, if stakeholders' time is limited [235] or their ability to think numerically is constrained [296].

Given their relative strengths and limitations, choice between these types of methods will depend less on theoretical, and more on cognitive and practical limitations encountered in different decision problems. Given both types of methods had to be administered online, choice of method between the project selection (**Paper III**) and portfolio selection (**Paper IV**) problems was driven primarily by differences in the number of criteria considered and sample size.

(5) Balancing procedural and analytical techniques for handling uncertainty

The EID vaccine R&D prioritization problem is characterized by deep and multiple uncertainties. It is therefore logical for such uncertainties to be dealt with in different ways within prioritization models. From a technical point of view, stochastic models help capture the range of likely outcomes and their sensitivity to parameters characterized by imprecise measures and variability in data sources for their estimation [106, 297]. Simulation-based techniques explicitly capture such uncertainties through ranges instead of misleadingly precise point estimates. The variance in outcomes that surfaces from these methods facilitates the use of different techniques to test for dominance or robustness of prioritization model outputs. However, as such techniques simply compute the results of underlying models, they are also naturally expected to share any shortcomings of these models [110].

Stakeholder procedures are essential complements to technical approaches to handing uncertainty in prioritization models. They allow for the testing of stakeholders' intuition and their exploration of alternative model structures or problem solutions [149]. For instance, stakeholder engagement early in problem structuring can help identify areas of disagreement with model assumptions and influence how criteria are defined, or how weighting methods are applied. Once model outputs have been generated, processes to familiarize stakeholders with the sources and impact of uncertainty in prioritization models can increase their confidence in model outputs.

Inevitably, whether models and their outputs hold in practice will depend on the degree to which they represent the reality of a shared understanding of the problem by the stakeholders involved [298]. Consequently, a balance will need to be achieved between stakeholder confidence in models and their outputs *versus* complexity of model structures and analyses, including uncertainty implications [238].

5.3. Limitations

The research presented in this thesis comes with a number of limitations. Whereas limitations specific to prioritization model applications are discussed thoroughly in **Papers I-IV**, this section focuses on aspects associated with the overall development of the prioritization framework and its application.

5.3.1. Framework development

The perspectives feeding into the development of the prioritization modelling framework are limited primarily to the evidence emerging from the health product development

prioritization literature. It is my view that this body of literature is representative enough to serve the purpose of identifying the types of prioritization problems, the types of criteria, and the types of processes and analytical tools that ought to be considered when designing prioritization models with a product development focus. I argue this because the theoretical and empirical foundations underpinning this literature are sufficiently broad to capture a variety of norms from ethical theories, decision analysis and operations research, which are not just limited to product development or to health alone. Indeed, the same decision analytic and operations research norms and methodological perspectives become apparent in reviews of the R&D prioritization literature more broadly (e.g. see [110, 299-301]); though the menu of optimization, uncertainty or preference measurement techniques in these reviews is wider. Moreover, whereas it would become an intractable exercise to review all approaches within the broader health research prioritization literature [104], which is substantial, several reviews [58-63] indicate a similar variety of policy, governance and ethical norms that become apparent, though less frequently, in the health product development prioritization literature. It is also worth noting that the list of criteria and other valued goals become much longer in these broader bodies of the literature but are probably also less relevant to health product development, as different types of priority setting questions and problems are often being addressed.

Nonetheless, there is one type of question that policy and ethical strands of health priority setting theory and practice pose, which the framework developed in this thesis does not explicitly address: to what extent are prioritization processes legitimate and prioritization outputs justifiable against principles of fairness or equitability, societal relevance or need? This omission is because legitimacy, societal relevance and fairness of prioritization were assumed implicit in the formal formation of a globally relevant organization to address an area of urgent social need. Where these conditions do not apply, e.g. in less formal disease priority setting contexts, the development of prioritization frameworks would benefit from a more thorough investigation of processes to capture societal value expectations as well as ethical externalities for stakeholder groups and target users.

5.3.2. Framework application

First, success in application of the framework is hard to define and measure. There is generally little evidence in the literature of the validity of priorities generated through prioritization models. And there are few reflections on whether the generated priorities are contingent on choice of method or how they result in improvements to important outcomes (e.g. see [62]). It is therefore reasonable to assume that merits cannot be adequately attributed to any method unless these are also repeatedly tested, validated and updated in practice. Practical validity should not be merely viewed as conformity of model outputs to actual decision making but more importantly as the degree to which real-life preference orderings are captured in a manner consistent with the requirements of the model being employed [236].

The choices and uses of prioritization models in this thesis are pragmatic. However, they are by no means expected to be the only options as choice and use of methods is a process in its own right and should include the impact of learning and adaptation through feedback. This learning and adaptation becomes particularly apparent between the project selection (**Paper III**) and portfolio selection problems (**Paper IV**), and in the way that decision criteria were updated, interdependencies between alternatives were acknowledged, and a calibration step

of initial performance assessments was added. Building on the lessons from the project selection model application, these changes led to a better alignment between model outputs and decision-maker preferences for portfolio selection. Indeed, deviations between model outputs and decisions should be anticipated even if not desired, and their sheer presence should not be viewed as good enough a reason for invalidating a model. Instead, it is the understanding of the reasons behind any deviations that may help explain to what extent prioritization models are valid, and to what extent they require updating to more effectively support real-life decision making. One benefit of using an integrated framework of prioritization modelling in repeated decision contexts, such as that of EID vaccine development, is the opportunity for continuous learning and periodic adaptation of models, without loss of relevance to an overarching strategic frame.

Second, practical limitations ought to be acknowledged. As chapters 2 and 3 highlighted, choice of analytical tools to support real-life prioritization problems will be dependent on both the nature and the level of awareness of the problem; as well as practical constraints, such as time availability, sample sizes, cognitive burden, and diversity in perspectives of stakeholders involved in the prioritization process. Real-life constraints of this nature will naturally limit the degree of sophistication that can be built into prioritization models, if models are to become an accepted way of decision support in practice. Methods employed in the thesis were relatively simple, drawing on well-established methodologies from the literature with low modelling complexity, especially in comparison to what is available in specific literature niches. Analytical tools, especially as these related to preference elicitation, were tailored according to the number and diversity of stakeholders involved, their cognitive capacity, time availability and geographical disbursement.

Striking a balance between modelling sophistication and practical utility is not easy. But there is also a learning curve that stakeholders go through as they familiarize themselves with prioritization models. An advantage of prioritization models in repeated decision contexts is that they can gradually increase in sophistication to more accurately reflect problem complexities as stakeholders improve their understanding and recognize the benefits from working with more accurate models. A practical challenge however is maintaining consistency of the models as these are adapted to address new problems within repeated decision contexts, especially as sophistication requirements increase. A certain level of consistency between models was maintained in the thesis, perhaps because of the ‘universality’ of the criteria used and their linkage with an overarching strategic frame. Another reason for this was perhaps the fact that the same stakeholders were, to some extent, engaged throughout all stages of the EID vaccine R&D prioritization problem. A third factor was perhaps the fact that the decision analyst was a member of staff of the investment entity, championing the use of methods internally and generally being available to resolve questions and concerns throughout the prioritization modelling process. More research would be needed to understand to what extent practical constraints limit the appropriateness of prioritization models and whether biases in method choice and implementation are influenced by the relationship between the decision analyst and the decision maker.

Furthermore, prioritization modelling approaches vary considerably in how they balance human judgement and use of evidence to generate quantitative inputs to the analysis, as demonstrated by the literature review in Chapter 2. The approaches presented in this thesis adopted a quantitative approach to prioritization modelling within an integrated frame.

Primary emphasis was placed on analytical support aspects, and less so on stakeholder engagement process (e.g. how to design a workshop to elicit performance estimates or value judgments from stakeholders). Whereas further work would be required to determine the appropriate prioritization modelling approach in different settings, Good Practice guidelines have recently been developed [104, 106, 155, 239, 240], which this thesis has adhered to when designing the reported methods.

5.3.3. Evidence from framework's application

A key limitation of multi-criteria prioritization models that account for stakeholder preferences is that the evidence they generate is often decision context- specific. This relates to both the types of criteria stakeholders identify as relevant for addressing a problem, and to the value stakeholders place on these when ordering decision alternatives against them. In the context of the EID vaccine development prioritization problem reported in this thesis, strategic objectives (**Paper I**), decision criteria and preference trade-offs (**Papers III-IV**) were deemed relevant and served a practical, supportive function to the stakeholders involved. However, the exclusion of stakeholder groups is expected to have an impact on objectives and criteria considered in a prioritization context, affecting the generalizability and applicability of prioritization outcomes across different settings. This raises the question: whose values should be used to structure prioritization problems? For instance, it is often argued that in health settings it is the preferences of the public that should be employed to allocate resources [65, 66, 302-304]. This thesis argues that the added value of prioritization modelling rests mainly on its methods for structuring and elicitation of values as these become relevant to stakeholders that carry decision-making authority for investments, ensuring this way accountability in decision making. Indeed, if applied appropriately, prioritization models can justify differences in criteria while ensuring analytical rigor and transparency in a variety of decision-making contexts. However, in an international multi-stakeholder setting that prioritizes public, private and philanthropic sources of funding for the public good, how representative are the values of those stakeholders engaged in driving priorities for R&D investment? Further research and discussion of whose value should inform strategic objectives, decision criteria and choices for investment is required to further test and validate the legitimacy and representativeness of some of this thesis's findings.

A second limitation on evidence relates to cost and PoS estimates reported in the thesis. These estimates were driven mainly by forward-looking projections, in absence of any substantial data on realized EID vaccine R&D expenditure or performance in the literature. They also assumed largely sequential pathways for vaccine development as well as presence of financial and operational challenges that are common in any vaccine development under normal conditions. Accounting for the uncertainty that characterizes the assessments, as reflected by the reported confidence ranges, these estimates provide an overall cost and risk tag for bringing projects against priority EIDs successfully through to end of R&D target endpoints. Although both types of estimates fall within range of published benchmarks, factors may well drive realised estimates either way – downwards or upwards – compared with the cost and risk expectations provided in this thesis. This point is exemplified by the COVID-19 response experience. Here, substantial investment and global support has been provided to developers for parallel vaccine development [18, 305]. This has so far resulted in the minimization of business and financial risks for vaccine developers; and in a higher technical and regulatory success rate over an unprecedently compressed time horizon, as

demonstrated in particular by the RNA and Viral Vector vaccine approvals [306-308]. Practically, these discrepancies point to the importance of ongoing research on costs and risks and to the caution in extrapolating from predictive estimates in different decision contexts as well as different development pathway paradigms.

5.4. Implications for future research and practice

Drawing from the research findings and its limitations, two sets of implications can be considered for future research and for policy and practice.

5.4.1. Implications for research

First, more research is needed to test and validate the prioritization framework. This should include a better understanding of practical constraints and biases on uptake of models by practitioners to better bridge theory with practice. It is worth noting that while the framework applications faced methods challenges, requiring a novel combination of methods, performance of these methods were not formally tested. Testing and validation will also be required in different decision contexts within EID vaccine development. This may require an update of current key information e.g. on PoS and cost estimates of vaccines and technology platforms, or of sources of preference e.g. on attitudes to risk, if this is to become more globally relevant to policy makers and practitioners beyond the context of application of this thesis. Finally, broader societal value expectations will need to be captured, as well as ethical externalities for stakeholder groups and target users, especially in more exploratory contexts of re-assessing strategic objectives and priorities in EID vaccine development, post-COVID-19.

Second, given the world's ongoing experience with COVID-19, more research will be needed to understand the direct and indirect impact of COVID-19 on: (1) strategic objectives for EID vaccine R&D; (2) costs of vaccine development; (3) PoS estimates for both vaccines and technology platforms; (4) stakeholder preferences for prioritizing new EID vaccine development investments. Importantly, the COVID-19 pandemic exemplifies the need for prioritization models to better capture health outcomes and socio-economic implications from investments. This has been challenging to do in the context of this thesis, partly because of the extreme uncertainties around disease progression in event of sporadic and unpredictable outbreaks of EIDs. Partly this was also a reflection of stakeholder views on what criteria and outcomes mattered for models to serve a practical, supportive function to real-life investment decisions. However, given the disruptive impact that COVID-19 has had so far on economies and health systems worldwide, more explicit health-economic models may be needed to assess resource allocation trade-offs between EIDs and other areas of importance in global health in the future.

Third, more research is needed to test the practical utility and validity of the prioritization framework across different application domains. The framework presented in this thesis could be relevant to any newly established organization or collective entity responsible for R&D investment and coordination in face of decision uncertainty, especially where there are clear societal needs but poor market incentives. For instance, it would be interesting to see through such new applications to what extent the framework's basic structure remains

resilient *versus* how prioritization models adapt procedural and analytic tools to different problem characteristics, such as other decision criteria and stakeholder trade-offs.

5.4.2. Implications for policy and practice

The thesis illustrates how prioritization of investments in EID vaccine development can benefit in practice from:

- clear formulation of strategic objectives and funding boundaries to set the context in which consequent decisions can be made;
- rational and transparent decision support tools that are tailored to identified stakeholder needs, balancing rigor with a practical, supportive function.

For these reasons, the prioritization framework presented in this thesis lays some foundations for how to support repeated decision-making in EID vaccine development. This is further exemplified by adaptations of reported models to support additional investment opportunities by CEPI for other technology areas beyond the scope of this thesis – e.g. Rift Valley Fever and Chikungunya vaccines; rapid response technology platforms; and COVID-19 [309] – capturing performance of investments along a common scale of measurement and measuring value against a common set of fundamental objectives.

It is likely that the framework will prove useful also for newly established entities supporting R&D more broadly; where a structured approach to planning and management of investments will be needed, and where societally valued goals are present but monetary gains are less important. In such complex settings, prioritizing investments can benefit from clear strategic frames within which multi-criteria models can meaningfully support consequent R&D decisions. As new strategies and governance structures for R&D continue to emerge, it will be important to apply such techniques to set priorities and prioritize investments through participatory and transparent means.

6. Conclusion

Vaccines for EIDs are needed to respond effectively to epidemics and avert global crises. This thesis has offered an analytical framework and a new evidence base around costs, risks, and value considerations for prioritizing investments in EID vaccine R&D. It has done so through the development and application of multi-criteria prioritization models within an integrated frame to support decisions of an EID vaccine R&D funding organization operating in an international multi-stakeholder setting.

The findings suggest that decision analytic and optimization modelling methodologies can rationalize the allocation of resources in a complex global health R&D prioritization context, characterized by: strong stakeholder interests and conflicting priorities; uncertainty in funding needs to satisfy strategic R&D portfolio targets; uncertainty in performance of R&D investment alternatives; and portfolio-level interdependencies. As the global governance structure for EID R&D investment continues to emerge in response to COVID-19, it will be important to apply an appropriate prioritization framework to elicit clear priorities through systematic means, and in doing so, to improve the desired EID mitigation efforts.

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APPENDIX – PAPERS I-IV

I. Gouglas D, Hoyt K, Peacocke E, Kaloudis A, Ottersen T, Røttingen JA. Setting Strategic Objectives for the Coalition for Epidemic Preparedness Innovations: An Exploratory Decision Analysis Process. INFORMS Journal on Applied Analytics. 2019; 49(6):397-459; https://doi.org/10.1287/inte.2019.1011.

II. Gouglas D, Thanh Le T, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen JA. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. The Lancet Global Health. 2018; 6(12): e1386-e1396; https://doi.org/10.1016/S2214-109X(18)30346-2.

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PAPER I

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Setting Strategic Objectives for the Coalition for Epidemic Preparedness Innovations: An Exploratory Decision Analysis Process

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Abstract. The Coalition for Epidemic Preparedness Innovations (CEPI) was established in 2016 in response to the West African Ebola epidemic. The vision for CEPI is to develop vaccines to prevent future emerging infectious disease outbreaks from becoming humanitarian crises. Leaders from governments, foundations, industry, and civil society convened earlier that year to formulate strategic objectives to support CEPI's first business plan. We demonstrate how decision analysis can support a rational and transparent approach to strategy formulation that accounts for and ranks the preferences of multiple stakeholders in an international coalition setting. We use value-focused thinking to identify and structure objectives and we combine this with an explorative discrete-choice experiment to elicit preferences between objectives. Our findings suggest that decision-analytic methodologies can rationalize strategic objective setting in a highly complex global health research and development planning context characterized by strong stakeholder interests and conflicting priorities.

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Epidemics of emerging infectious diseases (EIDs) are a growing threat to global health and prosperity. Recent outbreaks of Ebola, Zika, MERS (Middle East respiratory syndrome), and SARS (severe acute respiratory syndrome) have caused significant mortality, morbidity, and socioeconomic disruption across multiple continents (Kieny et al. 2016, Sands et al. 2016). Timely vaccine development can avert humanitarian crises and limit the socioeconomic damage associated with these outbreaks (Coalition for Epidemic Preparedness Innovations 2016). However, safe and effective vaccines for most epidemic infectious disease threats are lacking (Plotkin et al. 2015, Gouglas et al. 2018).

The World Health Organization (WHO) has argued that without coordinated investments, the world will not be able to effectively respond to future epidemics (Kieny et al. 2016). Along similar lines of reasoning, various post-Ebola outbreak reports have called for either vaccine-specific or broader product-focused research and development (R&D) funds (Plotkin et al. 2015, United Nations Secretary General 2016), financing facilities (Moon et al. 2015), partnerships (Norheim et al. 2014), or strategies (Center for Infectious Disease Research and Policy 2015) to improve global preparedness against EIDs in the future.

To address these challenges, leaders from governments, intergovernmental organizations, foundations, industry, and civil society came together in 2016 to explore new ways to drive vaccine R&D for priority EIDs (Brende et al. 2017, Røttingen et al. 2017). Between February and July of 2016, three expert task teams convened to assess problems and potential solutions for (1) pathogen prioritization, product development,

and regulatory pathways; (2) partnership models; and (3) financing strategies (Røttingen et al. 2017). Several authors of this article were initially involved in the task team responsible for identifying appropriate partnership models and bringing together all task team policy recommendations into a strategy document to establish the Coalition for Epidemic Preparedness Innovations (CEPI; Coalition for Epidemic Preparedness Innovations 2016).

Task team proceedings revealed the need to identify and agree on a number of well-defined strategic objectives and operating principles for CEPI. Given the large number of stakeholders with diverse perspectives (over 100 stakeholders from industry, government, foundations, and civil society), efforts to generate consensus were at risk for devolving into a social bargaining process that could generate results that were not representative and/or were ambiguous. In an effort to lend transparency, accountability, and clarity to this exercise, we implemented a combination of value-focused thinking (VFT) and an exploratory discrete choice experiment (DCE) to identify, structure, and explore the relative importance of CEPI's strategic objectives.

An Exploratory Decision-Analytic Approach

VFT is a long-established decision-analytic approach appropriate for identifying and structuring objectives in strategic decision problems (Keeney 1992). Such problems—framed in the management literature as wicked problems of organized complexity (Rittel and Webber 1973, Ackoff 1974, Mason and Mitroff 1981)—reflect states of extreme complexity, whereby the problems and solutions are neither obvious nor easy to agree on (Belton and Stewart 2010); multiple stakeholders are involved with multiple and often conflicting objectives (Montibeller and Franco 2010, Punt 2017); and stakeholder perspectives are negotiated through social bargaining, that is, intense dialogue processes (Thomas 1984, McMillan and Overall 2016).

The premise of VFT is that early and systematic attention to stakeholder values can lead to meaningful descriptions of objectives and justifications on why these are important, including, where possible, associations of their relevance to other objectives. Analytically, VFT defines values within a given decision context as explicit statements of what one wants to achieve (Keeney 1994), distinguishing between two types of objectives: (1) fundamental objectives, which characterize the essential reasons or endpoints for a given decision, and (2) means objectives, which enable the achievement of fundamental objectives (Keeney 1992).

A number of tools and techniques can be applied to distill the relationship between means and end objectives in VFT frameworks, several of which are reviewed in Parnell et al. (2013) and Kunz et al. (2016). Evidence of the method's application in setting strategic objectives is rich across several domains (Keeney and McDaniels 1992, Keeney 1996, Parnell et al. 1998, McDaniels and Trousdale 1999, Tan et al. 1999, Yoo et al. 2001, Bullock et al. 2008, Morais et al. 2013, Simon et al. 2014, Kunz et al. 2016 Abuabara et al. 2017). However, VFT has rarely been explicitly applied in the health space. Its limited application, for example, in evidence-based medicine may be because values have been traditionally seen as sources of bias that can and should be controlled for (Kelly et al. 2015, Neumann and Cohen 2015). This may also be because a great deal of thought has already gone into the concept of value in health, with some consensus as to what values should be achieved (Porter 2010). Consequently, the benefit of using tools to support problem structuring in a priori relatively well-defined problems is expected to be only marginal (Marsh et al. 2016). However, VFT was recently applied to help construct a multicriteria evaluation model for new medicine reimbursement decisions (Angelis and Kanavos 2017), and it has been proposed as an analytical approach to support strategy formulation for healthcare management through means–ends objective structuring (Ginter et al. 2013).

Whereas VFT can help identify and structure objectives for strategic planning, specifying the relative importance of such objectives requires appropriate preference elicitation techniques. There are numerous preference elicitation techniques in the health literature (Marsh et al. 2016). One such methodology is the DCE (Bridges et al. 2011b), which is particularly helpful in the absence of revealed preference data (Mangham et al. 2009). DCEs have become increasingly popular in health valuation (Thokala et al. 2016) and priority setting (Marsh et al. 2012, Franken and Koolman 2013, Grepin et al. 2018). They can be relatively quick preference elicitation instruments (Lagarde and Blaauw 2009), which is an advantage in time-constrained strategic decision-making contexts.

To our knowledge, no explicit VFT approaches have been applied to date to identify and structure strategic objectives of organizations investing in global health R&D. And we are aware of only one other study that has applied a DCE for health systems goal valuation (Franken and Koolman 2013). In combining VFT with DCE, we demonstrate an important role of decision analysis in strategy formulation, where the consideration of multiple objectives and their relative importance can facilitate structured dialogue processes between stakeholders making strategic decisions in global health R&D.

Our article is structured as follows. The methods section provides an overview of the analytical steps—from VFT to DCE methods—undertaken to help CEPI

decision makers define and structure strategic objectives as well as determine their relative importance. The results section presents the VFT and DCE findings. Theoretical and practical lessons learnt from the application of the methodology in CEPI context are discussed in the discussion and conclusion sections.

Methods

We undertook four analytical steps to help CEPI decision makers—CEPI task teams, founding partners, and leadership group (Coalition for Epidemic Preparedness Innovations 2016)—define and structure CEPI's strategic objectives and to determine their relative importance. First, we conducted stakeholder consultations to identify needs, challenges, potential objectives, and benefits of establishing new mechanisms for EID vaccine R&D. Second, we constructed means–ends argument chains from problem statements to fundamental objective concepts relevant to CEPI's strategy formulation. Third, we refined the results of this objective structuring exercise with CEPI stakeholders through teleconferences and face-to-face group discussions. Fourth, we elicited preferences over alternative strategic objective formulations through a DCE. This section provides an overview of the approach adopted. More details on the methodology can be found in Appendices A and B in the online supplement to this paper.

Stakeholder Consultations

We conducted 31 in-depth, semistructured one-on-one consultations with official representatives of organizations and individual experts comprising members of CEPI task teams. Although there is no correct number as to how many such interviews one should conduct, approximately 30 is the average number of interviews conducted in exploratory, qualitative research before saturation is reached (Mason 2010). The chance of obtaining most possible answers to kick-start the VFT process was maximized by means of a saturation criterion, that is, no new ideas generated after three consecutive interviews per subject-matter expertise or sectoral affiliation (Francis 2010, Saunders et al. 2018). Saturation was reached after 28 interviews. This procedure was intended to increase the baseline content validity of the VFT exercise.

Stakeholders selected for consultation were key partners in the establishment of CEPI and who met at least one of the following criteria:

- had subject matter expertise on epidemic infectious pathogens; vaccine R&D, including nonclinical and clinical development aspects, manufacturing capacity, and regulatory pathways; partnership models; and funding strategies;
- had sectoral representation (industry, government, philanthropic sectors);
- had geographical representation (north–south balance); or
- were in a group likely to be affected by decisions on CEPI operations (i.e., industry, WHO, civil society, representatives of regions likely to be affected by EID outbreaks).

The number of interviewees and the criteria considered for stakeholder inclusion in the consultation process allowed us to ensure a sufficiently broad set of perspectives and informed the effort to identify objectives. Following good practices identified elsewhere in the literature (Keeney 1994, Kunz et al. 2016), all interviews followed the same approach (see Appendix A in the online supplement to this paper) and included questions about

- lessons for R&D partnership building from experiences with recent EID outbreaks in terms of needs and priorities, opportunities, and roadblocks;
- operating principles that should define the space within which CEPI was to operate;
- strategic objectives CEPI should aim for and prioritize to address the needs, opportunities, and roadblocks in this field;
- partnership model alternatives that CEPI should consider; and
- benefits that CEPI should anticipate from the operation of such partnership models.

The questions included in the questionnaire were crafted based on Keeney's (1992) recommended techniques to identify objectives. Although somewhat redundant in their guidance, these questions were purposefully repetitive to allow us to make implicit objectives more explicit (Keeney 1996) and, in an implicit way, to also test for stakeholder response consistency in a qualitative manner.

In line with good practices (Kunz et al. 2016), we drew, where possible, potentially relevant concepts from the literature to steer discussions with stakeholders toward critical issues previously raised in the literature but that were not addressed adequately during the consultations.

Means–Ends Mapping

The initial consultations generated some results that were not exclusively objectives (e.g., problem statements, preferred partnership models, relevant actors and functions for CEPI, operating principles for CEPI). We separated these concepts and established relationships between them by examining the reasons for each, and, where possible, their implications. This allowed us to determine potentially fundamental objectives and policy values for CEPI, as well as to link these through means–ends argument chains. For a

review of means–ends mapping methods, see Belton and Stewart (2002), Montibeller and Belton (2006), Montibeller et al. (2008), and Franco and Montibeller (2011); for further examples of means–ends mapping theory and applications in problem structuring and decision making, see Howard (1988), Belton et al. (1997), Eden and Ackermann (1998, 2013), Bana e Costa et al. (1999), Ensslin et al. (2000), Rosenhead and Mingers (2004), Bryson et al. (2004), Eden (2004), Ackermann et al. (2007), and Rodriguez et al. (2017). We depicted these objectives as a network of concepts connected by links denoting chains of arguments within and between seven reasoning clusters:

- *Problems*: What are the perceived problems for R&D partnership building from experiences with Ebola and other recent EID outbreaks? Why are these problems important, and what are the potential implications if these problems remain unaddressed?
- *Actors*: What actors can address these problems and why?
- *Functions*: What types of functions could and should these actors offer, including resource assets or other types of competencies and capabilities?
- *Alternative models*: What modes of action or partnership approaches could and should these actors establish to provide these functions?
- *Priorities*: Which of these modes of action or partnership approaches are most important and why?
- *Expected benefits*: What are the expected benefits associated with each of these partnership approaches, and why?
- *Objectives*: Why are these anticipated benefits important?

Although the final question listed here may not quite sound like an objectives-focused question, it is important to highlight that one often begins to think hard about fundamental objectives after some benefits become apparent as well as the reasons why these are likely to be important (Keeney 1996). Articulating the features that distinguish revealed benefits provides, therefore, a sound basis for identifying fundamental objectives within a VFT framework, ideally with such a question being logically structured toward the end of the discussion process.

Based on interviews with CEPI stakeholders, we initially identified 464 concepts and 1,274 relationships between these. After clustering the concepts and their relationships into means–ends chains of arguments according to the above procedure, we generated a reasoning map with 62 concepts and 251 means–ends argument chain connections. Redundancies of previously reported concepts were eliminated from this map (see details in Appendix B in the online supplement to this paper). In addition to serving as a practical consistency check between stakeholder responses, this last step also helped us bridge the theoretical gap between strict assumptions on attribute properties commonly required in multiattribute valuation methods versus the desired flexibility in structure and fewer modelling assumptions commonly observed in causal mapping (Montibeller and Belton 2006).

Group Discussions

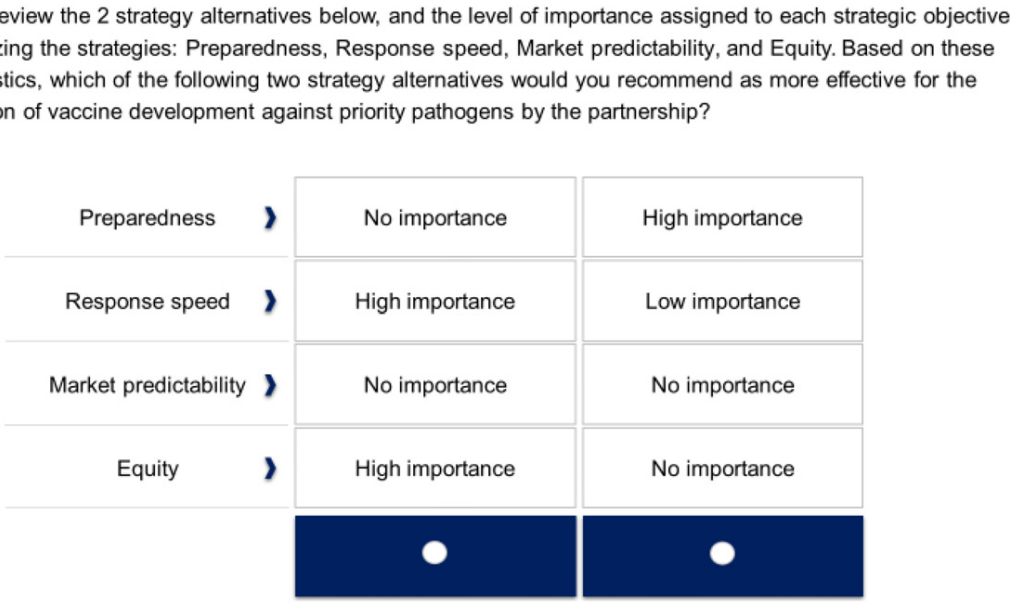
A series of teleconferences, email exchanges, and face-to-face meetings (Kristensen 2016) took place with a broader set of stakeholders to validate the results of the initial consultation exercise and to clarify CEPI's potential objectives and policy values, which would determine the context and goal orientation for CEPI's strategy formulation. These discussions led to the specification of a provisional hierarchy of preferentially independent means–ends objectives as well as a set of policy values—such as operating and governance principles—that set the overall frame within which appropriate definitions of strategic objectives would be obtained.

Discrete-Choice Experiment

A DCE was employed to elicit stakeholder preferences among objectives and to combine these into an overall probability of attractiveness associated with alternative strategic objective formulations. DCE participants were given a series of choice sets in which they were asked to choose between strategies defined by the level of importance by strategic objective. Strategy attractiveness against each strategic objective (attribute in the DCE) was defined as one of three levels, reflecting the level of importance for a strategic objective within the strategy formulation (see Table 2). Given the time constraints on the analysis, the three levels of performance were based on initial stakeholder consultations and definitions that were derived from these. Table 2 summarizes the strategic objective definitions (attributes) and importance levels.

Following good practices in DCE implementation (Ryan et al. 2008, Mangham et al. 2009, Johnson et al. 2013, Hauber et al. 2016), an experimental design of two blocks of 9 choice sets (i.e., 18 choice sets in total) was generated using SAS JMP® Pro 12 software (SAS Institute Inc. 2016). The software generated 1,000 alternative designs so that we could select the most optimal design based on the D-efficiency statistic. The orthogonality of the selected design was assessed based on the correlations in the covariance matrix. The highest correlation in the covariance matrix was 0.5, and the average correlation was 0.003. Manual edits to this design were made to remove any dominant choice sets and, in doing so, to improve the balance of the design.

Figure 1. (Color online) An Example Illustrates the Types of Questions Included in the DCE



Two other choice sets were added to each of the two blocks of choice sets: a dominance test and a consistency test. The survey was administered online using Questback Essentials®. The order of the 18 experimental choice sets within these sets was randomized between participants.

The survey was sent to 72 recipients: members of the three CEPI task teams and the leadership group; see "Annex 3: List of CEPI members" in CEPI business plan (Coalition for Epidemic Preparedness Innovations 2016, pp. 57–59). Where multiple persons represented a single organization, a survey invitation was sent once and consolidated responses were requested for these organizations. The survey was completed by 55 respondents, representing over 100 individuals engaged in CEPI's establishment. Figure 1 shows an example of a question included in the survey.

To assess the contribution of attribute performance to strategic objective preference, a dummy-coded, linear, conditional logistic regression was applied using JMP, version 12 (SAS Institute Inc. 2016). This type of analysis is a well-established and suitable approach for modelling discrete choices through the estimation of the probability of individuals making a particular choice from presented alternatives (McFadden 1974). Here, the utility for each choice option depends on the criterion levels defining that option. Therefore, it is not the characteristics of the DCE participants that are modelled, but the choice options.

The results of the model were used first to estimate the overall statistical significance of the attributes considered in the DCE (i.e., logworth values and likelihood ratios). Conditional on these overall attribute significance findings, the results of the model were then used to estimate the main effects of the different attribute levels; see the parameter coefficients in Table 4. Given the nature of the model and total number of survey responses received, the statistical significance of each attribute level was calculated using the Wald statistic, which is asymptotically distributed as a standard normal distribution (Wasserman 2006). The most desirable strategy formulation was identified as the one with the highest utility, defined as the sum of all statistically significant parameter coefficients associated with attribute levels in the model. Finally, the probability of different strategy formulations being preferred was estimated, for each alternative, as the ratio of the expected utility to the sum of this expected utility and the expected utility of the most preferred strategy (i.e., the baseline comparator).

Results

Our findings demonstrate that the prioritization of preparedness and market predictability objectives is likely to generate the most-supported vaccine R&D strategies against EIDs only if some importance is also placed on equity and response speed objectives.

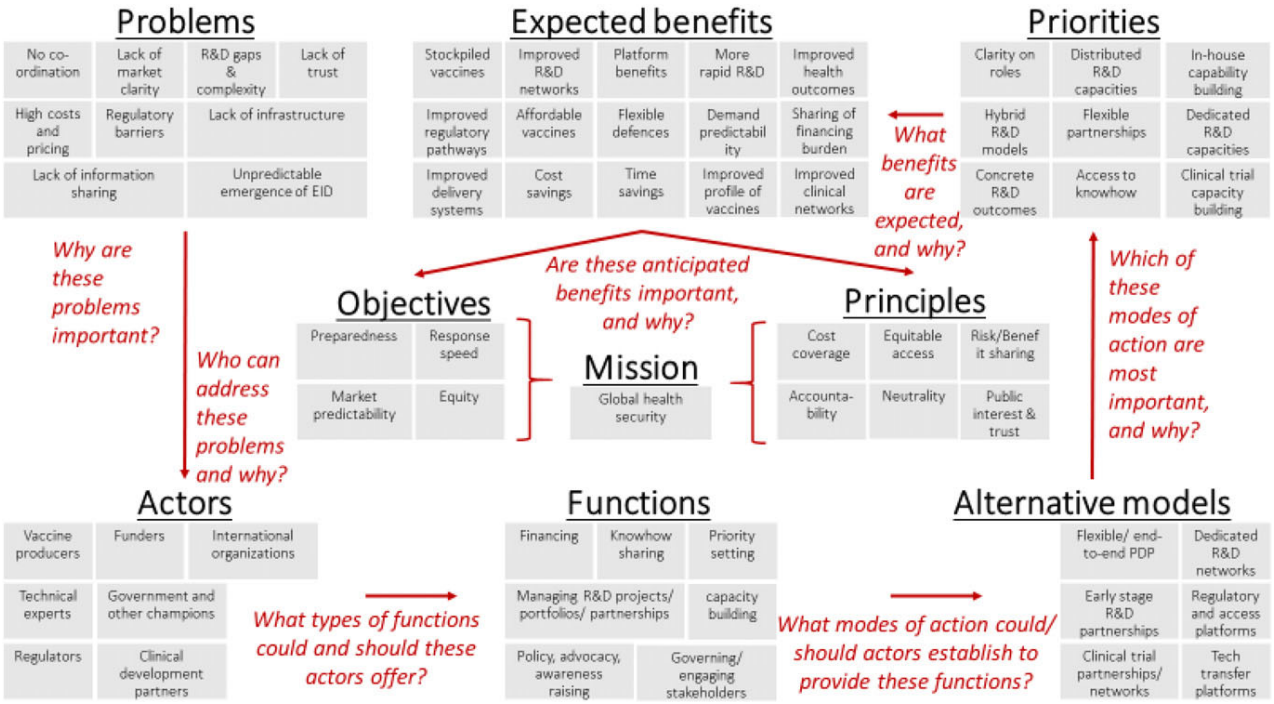
Table 1 summarizes needs and potential objectives for EID vaccine R&D partnerships as prompted by the literature up to February 2016, aimed to facilitate ideation fluency in stakeholder consultations. For a comprehensive reporting of stakeholder input, see Table B.1 in Appendix B in the online supplement to this paper. Needs range from fully dedicated and centralized approaches to highly flexible coordination approaches between existing actors. Potential objectives vary from increasing the level of R&D preparedness

Table 1. Various Needs and Potential Objectives for EID Vaccine R&D Emerged from Consultations and the Literature

Needs	Potential objectives for a new institutional response
Flexible and sustainable partnership models for EID vaccine R&D (Gronvall et al. 2007, Norheim et al. 2014, Center for Infectious Disease Research and Policy 2015, Moon et al. 2015, Plotkin et al. 2015, World Health Organization 2015, United Nations Secretary General 2016)	• Contain outbreaks of EIDs of epidemic potential, and market failure (World Health Organization 2015) • Accelerate vaccine development as part of outbreak control strategies however epidemics evolve (Castillo-Chavez et al. 2015, World Health Organization 2016b) • Improve our ability to respond to new threats and prepare with novel R&D paradigms to address future epidemics (Gronvall et al. 2007, World Health Organization 2015)
Platforms that expedite flexible and ethically acceptable vaccine testing and data sharing, as well as promote community trust, accountability and transparency of funding (Cohen and Kupferschmidt 2014, World Health Organization 2015, International Crisis Group 2015, Osterholm et al. 2016)	• Manage international health crises in a collaborative spirit (Tully et al. 2015) • Build trust through research and encourage policy change in countries likely to be affected by EID outbreaks (Silkavute et al. 2013)
Incentives for vaccine developers to proactively develop vaccines, to break regulatory barriers, establish operating principles, improve governance processes, and reduce commercial disincentives (Kamal-Yanni 2015, World Economic Forum 2015, Lucey and Gostin 2016)	• Minimize business disruption for industry by covering costs and rewarding risk (Plotkin et al. 2015) • Reduce the impact of liability exposure (Knobler et al. 2004, Sands et al. 2016) • Accelerate approval timelines for products developed on novel technology platforms (Institute of Medicine 2010)
Cross-sectoral collaborations to secure vaccine-led preparedness in the absence of other interventions (Knobler et al. 2004, World Health Organization 2010, U.S. Department of Health and Human Services 2012)	• Improve global development and manufacturing capacity for rapid and reliable vaccine production, satisfying biocontainment conditions (U.S. Department of Health and Human Services 2012, Sands et al. 2016) • Streamline the vaccine production process and offer flexible defense strategies (U.S. Department of Health and Human Services 2012, Osterholm et al. 2016) • Create special regulatory pathways and regulatory science standards (Maher et al. 2012, U.S. Food and Drug Administration 2014) • Ensure access and distribution of vaccines in response to outbreaks at affordable prices to reach those at greatest risk (Ton 2015, Sands et al. 2016)
Dedicated and centralized management of assets and resources in advance of EID outbreaks (Moss and Michaud 2013, World Economic Forum 2015, Hoyt and Hatchett 2016)	• Advance EID vaccine R&D through the pipeline where funding is the bottleneck (Saito and Takeuchi 2009, Boddie et al. 2014, Boddie 2015) • Stimulate new and more efficient approaches to vaccine development and production (Smith et al. 2003, Gilfillan et al. 2004, Relman 2006, Gronvall et al. 2007) • Reduce risks of global supply and also support a quick manufacturing scale-up and delivery where needed (Fuerst et al. 2009, Pagliusi et al. 2016, Sands et al. 2016)
Alignment with existing normative bodies and initiatives (World Health Organization 2016a)	• Set R&D priorities and pathogen-specific R&D road maps (World Health Organization 2015; 2016a, b) • Share resources and services around the development of products (Gronvall et al. 2007), the purchasing of products (Global Alliance for Vaccines and Immunisation 2014), and the management of partnerships (Hafer et al. 2010)

around R&D, manufacturing, and regulatory processes to improving institutional response speeds to EID outbreaks, improving incentives for private sector participation, and ensuring access and trust in vaccines through affordable pricing and regional R&D capability strengthening in countries likely to be affected by EID outbreaks. Figure 2 illustrates constructed means–ends argument chains from perceived problem statements to anticipated benefits that enabled the structuring of stakeholder objectives and values; see Table B.1 in Appendix B in the online supplement to this paper for a full mapping of means–ends argument chains. It demonstrates that CEPI stakeholders perceived the sporadic and unpredictable emergence of EIDs and the lack of coordination and cooperation frameworks to address these as the greatest challenges in efforts to improve global health security associated with EID epidemics. They argue that vaccine R&D can contribute to better EID outbreak preparedness. However, they flagged many problems that would need to be resolved, such as misconceptions about the value of vaccines, lack of interest and infrastructural capacities to support R&D, large R&D complexities and costs, and low willingness for information access and sharing to support vaccine development, testing, and emergency use. Stakeholders

Figure 2. (Color online) A Reasoning Diagram Illustrates the Means–Ends Chain of Arguments Constructed to Identify Strategic Objectives for CEPI



Notes. To reduce the visualisation complexity of the reasoning diagram in this figure, not all means–ends relationships are illustrated among arguments within and between chain blocks. For details, see Table B.2 in Appendix B in the online supplement to this paper.

predicted different types of actors—such as vaccine developers, funders, governments, regulators, and international expert organizations—could tackle several of these problems by serving different functions. These could include financing and incentivizing R&D, sharing data and know-how, scoping disease threats and setting R&D priorities, managing R&D efforts and building R&D capabilities, raising awareness of the critical issues, and improving global levels of stakeholder engagement in this space. Such functions could be provided through institutional partnerships and networks between product developers, regulators and governments, and clinical trial partners.

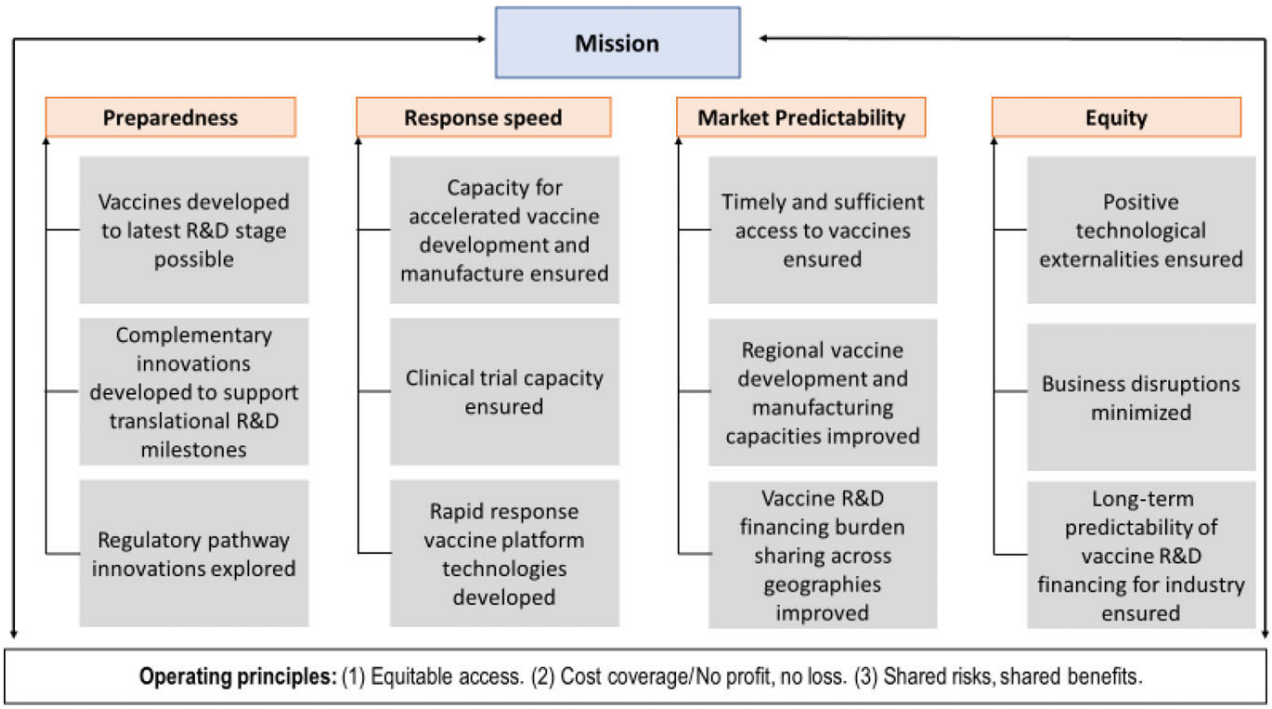
Clarity on operating principles around equitable access, cost, and risk sharing would be needed regardless of the coordination mechanism chosen. Such an organizational design should aim to generate a pipeline of vaccines for priority EIDs, build technical and institutional capabilities that can accelerate vaccine development and manufacturing in response to newly emerging disease threats in the future, minimize disruptions for vaccine developers, and improve the distribution of R&D capabilities and financing responsibilities across geographical regions. Stakeholders perceived the ultimate objective as securing the world from future EID outbreaks becoming humanitarian and economic crises.

Figure 3 summarizes the strategic objective hierarchy and values for CEPI identified through the objective identification and structuring process. This analysis suggests that to achieve its mission, CEPI should consider four objectives:

- *improve R&D preparedness* through the development of vaccines to the latest R&D stage possible, complemented by other translational R&D milestones and regulatory innovations;
- *improve the speed of R&D response* through the availability of manufacturing capacity on-demand, clinical infrastructure to test vaccine candidates, and rapid-response vaccine platform technologies for EIDs;
- *improve market predictability* through the generation of positive externalities to businesses and to the public, the minimization of disruptions to other business or public health work, and the availability of incentives for vaccine developer engagement in EID vaccine R&D;
- *improve equity* through the availability of vaccines to priority populations, the strengthening of low- and middle-income country (LMIC) capacity, and the promotion of shared responsibility in financing across geographical regions.

According to stakeholder preferences, equitable access, cost coverage, and risk/benefit sharing are principles, or boundaries within which they would like to see CEPI strategy operationalized; for details,

Figure 3. (Color online) The Figure Illustrates the Provisional Strategic Objectives Hierarchy for CEPI



see CEPI business plan (Coalition for Epidemic Preparedness Innovations 2016).

Table 2 presents the criteria definitions and their associated levels of importance considered in the DCE, because these were derived through the objective structuring process.

Table 3 presents the overall effect and statistical significance of the strategic objectives (attributes in the DCE) on the attractiveness of CEPI's strategy. As these figures demonstrate, all four strategic objectives included in the DCE are significant and should be considered in the formulation of an attractive CEPI strategy.

Table 4 presents the independent effect that different importance levels assigned to each strategic objective would have on the overall attractiveness of CEPI's strategy, based on the DCE. We define strategy attractiveness as a function of the level of importance placed on preparedness, response speed, market predictability, and equity objectives, and the means objectives' targets associated with each of these ends and their importance levels. As the parameter estimates in the table suggest, placing low or high importance on preparedness and on market predictability would have a strong positive effect on the attractiveness of CEPI's strategy. In contrast, placing low importance on equity and on response speed would have a positive effect on strategy effectiveness but a diminishing and statistically uncertain effect if they were given high importance.

Based on the dominance and consistency tests included in the survey choice sets, 95% of DCE survey respondents appear to have provided a consistent response and 80% of them correctly addressed the dominance question. When the probability that the dominance question was preferred was modelled based on the choice model (Tervonen et al. 2018), we estimated that only 35% of respondents would be expected to select the dominant option, suggesting that DCE respondents attended to the task.

Figure 4 presents the predicted probabilities associated with formulating a desirable CEPI strategy given different combinations between low and high levels of importance of the strategic objectives and comparing these to a baseline strategy. These results indicate stakeholder preferences for the strategic objectives assessed. Specifically, 16 alternative strategy formulations were ranked based on their likelihood of being considered attractive. The baseline comparator was a strategy that places high importance on preparedness and market predictability, and low importance on response speed and equity. The least attractive strategy is one that places low importance on all strategic objectives. There would be approximately a 61% chance that a CEPI strategy would be desired if high importance was placed on all objectives, ignoring statistical significance values. And there would be a 10% chance that a CEPI strategy would be desired if low importance was placed on all objectives.

Table 2. A Number of Attributes and Levels of Importance Were Used in the DCE

Attribute (ends objective)	Indicator (means objective)	Description
Maximize level of preparedness	Advance vaccines developed to latest stage possible	• A collection of vaccines through end of Phase II and/or stockpiles in the next few years
	Achieve translational R&D milestones	• A number of complementary innovations such as standardized assays, reagents, and animal models, to support vaccine development
	Achieve regulatory innovations	• New or improved decision-making processes for accelerated assessment of safety, efficacy, quality, and performance of EID vaccine candidates by regulators
Maximize response speed	Get facilities ready to manufacture	• Facilities ready to develop and scale up manufacture of vaccines in response to priority disease outbreaks
	Get clinical infrastructure ready to test	• A network of clinical trial centers brought together and utilized effectively when efficacy testing is needed
	Develop rapid response platform technologies	• Vaccine platform technologies ready to use for the rapid development of vaccines against unexpected pathogens
Improve market predictability	Achieve positive externalities	• Benefits from use of platform technologies for vaccine development in other disease areas with different public health impact or commercial use potential
	Minimize disruptions	• Capacity to redirect R&D efforts to pathogens for which no vaccine is available when need occurs, without disrupting ordinary business and public health work
	Secure long-term predictability of financing	• Cost recovery for R&D guaranteed and market size expectations clarified through appropriate incentives established
Improve equity	Promote vaccine access	• Timely and sufficient access to licensed or stockpiled Phase I/II vaccines by countries/populations in need in case of outbreaks, utilizing WHO guidance
	Promote LMIC capacity benefits	• Increased vaccine development and scale-up manufacturing capacity for local responses to outbreaks, regionally dispersed across LMIC geographies
	Increase sharing of responsibilities	• Shared burden of financing vaccine development and rational distribution of governance roles and responsibilities across north- and south-based entities

Note. The levels of importance used in the DCE are as follows: At the high importance level, the targets for all three indicators must be met. At the low importance level, the targets for at least one indicator *may* be met. At the no importance level, it does not matter whether targets for any of the three indicators are met or not.

Given the statistical uncertainty around high importance levels preferred for equity and response speed, and accounting for objective definitions (Table 2), the above results suggest that priority should be given to the development of vaccines to the latest phase possible and at least through the end of Phase IIa (i.e., clinical safety and immunogenicity studies in humans), complemented by enabling science and regulatory innovations. Priority should also be given to generating incentives for vaccine developers and minimizing disruptions from engaging in EID vaccine R&D. Furthermore, at least one of the following activities should be prioritized under the response speed objective: developing rapid-response vaccine platform technologies, ensuring the availability of manufacturing capacity, or strengthening clinical infrastructure to test EID vaccines. And at least one of the following activities should be prioritized under the equity objective: ensuring availability of EID vaccines to priority populations, strengthening LMIC capacity for vaccine R&D, or promoting shared responsibility in financing across geographical regions.

Discussion

This study demonstrates how decision analysis can support a rational and transparent approach to strategy formulation that accounts for and ranks the preferences of multiple stakeholders in an international health policy setting. There are three key lessons and implications that can be drawn from the study. First, it is possible to combine rigorous problem structuring and quantitative preference elicitation methods to support strategy development and objective setting in a highly complex R&D planning

Table 3. The DCE Generated a Number of Overall Effects and Statistically Significant Attributes

	Effect summary		Likelihood ratio tests	
Attribute	Logworth	*p*-value	Likelihood ratio χ^2	Prob. > χ^2
Preparedness	21.078	0.000	97.066	<0.0001
Market predictability	6.186	0.000	28.487	<0.0001
Response speed	5.994	0.000	27.604	<0.0001
Equity	5.874	0.000	26.637	<0.0001

context with many diverse and strong interests. We show how the VFT approach can be used to identify and structure stakeholder values to clarify strategic objectives in global health R&D when the diversity of stakeholder perspectives and the complexity of decision making are both high. Furthermore, the application of the DCE demonstrates how it can be used to elicit preferences over difficult strategic choices prior to their implementation.

Second, as the global governance structure for outbreak response continues to emerge, it will be important to apply these techniques to elicit clear strategic objectives and means that will frame the desired response, and in doing so, to improve EID mitigation efforts. Given the large number of stakeholders with different and sometimes competing objectives, there is a danger that more widely held values and strategic objectives can be hijacked or lost through an interest-heavy social bargaining process. The application of value-based thinking and choice trade-offs can rationalize and democratize this process in the future.

Third, decision analysis can be implemented in a dynamic way, allowing it to adapt to rapidly changing decision-making contexts. It is important to demonstrate this quality to maintain confidence in its practical, supportive function (Keeney 1996). For example, a new R&D investment strategy to combat antimicrobial resistance would likely require a different set of objectives and would suggest a different structuring of means and ends and their respective trade-offs, even if objectives appeared to be the same in name (imagine how many different meanings equity can have in health; Mooney 1987). This should reduce the generalizability of decision-analytic outcomes across different settings. However, the utility of decision analysis rests mainly on its methods for value structuring and elicitation, which, if applied appropriately, can justify differences in content while ensuring analytical rigor and transparency in a variety of management decisions.

What is Known on This Topic

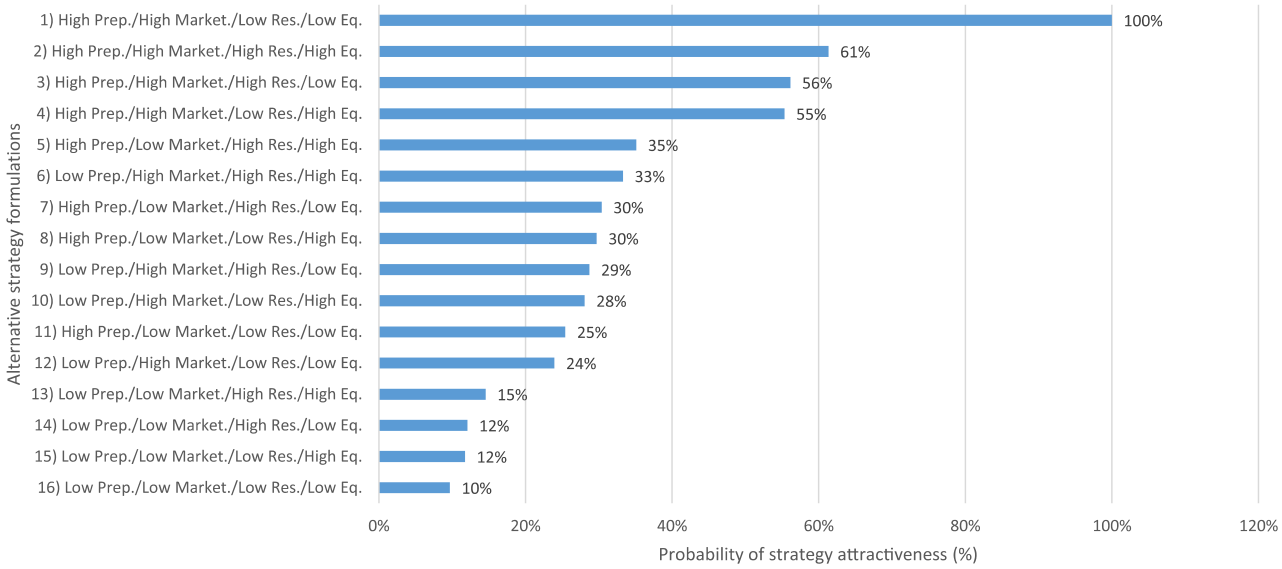
Decision analysis can enhance transparency and offer an explicit measure of comparison among options to promote rational decision making. This attribute is well documented in the strategic management literature (Montibeller et al. 2006) even when social bargaining processes tend to otherwise dominate (Thomas 1984, Montibeller and Franco 2010). Even though the application of decision analysis for strategic goal setting in health is limited (Franken and Koolman 2013, Ginter

Table 4. The Relative Importance of Strategic Objectives Varied in CEPI Strategy Choice

Parameter	Coefficient	Standard error	Lower 95%	Upper 95%	*p*-value
Preparedness (low importance)	1.56	0.22	1.15	2.04	0.00
Preparedness (high importance)	1.16	0.29	0.59	1.75	0.00
Market predictability (low importance)	0.71	0.20	0.33	1.14	0.00
Market predictability (high importance)	1.08	0.28	0.53	1.64	0.00
Response speed (low importance)	0.81	0.17	0.48	1.14	0.00
Response speed (high importance)	0.25	0.27	–0.28	0.78	0.36
Equity (low importance)	0.83	0.18	0.49	1.19	0.00
Equity (high importance)	0.21	0.25	–0.28	0.71	0.39
Model fit criteria					
Negative log-likelihood[a]	470.45				
Negative Firth log-likelihood[a]	442.78				

[a]The values of the negative log-likelihood indicate, overall, a good model fit. However, small sample sizes may also suggest biased parameter estimates, and in order to address this problem, all estimates presented in Table 2 are Firth (1993) bias adjusted.

Figure 4. (Color online) Predicted Probabilities that a CEPI Strategy Will Be Preferred Vary According to Different Combinations of Levels of Importance Considered Among the Strategic Objectives



Note. Prep., Preparedness; Market., market predictability; Res., response speed; Eq., equity objectives.

et al. 2013), evidence from other sectors suggests that at least half of all strategic decisions fail as a result of poor decision-making processes (Nutt 2002, Bryson 2018). Premature dispute resolution and consensus building approaches can prevent choices from becoming apparent to decision makers and therefore promote inferior, internally inconsistent policy choices, in the absence of decision-analytic approaches that structure and address the relative importance of stakeholder values (McDaniels and Trousdale 1999, Abuabara et al. 2017). Organizations that satisfy key stakeholders' values are more likely to enhance the legitimacy of their strategies (Ackermann and Eden 2011). However, the impact of decision analysis on commitment to action, it has been argued, cannot be proven easily at an empirical level (Montibeller and Franco 2010). Moreover, decision analysis can lose its meaning if the skills, resources, or commitment of stakeholders are lacking when engaging in deliberative strategic planning (Bryson 2018).

The evidence base from previous research and practice on strategic objectives for EID vaccine R&D is limited. Following the 2015–2016 Ebola outbreak in West Africa, the WHO created a R&D Blueprint for EID preparedness and response coordination at the global level (Kieny et al. 2016). Recent outbreaks (Ebola and subsequently Zika) also revealed that few reward systems are in place to compensate companies for the costs they incur in responding to these outbreaks, lending weight to other preexisting disincentives to private sector participation such as poor commercial prospects, uncertain regulatory pathways, and a lack of preestablished operating principles for coordination (Kamal-Yanni 2015, World Economic Forum 2015, Lucey and Gostin 2016). Equity is an important concept and common objective in global health financing organizations, such as the Bill & Melinda Gates Foundation (2018), Wellcome Trust (2018), and Global Alliance for Vaccines and Immunisation (2018). This principle has been well addressed in strategies of product-development partnerships and global health R&D initiatives in the endemic, poverty, or neglected disease space; examples include the Drugs for Neglected Diseases Initiative (2009), Medicines for Malaria Venture (2017), and Program for Appropriate Technology in Health (2018).

What This Study Adds

Our study attempts to overcome some of the challenges identified in the literature in two ways. First, definitions of preparedness and response objectives were constructed, especially as they relate to vaccine development. Moreover, this is the first time that equity and market predictability concerns for EID R&D have been explicitly addressed at the level of strategic priority setting.

Second, the systematic structuring of values and some quantitative thinking about value trade-offs has brought strategic decisions stemming from CEPI's social bargaining processes closer to actual commitments for action, as reflected in CEPI business plan and actions taken thereafter. On one hand, CEPI's leadership group and founding partners endorsed these means–ends strategies as part of CEPI's business plan launch in late 2016, after numerous formal decision-making forums and deliberations informed

by different versions of the decision-analytic findings (Coalition for Epidemic Preparedness Innovations 2016, Kristensen 2016, Brende et al. 2017). Not all quantitative data presented in this article (e.g., Table 4 and Figure 4) were presented in detail to the decision makers, because of both cognitive burden concerns and a perceived risk of diverting too much attention from social bargaining in an extremely time-constrained environment. However, overall analytical outcomes—such as logworth values, likelihood ratio statistics, and overall utility functions of the most preferred strategy formulations (Table 3)—were reported and offered stimuli for discussions around policy values and fundamental objectives.

In addition, since CEPI's official launch (Reuters 2017), the organization has issued three separate investment opportunities under the just-in-case preparedness and response speed (just-in-time preparedness) objectives: two calls for proposals (CfPs) to support vaccine development against five priority EIDs (Coalition for Epidemic Preparedness Innovations 2017, Christodoulou 2019) and a CfP to support the development of rapid, multipurpose vaccine platform technologies (Coalition for Epidemic Preparedness Innovations 2018). All CfPs are supported by decision-analytic frameworks that are aligned with CEPI's strategic goals (Gouglas and Marsh 2019, Gouglas et al. 2019). Under the just-in-case preparedness objective, CEPI has also been advancing efforts on standardized assays and regulatory pathways for emergency use through various working groups in close collaboration with the WHO (Gouglas et al. 2019). Under the equity objective, advocacy and resource mobilization efforts are under way to improve the equity in EID vaccine R&D financing across geographic regions. CEPI is working closely with several partners to improve the long-term predictability of financing EID vaccines, including through stockpile commitments, among other examined market incentives (Gouglas et al. 2019). Under the platform technology CfP, CEPI is also working with industry to leverage positive technological externalities to other vaccine areas, thus contributing to CEPI's commitment to the market predictability objective. Retrospectively, this evidence of CEPI's commitment to action comes in contrast with the prevailing skepticism in the literature about the lack of impact that decision analysis can have on strategic decisions in practice.

Limitations

VFT is only one of many problem-structuring techniques in decision analysis (Leon 1999, Belton and Stewart 2010, Marttunen et al. 2017). VFT assists with strategy setting because it clarifies stakeholder preferences and objectives in ill-structured decision problems (Keeney 2008, Montibeller and Franco 2010). It does not, however, enhance perceptions of the course of future events that may impact decision making, which other techniques may be better suited to stimulate (Kunz et al. 2016).

The elusive and often conflicting nature of value statements can prevent them from conforming to the classical concept of goal hierarchy that is also used in VFT (Wenstøp and Myrmel 2006). Moreover, VTF can be mentally challenging (Arvai et al. 2001), may require time and effort to be understood (Kunz et al. 2016), and can become complex in its visualization (Becker et al. 1995). A wider range and creative use of problem-structuring tools may therefore be required to identify and understand the interaction of stakeholder values within an overall analytical frame of means–ends objectives (Kunz et al. 2016). The application of a number of tools presented in our study, including evidence drawn from the literature, semi-structured interviews, group discussions, and means–ends mapping, demonstrates how their use can help VFT specify and structure the objectives and then use them to inform the decision process.

This study attempted to address several drawbacks associated with DCEs. First, a systematic approach to criteria development in DCEs is generally lacking (Helter and Boehler 2016). When cognitive shortcuts are used or erroneous interpretations are made of criteria and their preferential relationships, DCEs can generate unreliable inputs for policy decisions (Ali and Ronaldson 2012). Our study has attempted to address this limitation through the use of a rigorous method to identify and structure criteria prior to DCE design.

Second, DCEs require precise criteria definitions, and ambiguity in the specification of their assessment levels can lead to less realistic or meaningful analytical outcomes (Hall et al. 2004, Ryan 2004, Mangham et al. 2009). Drawing directly from the results of the problem-structuring process, the specifications of criteria levels in our model reflected the early maturity of the organization. As CEPI strategy becomes more focused over time, future decision-analytic exercises should improve the specificity of criteria descriptions and assessment levels and should consider additional trade-offs between subcriteria where preferential independence between these is observed.

Third, the sample size for the DCE was small in relation to many DCEs commonly found in the literature (de Bekker-Grob et al. 2012, de Bekker-Grob et al. 2015), which may have influenced our findings. Given the sample size, number of choice sets, alternatives, and criteria levels included in the design, the DCE presented here was viewed as explorative (Baltussen et al. 2006). Although there is no agreement on what the minimum sample size or method for calculating this in the DCEs should be (de Bekker-Grob et al. 2015),

our working assumption during the DCE design was that as few as 20 respondents should suffice to estimate broadly reliable preference data in exploratory DCE contexts (Orme 2010, Lancsar and Louviere 2008, Bridges et al. 2011a). We received 25 responses to Version 1 and 30 responses to Version 2 of our survey. Using the Johnson and Orme rule of thumb (Johnson and Orme 2003, Orme 2010), which is the most commonly applied minimum sample-size calculation rule in DCEs in healthcare (de Bekker-Grob et al. 2015), the minimum sample size required for both survey versions was met, given the number of attributes and levels included in the design.

Stakeholder preferences varied moderately, as reflected in the standard deviation estimates (Table 4), even after accounting for bias effects in the design of the survey. Preference variation was most evident around placing high importance on market predictability, response speed, and equity objectives. This variation was statistically significant in the case of market predictability but not so for response speed and equity objectives. Perhaps a larger sample size in the future could give a more definitive answer as to the expected coefficients and associated variation on high levels of importance for response speed and equity objectives.

Finally, we should acknowledge some additional, practical limitations with the method's application. First, while the DCE allowed for a rough ordering of objectives in the face of preference variation, the methodology did not remove this variation, and it was important to engage stakeholders in thoughtful discussion without too much emphasis on quantitative data, given practical time constraints. On one hand, this meant a missed opportunity for validating stakeholders' preference inputs into the DCE, which is generally considered a good practice in the decision analysis literature (Salo and Hämäläinen 2010, Montibeller and Winterfeldt 2015, Marsh et al. 2016). On the other hand, considering the practical constraints—cognitive burden, sample size, and timeline limitations—strategic decision-making processes are not always amenable to rigorous preference elicitation.

Second, in the context of sample-size limitations, as is often the case when working with expert and decision-making committees, there are limitations on the complexity of the value models that can be characterized by choice models, such as DCEs. However, this will be less of a concern when stakeholders whose values are of interest are a larger group, such as patients or the general population. Nevertheless, a DCE was employed because the expert and decision-making groups were quite representative of the global community relevant to EID mitigation, and logistical limitations meant that it was necessary to elicit preferences using a survey. This decision was vindicated by the results of the choice analysis, which was sufficiently precise to allow us to differentiate preferences associated with many of the levels in the choice sets. Other preference elicitation methods could also be employed, such as workshop-based swing weighting (e.g., Phillips and Bana e Costa 2007); however, such methods are generally restricted by practical constraints of time, location, and availability of stakeholders engaged.

Conclusions

The analysis reported in this study demonstrates the use of an exploratory decision analysis process to support the identification, structuring, and prioritization of strategic objectives of a new organization aimed at improving global R&D preparedness against EID epidemics. The systematic structuring of values and some quantitative thinking about value tradeoffs helped CEPI stakeholders explicitly agree on a commonly preferred set of strategic commitments for action, as reflected in CEPI's business plan, despite differences in their perspectives. In doing so, the analysis has provided a strategic narrative upon which the organization still bases its investment objectives, as reflected by several major funding opportunities issued over the past three years.

More broadly, our study highlights how formal decision analysis supports priority setting for international strategic initiatives with multiple stakeholders. It provides analytical rigor to problem structuring and preference elicitation, increasing the level of transparency and explicitness of complex strategic decision processes and outcomes in global fora. In settings where large numbers of stakeholders with conflicting objectives prevail, negotiations can devolve into social bargaining processes that do not accurately reflect the strategic objectives perceived as important by all stakeholders. As new strategies and governance structures for global health continue to emerge, it will be important to apply such techniques to elicit clear strategic objectives through democratic means. The application of value-based thinking and choice tradeoffs can rationalize and balance strategic decision-making processes in the future.

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Verification Letter

Dr. Frederik Kristensen, Deputy CEO, CEPI – Coalition for Epidemic Preparedness Innovations, Marcus Thranes Gate 2, 0473 Oslo, Norway, writes:

"On behalf of CEPI, I hereby confirm that the decision analytic approach presented in the article submitted for your consideration and titled 'Setting Strategic Objectives for the Coalition for Epidemic Preparedness Innovations: An Exploratory Decision Analysis Process' was employed in 2016 to inform the establishment of CEPI's interim Business Plan and strategic objectives.

"The methodology employed was beneficial for structuring a complex dialogue process between multiple stakeholders with conflicting perspectives and helped determine the nature and structure of CEPI's interim strategic objectives in an analytically rigorous way."

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Setting Strategic Objectives for the Coalition of Epidemic Preparedness Innovations: An Exploratory Decision Analysis Process

Electronic Supplementary Materials

This supplement provides additional information on methods and results of the study we discuss in the main body of this paper. Appendix A provides the questionnaire template used for stakeholder consultations. Appendix B provides the aggregated list of objectives and relationships that were used to inform the means-ends reasoning map presented in the study.

Appendix A

Questionnaire for Stakeholder Consultations

1. In your view, what **lessons** can we derive for R&D partnership building from experiences with Ebola and/or other recent emerging infectious disease (EID) outbreaks, briefly explaining:
a. What are the *needs* and/or *priorities* for partnership building *now* vs *in the future*?
b. What are the *opportunities* and what are the potential *roadblocks now* vs *in the future*?

2. What should be the **objectives** of CEPI and how would you go about operationalizing them further – e.g.:
a. Increase level of R&D preparedness around R&D, manufacturing, regulatory processes, etc.?
b. Improve speed of response to outbreaks of epidemic or pandemic potential, e.g. in terms of speed of development, speed of manufacturing, speed of regulatory processes, etc.?

c. Improve market security for product developers, e.g. financial attractiveness, market predictability, market position, market protection, etc.?

d. Other (please specify)?

e. Any of the above combinations?

3. In your opinion, what are the R&D partnership model **alternatives** that should be considered in greater detail by Task Team 2, briefly explaining:

a. What is appropriate by pathogen, R&D stage, geography, market potential, etc.?

b. What is feasible by pathogen, R&D stage, geography, market potential, etc.?

4. What key **functions** would you expect a new EID vaccine R&D partnership to serve and why? Discuss in light of examples, such as:

a. Financing and/or rewarding R&D

b. Implementing and/or managing R&D

c. Developing and/or managing Intellectual Property (IP)

d. Manufacturing

e. Capacity building in potentially endemic settings in terms of R&D, manufacturing, other (please specify)

f. Data sharing

g. Other (please specify)

5. What **benefits** would you anticipate from the operation of a new EID vaccine R&D partnership?

Discuss in light of specific examples, such as:

a. Addressing unmet medical needs for specific pathogens?

b. Stimulating flexible defences against multiple and/or unknown pathogens?

c. Building R&D, manufacturing and/or supply capacity for better preparedness to respond to international public health emergencies?

d. Accelerating speed of R&D, manufacturing and/or regulatory response to emerging epidemics or pandemics?

e. Achieving market security, e.g. financial attractiveness, market predictability, market position etc.?

f. Other and/or any combinations of the above (please specify)?

6. What types of **assets** and/or **competences or capabilities** should (and could) different types of actors bring to such partnerships and why? Discuss in light of examples from:

a. public, private, non-profit sectors

b. funding, product development, regulatory and/or other function

7. What are your **preferences** in terms of:

a. Best partnership model(s) going forward, most attractive features and conditions for feasible implementation?

b. Most important partnership functions given different budget levels, partner competences, pricing / reward options, political / regulatory constraints?

c. The role if any and the potential capabilities, you see for your organization as a member of the Partnership

8. Any concluding comments and/or additional thoughts…

Appendix B

Aggregated List of Objectives and Relationships Informing the Means-ends Reasoning Map

Table B.1. The Table Shows an Aggregated List of Identified Objectives and Means-ends Argument Chains

Reference ID	Concept cluster	Concept	Reporting frequency (#times mentioned)	Within chain block reasoning direction	Between chain block reasoning direction
1.3.	Problems	Lack of coordination & cooperation frameworks	18	From 1.3. to 1.5., 1.9.	From 1.3. to 5.1., 5.2., 5.3., 5.4., 5.5., 5.6., 5.7.
1.1.	Problems	Lack of market clarity	14	From 1.1. to 1.3., 1.4., 1.6., 1.9.	From 1.1. to 5.2., 5.3., 5.4., 5.6.
1.5.	Problems	R&D gaps & complexities	7	From 1.5. to 1.7., 1.9.	From 1.5. to 5.1., 5.2.
1.8.	Problems	Misconceptions & lack of trust	7	From 1.8. to 1.3., 1.10.	From 1.8. to 5.4., 5.5.
1.10.	Problems	Lack of stakeholder engagement	6	From 1.10. to 1.3.	From 1.10. to 5.1., 5.2., 5.3., 5.4., 5.5., 5.6., 5.7.
1.4.	Problems	Regulatory and legal constraints	5	From 1.4. to 1.3.	From 1.4. to 5.3., 5.4., 5.5., 5.6.
1.7.	Problems	Lack of infrastructural capacities	4	From 1.7. to 1.3.	From 1.7. to 5.1., 5.2., 5.7.
1.2.	Problems	High R&D costs and unaffordable pricing	3	From 1.2. to 1.3., 1.5.	From 1.2. to 5.1., 5.2.
1.6.	Problems	Lack of information access and sharing	2	From 1.6. to 1.3., 1.4.	From 1.6. to 5.3., 5.4., 5.5.
1.9.	Problems	Sporadic and unpredictable emergence of epidemic infectious disease	2		From 1.9. to 5.6.
5.1.	Actors	Vaccine developers/ manufacturers	26		From 5.1. to 4.2., 4.3., 4.6.
5.2.	Actors	Funders	9		From 5.2. to 4.1., 4.4.
5.4.	Actors	International organizations	9		From 5.4. to 4.1., 4.2., 4.3., 4.4., 4.5., 4.6., 4.7.
5.6.	Actors	Technical experts	8		From 5.6. to 4.2., 4.6.
5.5.	Actors	Government and other champions	6		From 5.5. to 4.1., 4.3., 4.5., 4.7.

5.3.	Actors	Regulators	5		From 5.3. to 4.2., 4.5.
5.7.	Actors	Clinical development partners	1		From 5.7. to 4.3., 4.6.
4.1.	Functions	Financing/ incentivizing	28	From 4.1. to 4.2., 4.3., 4.6.	From 4.1. to 3.1., 3.2., 3.6.
4.2.	Functions	data/ knowhow sharing	17	From 4.2. to 4.3.	From 4.2. to 3.1., 3.2., 3.3., 3.4., 3.5., 3.6.
4.4.	Functions	scoping/ priority setting	15	From 4.4. to 4.1., 4.6.	From 4.4. to 3.1., 3.2., 3.6.
4.6.	Functions	Managing R&D projects/ portfolios/ partnerships	14	From 4.6. to 4.2., 4.3.	From 4.6. to 3.1., 3.2., 3.6.
4.3.	Functions	capacity building	11		From 4.3. to 3.1., 3.2., 3.3., 3.5., 3.6.
4.5.	Functions	policy, advocacy, awareness raising	6	From 4.5. to 4.1.	From 4.5. to 3.4.
4.7.	Functions	Governing/ engaging stakeholders	3	From 4.7. to 4.1., 4.3., 4.5., 4.6.	From 4.7. to 3.1., 3.2., 3.3., 3.4., 3.5., 3.6.
3.6.	Alternative models	Flexible/ end-to-end Product Development Partnership model	17		From 3.6. to 7.1., 7.2., 7.3., 7.4., 7.5., 7.6., 7.7., 7.9.
3.1.	Alternative models	Advanced development and manufacturing networks	15		From 3.1. to 7.1., 7.4., 7.5., 7.6., 7.7.
3.2.	Alternative models	Early stage R&D partnerships	7		From 3.2. to 7.4., 7.5., 7.6., 7.7.
3.4.	Alternative models	Regulatory and access platforms	4		From 3.4. to 7.7.
3.3.	Alternative models	Clinical trial partnerships/ networks	3		From 3.3. to 7.2.
3.5.	Alternative models	Tech transfer platforms	3		From 3.5. to 7.3., 7.4.
7.8.	Priorities	Prioritize clarity on principles and stakeholder roles for governance and coordination	19		From 7.8. to 6.2., 6.3., 6.4., 6.5., 6.6., 6.7., 6.8., 6.9., 6.11., 6.12., 6.13., 6.14.
7.4.	Priorities	Prioritize distributed R&D and manufacturing capacities	7		From 7.4. to 6.2., 6.4., 6.9., 6.10., 6.14.
7.6.	Priorities	Prioritize in-house expertise/ capability building for coordination	6		From 7.6. to 6.1., 6.9., 6.13.
7.9.	Priorities	Prioritize flexible/ hybrid partnership models	6		From 7.9. to 6.1., 6.2., 6.4., 6.9., 6.14.

7.7.	Priorities	Prioritize loose partnerships for coordination	5		From 7.7. to 6.1., 6.9., 6.13.
7.1.	Priorities	Prioritize dedicated R&D and manufacturing capacities	4		From 7.1. to 6.1., 6.2., 6.4., 6.9., 6.14.
7.5.	Priorities	Prioritize concrete vaccine development outcomes	4		From 7.5. to 6.1., 6.2., 6.9.
7.3.	Priorities	Support tech transfer partnerships and access to knowhow	2		From 7.3. to 6.2., 6.6., 6.9., 6.10.
7.2.	Priorities	Prioritize clinical trial network/ capacity building	1		From 7.2. to 6.9., 6.15.
6.1.	Expected benefits	A collection of vaccines successfully developed through phase II and stockpiled in case of emergencies	15	From 6.1. to 6.4., 6.9., 6.14.	From 6.1. to 2.1.
6.13.	Expected benefits	Improved coordination for EID R&D, manufacturing and distribution	10	From 6.13. to 6.1., 6.2., 6.3., 6.4., 6.5., 6.6., 6.7., 6.9., 6.10., 6.11., 6.12., 6.14.	From 6.13. to 2.1., 2.2., 2.3., 2.4.
6.4.	Expected benefits	Positive spillovers from platform technologies	9	From 6.4. to 6.2., 6.11., 6.12., 6.14.	From 6.4. to 2.3., 2.4.
6.2.	Expected benefits	Improved manufacturing capabilities/ capacities available for timely development of vaccines against unexpected threats	5	From 6.2. to 6.9., 6.14.	From 6.2. to 2.2.
6.9.	Expected benefits	Improved health/ public health outcomes	5		From 6.9. to 2.1., 2.2.
6.7.	Expected benefits	Improved regulatory pathways for EID countermeasures	4	From 6.7. to 6.1., 6.5., 6.6.	From 6.7. to 2.1., 2.2., 2.3.
6.6.	Expected benefits	Access to affordable vaccines by priority populations	3	From 6.6. to 6.3., 6.9.	From 6.6. to 2.5.
6.14.	Expected benefits	Stimulating flexible defences against multiple and/or unknown pathogens	3	From 6.14. to 6.9.	From 6.14. to 2.1., 2.2.
6.5.	Expected benefits	Demand predictability	2		From 6.5. to 2.3., 2.6.
6.8.	Expected benefits	Improved distribution of responsibilities/ burden for supporting EID countermeasure development	2	From 6.8. to 6.10., 6.13.	From 6.8. to 2.4., 2.7.
6.10.	Expected benefits	Improved distribution of manufacturing capacities across geographies	2	From 6.10. to 6.2., 6.6.	From 6.10. to 2.4.

6.11.	Expected benefits	Improved cost efficiencies in R&D	2	From 6.11. to 6.6.	From 6.11. to 2.6., 2.7.
6.12.	Expected benefits	Improved time efficiencies in R&D	2	From 6.12. to 6.2., 6.11., 6.14.	From 6.12. to 2.2.
6.3.	Expected benefits	Improved reputation and perceptions of vaccines	1		From 6.3. to 2.2.
6.15.	Expected benefits	Improved clinical trial networks	1	From 6.15. to 6.6., 6.9., 6.12.	From 6.15. to 2.1., 2.2., 2.4.
2.1.	Objectives	Just-in-case preparedness	22		From 2.1. to M.1.
2.2.	Objectives	Just-in-time preparedness	19		From 2.2. to M.1.
2.3.	Objectives	Market predictability	17	From 2.3. to 2.1., 2.2.	From 2.3. to M.1.
2.4.	Objectives	Local response capacity strengthening	3	From 2.4. to 2.1., 2.2.	From 2.4. to M.1.
2.6.	Objectives	Cost coverage	3		
2.5.	Objectives	Equitable access	2		
2.7.	Objectives	Risk/benefit sharing	2		
M.1.	Mission	Global health security	1		

PAPER II

Gouglas D, Thanh Le T, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen JA. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. The Lancet Global Health. 2018; 6(12): e1386-e1396; https://doi.org/10.1016/S2214-109X(18)30346-2.

Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study

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Summary

Background The Coalition for Epidemic Preparedness Innovations was established in 2016, to develop vaccines that can contribute to preparedness for outbreaks of epidemic infectious diseases. Evidence on vaccine development costs for such diseases is scarce. Our goal was to estimate the minimum cost for achieving vaccine research and development preparedness targets in a portfolio of 11 epidemic infectious diseases, accounting for vaccine pipeline constraints and uncertainty in research and development preparedness outcomes.

Methods We assembled a pipeline of 224 vaccine candidates from preclinical through to phase 2 for 11 priority epidemic infectious diseases. We used a linear regression model to identify drivers of development costs from preclinical through to end of phase 2a. Drawing from published estimates of vaccine research and development probabilities of success, we simulated costs for advancing these 224 vaccine candidates through to the end of phase 2a. We combined these findings to determine minimum costs for progressing at least one vaccine through to the end of phase 2a per epidemic infectious disease by means of a stochastic optimisation model.

Findings The cost of developing a single epidemic infectious disease vaccine from preclinical trials through to end of phase 2a is US$31–68 million (US$14–159 million range), assuming no risk of failure. We found that previous licensure experience and indirect costs are upward drivers of research and development costs. Accounting for probability of success, the average cost of successfully advancing at least one epidemic infectious disease vaccine through to the end of phase 2a can vary from US$84–112 million ($23 million–$295 million range) starting from phase 2 to $319–469 million ($137 million–$1·1 billion range) starting from preclinical. This cost includes the cumulative cost of failed vaccine candidates through the research and development process. Assuming these candidates and funding were made available, progressing at least one vaccine through to the end of phase 2a for each of the 11 epidemic infectious diseases would cost a minimum of $2·8–3·7 billion ($1·2 billion–$8·4 billion range).

Interpretation Our analysis provides new evidence on vaccine research and development pipelines and associated costs for 11 epidemic infectious diseases, highlighting both funding needs and research and development gaps for achieving vaccine research and development preparedness targets.

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Introduction

Vaccines can be powerful tools for preventing potential outbreaks of epidemic infectious diseases from becoming humanitarian crises.[1] Developing these vaccines requires investment.[2] However, evidence on what it would cost to successfully develop a sound epidemic infectious disease vaccine portfolio is scarce.[3] This is partly because of a paucity of explicit, publicly available cost data. In addition, there is little agreement across global vaccine development funders on which epidemic infectious disease investments should be prioritised, which stems from an absence of global research and development portfolio strategy and coordination.[4]

In response to the 2014 Ebola epidemic in west Africa, WHO prioritised 11 pathogens that are most likely to cause severe outbreaks in the near future:[4] Crimean Congo haemorrhagic fever, chikungunya, Ebola, Lassa, Marburg, Middle East respiratory syndrome coronavirus, Nipah, Rift Valley fever, severe acute respiratory syndrome, severe fever with thrombocytopenia syndrome, and Zika. WHO has now updated this list,[5] however all 11 diseases remain of considerable epidemic preparedness importance.

In general, vaccine development from discovery to licensure can cost billions of dollars, can take over 10 years to complete, and has an average 94% chance of failure.[6] Where national health security concerns exist, whether due to naturally emerging disease or bioterrorism-related threats, governments such as those of the USA, the UK, France, and Germany invest in research and development even if global markets are extremely small, as the cases of Ebola and other African viral

Research in context

Evidence before this study

There are almost 600 literature references on vaccine candidates being developed against 11 priority epidemic infectious diseases (appendix). This information has previously neither been collated systematically nor has its actual development status been confirmed. Moreover, evidence on the cost of pharmaceutical research and development has been made available since at least the 1950s; however, this has been limited to mainly chemical drug products. Whereas publications by Di Masi and colleagues have provided the foundations on which numerous analyses or critiques of pharmaceutical research and development costs have since been conducted, evidence on vaccine-specific research and development costs for epidemic infectious diseases has been limited. The handful of articles published to date are either descriptive, based on expert opinions with limited data inputs to validate those claims, or focusing on single pathogens or only on clinical research and development phases. Recent studies have attempted to overcome several of the above limitations, focusing their analyses on poverty diseases or epidemic infectious diseases, as well as differentiating more systematically between costs associated with incremental versus breakthrough innovations.

Added value of this study

Our study presents a comprehensive dataset of vaccine research and development candidates against 11 epidemic infectious diseases, which combines a systematic search of a substantially sized literature and the confirmation of current development status of these candidates by vaccine developers active in the field. Moreover, our study attempts to overcome some of the limitations identified in previous vaccine research and development cost analyses in several ways. First, we consider probability of success distributions drawn from multiple published estimates, acknowledging uncertainties in research and development which cannot be explained by single sources. Second, we draw our cost data from both historically incurred and projected cost estimates in infectious disease vaccine research and development, as reported by vaccine developers who are active specifically in the field of epidemic infectious diseases. This gives us confidence that the baseline cost estimates informing our models can provide a more accurate reflection of total investments needed for vaccine development. Third, our collected data suggest that costs associated with new technologies may not differ from costs associated with well-established technologies—a finding that is contradictory to prevailing assumptions made in extant literature. Our analysis suggests that it is indirect costs, and variations in costs associated with different levels of experience of the organisations developing these products, that drive cost estimates in upward directions.

Implications of all the available evidence

We demonstrate that it is possible to combine up-to-date evidence on vaccine research and development pipelines with rigorous cost analysis methods to generate robust estimates of vaccine research and development investment needs in epidemic infectious diseases. Our methods and findings can benefit future assessments of global health research and development costs, improving the credibility of funding need claims and of portfolio planning.

haemorrhagic fevers have shown.[7] However, worldwide investments in epidemic infectious disease are small.[8]

A new entity, the Coalition for Epidemic Preparedness Innovations (CEPI), was set up in 2016 to stimulate, finance, and coordinate the development of vaccines against epidemic infectious diseases, especially in cases in which market incentives alone are insufficient.[9] Owing to the sporadic and unpredictable emergence of epidemic infectious diseases, large-scale vaccine efficacy studies (phase 2b–3) are almost impossible unless there are ongoing epidemic infectious disease epidemics. Part of CEPI's scope is to address the just-in-case research and development preparedness gap between late preclinical and early clinical safety and efficacy testing (phase 2a) of epidemic infectious disease vaccines, in advance of epidemic outbreaks.

CEPI has committed to fundraise and invest at least US$1 billion until 2021.[10] Our previous analysis, which was presented as part of the CEPI preliminary business plan 2017–21,[11] examined the total number of vaccine candidates CEPI would need to invest in today, to advance two to three candidates for two to three epidemic infectious diseases through to phase 2a and stockpile for phase 2b–3 and emergency use in 5 years, under a $1 billion budget constraint.

In this study we estimate the cost of epidemic infectious disease vaccine development from preclinical phase through to the end of phase 2a, on the basis of new data and analytical tools. Assuming that one phase 2b–3 ready vaccine candidate is a reasonable minimum vaccine research and development preparedness target per epidemic infectious disease, the study gives an indication of the number of minimum vaccine candidates and cost to achieve this.

Methods

Study design

We took four distinct analytical steps to help us ascertain costs for achieving minimum vaccine research and development preparedness targets in a given portfolio of 11 epidemic infectious diseases. First, we mapped existing epidemic infectious disease vaccine research and development pipelines and collected self-reported cost data from vaccine developers, associated with epidemic infectious disease vaccine research and development from preclinical phase through to phase 2a. Second, we

tested for drivers of vaccine development costs drawn from published studies, using various statistical techniques. Third, we drew vaccine research and development probabilities of success from published estimates. We combined these with self-reported cost data to simulate costs adjusted for probability of success for advancing vaccines from preclinical testing through to phase 2a, within a Monte Carlo framework. Fourth, we used the cost and probability of success parameters of the simulation to determine minimum portfolio costs required for achieving at least one phase 2b–3 ready candidate for each epidemic infectious disease through a stochastic optimisation model.

Data collection

The epidemic infectious diseases included in this study were selected from WHO's original blueprint list of priority emerging infectious diseases.[4] This list has recently been updated to exclude chikungunya and severe fever with thrombocytopenia syndrome,[5] but we include these in our analysis as they are still assumed to have considerable epidemic disruption potential. We drew our probability of success data from the preclinical phase literature (table 1).[3,6,12–16] The remainder of our data collection efforts focused on vaccine candidate identification and on associated costs. Whereas vaccine candidates were identified through a two-step approach involving a literature review and a survey, cost data were collected via self-reporting in a survey and via mining CEPI's own database of projects and associated budgets.

We searched PubMed, Google, Google Scholar, ClinicalTrials.gov, the International Clinical Trials Registry Platform, country-level trial registries, National Institutes of Health reporter, and WHO pipeline tracker using terms based on [pathogen name], [vaccine candidate name], [developer name], "vaccine" and combinations of these. Searches were limited to the last 11 years (Jan 1, 2006, to Aug 31, 2017). To ensure completeness, we also searched more freely in websites and press releases of organisations identified as epidemic infectious disease vaccine development partners, and scanned reference lists of relevant articles for any missed vaccine candidates from previous searches. Acknowledging that not all pipeline information is publicly available, nor updated regularly, we confirmed the status of the vaccines identified in the literature by sending a survey to 414 organisations. The survey asked recipients to: validate the current status of development of a pre-filled list of vaccine candidates that our team had collated via literature searches, grant database searches and clinical trial registries searches over the past 12 months prior to survey launch, including information on disease, phase of development, vaccine technology type, and product development partners; clarify current sources of funding, development costs incurred and future funding needs for bringing the vaccines through phase 2 and potentially phase 3 in response to potential disease outbreaks, including stockpile estimates for phase 3 trials and for emergency use (the latter not reported in the paper); specify main drivers of R&D costs and technical success to date and identify potential drivers of future costs and technical risks for bringing vaccine candidates through late phases of clinical development. Organisations were those whom we identified as owners, partners, or supporters of epidemic infectious disease vaccine research and development (appendix).

Through our survey and access to CEPI data, we collected new, confidential epidemic infectious disease vaccine research and development cost data. In total, we compiled a set of 138 vaccine research and development cost entries, associated with non-clinical, clinical, process development, and manufacturing activities (appendix). We checked for consistency between our survey data and CEPI's own data on vaccine research and development budgets prior to merging into a single database (appendix). This dataset excludes costs associated with basic laboratory research activities, phase 2b–3 efficacy testing, and stockpiles of investigational material for phase 2b–3 studies.

	Preclinical	Phase 1	Phase 2	Study period start (year)	Study period end (year)
Struck (1996)[13]	57%	72%	79%	1983	1994
Wilson (2010)[16]	40%	33%	33%	Expert based (phase 1 and 2 together)	Expert based (phase 1 and 2 together)
Davis et al (2010)[12]	48%	74%	58%	1995	2011
Pronker (2013)[6]	41%	81%	31%	1998	2009
Chit et al (2014)[15]	N/A	40%	74%	2000	2013
BIO (2015)[14]	N/A	70%	43%	2006	2015
WHO (2016; simple)[3]	41%	68%	46%	Data from Di Masi (2003)[17]	Data from Di Masi (2003)[17]
WHO (2016; complex)[3]	41%	50%	22%	Data from Di Masi (2003)[17]	Data from Di Masi (2003)[17]
Wong et al (2018; all indications)[18]	N/A	77%	58%	2000	2015
Wong et al (2018; orphan vaccines)[18]	N/A	90%	54%	2000	2015
Lowest PoS reported in literature	41%	50%	22%	N/A	N/A
Highest PoS reported in literature	57%	90%	79%	N/A	N/A

N/A=not applicable.

Table 1: **Published estimates of probability of success for vaccine research and development**

See Online for appendix

Drivers of vaccine development costs

The literature suggests that research and development timelines, indirect costs, sectoral affiliation (ie, commercial *vs* non-commercial public or private sectors) and licensure track record of vaccine developers, licensure track record of vaccines for a given disease, and platform technology complexity are all contributing factors to vaccine research and development costs.[3,16,17,19–36] Drawing from this evidence, we constructed several new variables, some of them dichotomous, and we performed various correlation, regression, analysis of variance (ANOVA) and pairwise *t* tests in order to: ascertain how strongly these variables

	Stage 1– How many vaccine candidates would ideally need to enter into preclinical, or phase 1, or phase 2, to achieve at least one phase 2a outcome by EID?	Stage 2*– How much investment would be needed to achieve at least one phase 2 outcome by EID, given existing and new preclinical vaccine candidates being made available?
Objective	Minimise number of phase 2b–3 ready vaccine candidates (95% CI)	Minimise US$ cost associated with developing at least one phase 2b/3 ready vaccine candidate per EID (95% CI)
Decision variables	Number of new vaccine candidates initiating investment at preclinical, or phase 1, or phase 2	Number of ideal vaccine candidates initiating investment by R&D phase; (number of existing vaccine candidates by R&D phase + number of new preclinical vaccine candidates)
Input parameters	Number of vaccine candidates available in the pipeline from preclinical through phase 2 (by EID); PoS by R&D phase (low *vs* high PoS scenario)†	Number of vaccine candidates available in the pipeline from preclinical through phase 2 (by disease); Number of vaccine candidates newly made available in the pipeline at preclinical phase (by disease); Cost by R&D phase (low *vs* high cost distribution scenarios)†; PoS by R&D phase (low *vs* high PoS scenario)†
Output parameters	Number of phase 2b/3 ready candidates (by disease; 95% CI)	Number of phase 2b–3 ready candidates (total and by disease) (95% CI); US$ for achieving phase 2b–3 ready candidates (total and by disease; 95% CI)
Constraints	Decision variables=integers; Decision variables=non-negative; Number of phase 2b–3 ready candidates (by disease) ≥1 (99% CI)	Decision variables=integers; Decision variables=non-negative; Decision variables≤available + new preclinical pipelines; Decision variables≥ideal minimum pipelines for at least one phase 2b–3 ready candidate expected (by disease); Number of phase 2b–3 ready candidates (by disease) ≥1 (95% CI)

PoS=probability of success. R&D=research and development. *Excluding Ebola owing to two phase 2 outcomes already having been achieved for this disease. †Cost and PoS distributions by R&D phase used in this model are provided in the appendix.

Table 2: **Stochastic optimisation model parameters across solution stages**

are related to each other; whether any of these variables are statistically significant explanatory factors of cost; and, if so, which of these can explain variations observed in estimated costs. We also ran a hierarchical cluster analysis to identify other potential factors not captured by the regression model. We did this by computing the distance between clusters using a Euclidean metric as the similarity measure for our data (appendix).

Expected vaccine research and development costs

We considered three key input parameters for estimating vaccine research and development portfolio costs from preclinical through to phase 2a: (1) vaccine development project costs by research and development phase; (2) probability of success by research and development phase; (3) the number of vaccine projects available in the pipeline. Given the relevance of vaccine developer licensure track record and a large variation in self-reported costs not explained by regression or clustering analyses (appendix), we incorporated this uncertainty into a Monte Carlo simulation. Specifically, we defined cost distributions for lower and upper bounds by dividing our sample into two groups: a lower bound group associated with costs reported by product developers with no vaccine licensure track record; and an upper bound group associated with costs reported by product developers with previous licensure experience. For each group, we constructed discrete cost distributions by research and development phase, assigning equal probabilities to the respective self-reported cost estimates. In addition to costs, we constructed triangular distributions for probability of success by research and development phase. Triangular distributions were chosen since they are commonly used to define ranges of values for uncertain variables where available data is either scarce or heterogeneous enough to not clearly dictate the appropriate range and frequency of the possible values of variables.[37] They are characterised by minimum, maximum, and modal, or most likely, values that collectively define the boundaries and shape of the distribution triangles (appendix).

To move from single vaccine candidate costs to portfolio costs accounting for probability of success, we ran the simulation 10 000 times, each time randomly drawing from the following: cost distributions—for each group and research and development phase, each iteration randomly selected one cost estimate from the respective distribution; probability of success distributions—for each research and development phase, each iteration randomly drew a probability of success estimate from the respective distribution.

Within each iteration, the sum of the product of the number of available vaccine candidates, probability of success, and cost was calculated as the vaccine candidates (their integers) advanced through to the end of phase 2a. This allowed the estimation of the mean and 95% CIs of costs adjusted for probability of success for each iteration of the simulation, which, when analysed across all iterations, allowed the calculation of the likely phase 2a outcomes associated with the number of vaccine candidates considered (appendix).

Stochastic optimisation of research and development portfolios and costs

Whereas simulation-based analyses can provide analytical depth to highlighted scenarios, they have a relatively low capacity to demonstrate optimal solutions on their own, such as how to minimise or maximise objectives in epidemic infectious disease vaccine research and development. Given the inherently risky nature of vaccine research and development, stochastic optimisation approaches are likely to represent realistic reflections of the uncertain expectations from the pharmaceutical research and development process. Several stochastic modelling approaches have been proposed in pharmaceutical research and development management to address various portfolio optimisation

	Average EID vaccine R&D cost (US$) by R&D phase (self-reported)*				Average EID vaccine R&D cost(US$) by R&D phase (simulation)†				PoS-adjusted EID vaccine R&D cost (US$; simulation)‡		
	Preclinical	Phase 1	Phase 2	Total	Preclinical	Phase 1	Phase 2	Total	Starting from phase 2	Starting from phase 1	Starting from preclinical
High cost/high PoS scenario											
Mean	26 284 880	14 207 067	28 002 370	68 494 317	26 285 345	14 207 153	28 002 393	68 494 335	112 005 164	200 890 239	468 538 014
SD	28 345 786	15 265 428	26 226 347	67 747 184	27 914 228	15 032 372	25 826 057	40 849 928	103 304 711	142 019 505	332 532 567
5th percentile	1 710 000	1 918 200	3 921 100	11 654 600	1 710 000	1 926 000	3 973 000	19 472 597	15 892 000	53 595 000	98 609 900
95th percentile	98 833 489	55 361 056	93 551 555	247 746 100	81 190 698	49 087 223	73 645 079	158 508 350	294 580 316	493 560 396	1 060 235 774
Minimum	1 710 000	1 900 000	3 800 000	9 500 000	1 710 000	1 900 000	3 800 000	7 410 000	15 200 000	22 800 000	36 636 000
Maximum	140 000 000	70 000 000	140 000 000	350 000 000	140 000 000	70 000 000	140 000 000	309 895 833	560 000 000	1 120 000 000	2 345 436 114
Low cost/low PoS scenario											
Mean	7 866 576	6 806 587	16 778 360	31 451 513	7 886 096	6 806 116	16 778 294	31 450 728	83 893 986	166 665 969	319 206 692
SD	5 925 791	5 722 608	10 508 552	18 975 332	5 895 823	5 694 263	10 458 030	13 377 017	52 306 472	86 375 514	150 096 592
5th percentile	2 000 000	2 000 000	4 600 000	9 500 000	2 000 000	2 000 000	4 600 000	13 749 750	23 000 000	60 495 500	136 327 312
95th percentile	19 501 799	18 800 657	37 045 400	66 489 160	19 227 000	17 872 540	36 918 000	56 741 358	184 590 000	333 504 000	593 891 509
Minimum	1 800 000	1 027 000	4 370 000	8 415 000	1 800 000	1 027 000	4 370 000	8 300 000	21 850 000	32 120 000	78 000 000
Maximum	37 441 000	30 155 280	54 474 105	117 057 000	37 441 000	30 155 280	54 474 105	95 704 246	272 370 526	602 459 509	1 266 053 842

R&D=research and development. PoS=probability of success. *Cost of advancing one EID vaccine through to end of phase 2a as self-reported through survey, assuming 100% PoS. †Cost of advancing one EID vaccine through to end of phase 2a based on simulation, assuming 100% PoS. ‡Cost of advancing one EID vaccine through to end of phase 2a based on simulation, accounting for PoS.

Table 3: **Cost estimates of epidemic infectious disease vaccine R&D, based on self-reported and simulation–optimisation data**

problems (see literature overview in appendix).[38] Drawing from previous evidence, we built a two-stage stochastic optimisation model—ie, a stepwise optimisation of objectives that includes uncertainty—to identify optimal research and development portfolios and costs for progressing at least one vaccine candidate per epidemic infectious disease through to end of phase 2a. In stage 1, we derived the minimum number of ideal candidates required to achieve at least one phase 2b–3 ready candidate for an epidemic infectious disease, starting from preclinical testing, to phase 1 and phase 2, respectively. Using this information against the evidence on available pipelines per epidemic infectious disease, we derived the minimum and maximum number of vaccine candidates needed by research and development phase to progress at least one of these through to end of phase 2a. In stage 2, we drew from stage 1 findings to define lower and upper boundaries of vaccine candidates by research and development phase, on the basis of which we estimated the minimum cost of successfully developing at least one phase 2b–3 ready candidate per epidemic infectious disease.

We provide a detailed overview of the stochastic optimisation model's rationale, formulation, and solution search method in the appendix. We summarise the objectives, decision variables, input parameters, output parameters, and constraints associated with each solution stage of the optimisation problem in table 2.

In this model, we treated cost and probability of success by research and development phase parameters as random variables with the same distributions as in the simulation. The stochastic modelling approach ensured the robustness of our optimisation findings—ie, allowed us to run probabilistic sensitivity analyses on all the outputs of the model, capturing both the sources of variability as well as the probabilities attached to different modelling outputs expected (see appendix for more details).

Role of the funding source

The funders had no role in the study design, data collection, data analysis, interpretation, or writing of the study. At the time of the initiation and design of this project, the chief executive of the funding source (J-AR) was the principal investigator of the grant. He had no role in the funding or follow-up of the project from the funder's side after taking on his current funding-source role. He was involved in study design, data interpretation, and writing of the study. DG had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From our literature search, we identified 262 vaccine candidates in preclinical to phase 2 stages for 11 epidemic infectious diseases. Of the 414 organisations we approached, we received survey responses from 64, covering 314 vaccine candidates for epidemic infectious diseases in total. Of these, 121 were confirmations of vaccine candidates that were active, not yet started, or on-hold owing to lack of funding, previously identified through the literature review. 193 were newly reported vaccine candidates, of which 97 candidates had infectious diseases of epidemic potential outside the scope of the WHO priority list. From the original set of 262 vaccine candidates identified in the literature for the 11 WHO

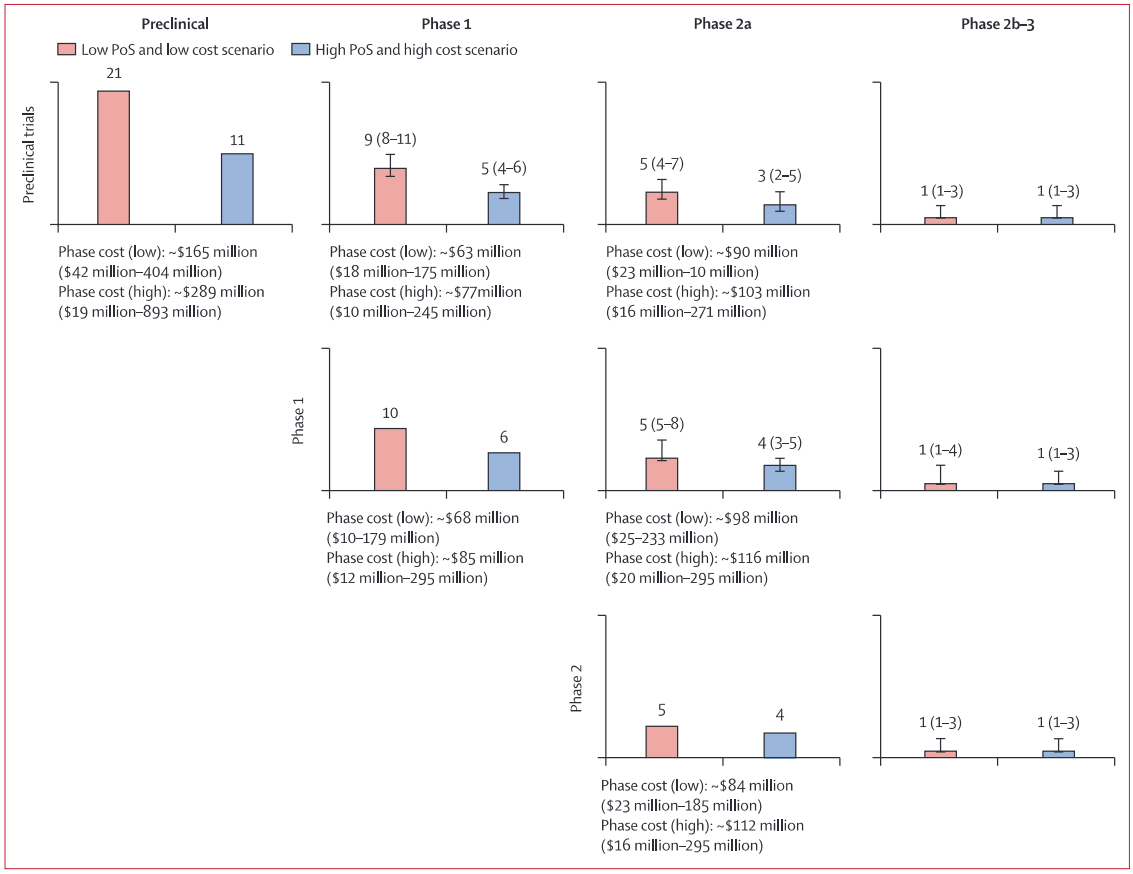

***Figure*: Estimated cost of progressing at least one epidemic infectious disease vaccine from preclinical through to end of phase 2a**
PoS=probabilities of success. Figures in US$.

priority epidemic infectious diseases, 104 remained unspecified owing to lack of responses at the end of the survey; 44 were confirmed as terminated, on hold for technical reasons or were not confirmed at all as active projects by survey respondents; and 114 were confirmed as active, not yet started, or on hold owing to lack of funding or other reasons not related to technical failures. In total, these pipeline searches amounted to 224 vaccine candidates from preclinical to phase 2, for 11 priority epidemic infectious diseases (appendix).

Reported vaccine development costs from preclinical testing through to end of phase 2a range from $8 million to $350 million (table 3). Based on the regression analysis, previous licensure experience and indirect costs associated with operating models of vaccine developers are statistically significant explanatory factors driving an increase in research and development costs. Previous licensure of vaccines for a given disease can potentially drive a reduction in research and development costs. However, a licensed prophylactic vaccine for humans does not exist for any of the 11 epidemic infectious diseases. A hierarchical clustering analysis suggests that increased research and development costs in clinical research and development phases may also potentially be associated with increased industrial sector affiliation. Substantial variation in reported costs cannot be explained despite considering several factors, including, in addition to the above, research and development timelines and previous licensure track-record of platform technologies (appendix).

The simulation suggests that the advancement of a single epidemic infectious disease vaccine candidate from preclinical through end of phase 2a can cost $31–68 million ($14–159 million range), assuming no risk of failure (table 3). However, the total cost of progressing one epidemic infectious disease vaccine successfully through to end of phase 2a is dependent on the probability of success and on the shape of the vaccine research and development pipeline. As the figure demonstrates, accounting for probability of success and assuming no clinical vaccine candidates exist for a given epidemic infectious disease, 11 to 21 preclinical candidates would be required if at least one of these were to progress through to end of phase 2a, at a cost of $319–469 million ($137 million–$1·1 billion range). Similarly, six to ten phase 1 candidates would

	Number of confirmed vaccine candidates			Expected US$ cost, preclinical through to phase 2a (95% CI)		Expected number of phase 2b/3 ready vaccine candidates (95% CI)	
	Preclinical	Phase 1	Phase 2	Low PoS–low cost scenario	High PoS–high cost scenario	Low PoS–low cost scenario	High PoS–high cost scenario
Ebola	37	4	1	661 million (297–1200 million)	1800 million (428–4100 million)	3 (1–7)*	9 (5–14)*
Zika	28	8	1	587 million (260–1100 million)	1500 million (391–3500 million)	3 (2–6)	9 (6–13)
Chikungunya	20	5	2	424 million (187–768 million)	1100 million (282–2500 million)	2 (1–4)	6 (4–9)
Lassa	28	..	..	431 million (183–800 million)	1200 million (270–2800 million)	2 (1–5)	6 (3–9)
MERS	21	4	..	389 million (172–703 million)	1100 million (257–2400 million)	1 (1–4)	5 (3–8)
Marburg	19	2	..	322 million (142–593 million)	901 million (210 –2000 million)	1 (1–3)	3 (2–6)
Rift Valley fever	15	..	2	258 million (112–466 million)	703 million (165–1600 million)	1 (1–3)	3 (2–5)
Nipah	13	..	..	191 million (82–359 million)	558 million (116–1300 million)	0 (0–2)	2 (1–4)
CCHF	6	1	..	95 million (39–179 million)	279 million (62–620 million)	0	0 (0–1)
SARS	6	..	..	81 million (34–154 million)	242 million (47–554 million)	0	0 (0–1)
SFTS	1	..	-	8 million (2–19 million)	26 million (2–81 million)	0	0
Total	194	24	6	3600 million (1600–6600 million)	9800 million (2400–21 600 million)	13 (6–34)*	43 (26–70)

MERS=Middle East respiratory syndrome. CCHF=Crimean Congo haemorrhagic fever. SARS=severe acute respiratory syndrome. SFTS=severe fever with thrombocytopenia syndrome. R&D=research and development. *New candidates, as two phase 3 ready candidates already exist.

Table 4: **Costs and expected R&D outcomes from advancing all available vaccine candidates for 11 epidemic infectious diseases from preclinical through to end of phase 2a**

be needed for at least one candidate to advance through to end of phase 2a, at a cost of $167–201 million ($61 million–$485 million range). Assuming vaccine candidates and funding were made available, progressing at least one vaccine through to end of phase 2a for each of the 11 epidemic infectious diseases would cost a minimum of $2·8–3·7 billion ($1·2 billion–$8·4 billion range). Finally, at least one candidate would progress through to end of phase 2a, out of initial investments of $84–112 million ($23 million–$295 million range) in four to five phase 2 candidates.

At the time of writing, there are 194 preclinical trials, 24 phase 1, and six phase 2 vaccine candidates under development for 11 epidemic infectious diseases. As table 4 demonstrates, 13 candidates (six to 34 range) would progress through to end of phase 2a at a cost of $3·6 billion ($1·6–6·6 billion range), in a low probability of success and low cost scenario (table 4). Under a high probability of success and high cost scenario, the cost for 43 phase 2b–3 ready candidates (26–70 range) would amount to $9·8 billion ($2·4–21·6 billion range). Seven epidemic infectious diseases—Zika, Ebola, chikungunya, Rift Valley fever, Marburg, and Lassa—have sufficient vaccine pipelines for investments (if made available) to guarantee successful phase 2a outcomes regardless of probability of success (in reality, phase 2b–3 ready candidates already exist for Ebola). Under a low probability of success scenario, the successful progression of a vaccine through to end of phase 2a cannot be guaranteed for Nipah, given the available candidates for this epidemic infectious disease. Vaccine pipelines for Crimean Congo haemorrhagic fever, severe acute respiratory syndrome, and severe fever with thrombocytopenia syndrome comprise too few candidates for any phase 2a outcomes to be predicted through investments in these, even under a more optimistic probability of success.

Based on the stochastic optimisation (table 5), lower investments would be needed in a smaller number of vaccine candidates to achieve phase 2a outcomes in chikungunya, Zika, Rift Valley fever, Middle East Respiratory Syndrome, and Marburg, as their clinical vaccine pipelines are modestly mature. Higher investments across a larger number of preclinical vaccine candidates would be needed for a Lassa phase 2b–3 ready vaccine to be guaranteed. 18 to 55 new preclinical candidates would need to be added to the vaccine pipelines of Nipah, Crimean Congo haemorrhagic fever, severe acute respiratory syndrome, and severe fever with thrombocytopenia syndrome collectively for a phase 2b–3 ready candidate to be guaranteed in each of these epidemic infectious diseases.

A probabilistic sensitivity analysis is embedded in the findings through stochastic modelling (appendix). This analysis demonstrates that whereas zero phase 2a outcomes are unlikely given the numbers of vaccine candidates supported by research and development phase under the low and high probability of success scenarios, outcomes previously mentioned and beyond one phase 2b–3 ready candidate per epidemic infectious disease are dependent on the probability of success. In a scenario in which low costs were associated with high probability of success distributions, the same numbers of vaccine candidates would need to be supported as per the high probability of success and high cost scenario to achieve minimum phase 2a outcomes per epidemic infectious disease, but the overall portfolio cost would reduce to US$1·6 billion ($715 million–2·9 billion range). In contrast, in a scenario where high costs were associated with low probability of success distributions,

	Number of preclinical candidates (high PoS/high cost to low PoS/low cost scenario)		Number of phase 1 candidates (high PoS/high cost to low PoS/low cost scenario): number of available candidates	Number of phase 2 candidates (high PoS/high cost to low PoS/low cost scenario): number of available candidates	Expected US$ cost, preclinical through phase 2a (95% CI)		Expected number of phase 2b/3 ready vaccine candidates (95% CI)	
	Number of available candidates	Number of new candidates needed			Low PoS/low cost scenario	High PoS–high cost scenario	Low PoS–low cost scenario	High PoS–high cost scenario
Chikungunya	0–3	..	2–5	2	155 million (66–289 million)	112 million (34–252 million)	1 (1–3)	1 (1–2)
Zika	..	..	4–8	1	149 million (54–299 million)	158 million (45–357 million)	1 (1–3)	1 (1–3)
Rift Valley fever	5–13	..	..	2	224 million (100–409 million)	244 million (61–570 million)	1 (1–3)	1 (1–2)
MERS	3–12	..	4	..	244 million (108–439 million)	245 million (71–543 million)	1 (1–3)	1 (1–3)
Marburg	7–16	..	2	..	274 million (119–495 million)	358 million (86–792 million)	1 (1–3)	1 (1–3)
Lassa	11–21	..	..	..	319 million (137–590 million)	469 million (99–1100 million)	1 (1–3)	1 (1–3)
CCHF	6	3–12	1	..	289 million (125–531 million)	414 million (94–911 million)	1 (1–3)	1 (1–3)
Nipah	11–13	0–8	..	..	319 million (137–590 million)	469 million (99–1100 million)	1 (1–3)	1 (1–3)
SARS	6	5–15	..	..	319 million (137–590 million)	469 million (99–1100 million)	1 (1–3)	1 (1–3)
SFTS	1	10–20	..	..	319 million (137–590 million)	469 million (99–1100 million)	1 (1–3)	1 (1–3)
Total	50–91	18–55	13–20	5	2800 million (1200–5000 million)	3700 million (900–8400 million)	10 (10–30)	10 (10–29)

Table 5: **Minimum R&D portfolios and costs for progressing at least one vaccine candidate through end of phase 2a, per epidemic infectious disease**

the same numbers of vaccine candidates would need to be funded as per the low probability of success and low cost scenario to successfully advance at least one vaccine through to end of phase 2a successfully. In this case, however, the associated portfolio cost would increase to $6·8 billion ($1·5–15·1 billion range; appendix).

Discussion

The vaccine research and development cost estimates produced in this study highlight the need for substantial investments in priority epidemic infectious diseases if minimum vaccine research and development preparedness targets—ie, at least one phase 2b–3 ready vaccine candidate per epidemic infectious disease—are to be achieved, given the relatively large number of preclinical candidates and the low probability of success associated with these. Our analysis identifies several disease areas for which the upstream vaccine research and development pipeline today is insufficient, and highlights the need for entry of new vaccine candidates into preclinical development if the chances of minimum vaccine research and development preparedness targets are to be increased. Moreover, we demonstrate that higher vaccine research and development costs, and in particular clinical research and development costs, are likely to be associated with greater industrial sector affiliation and previous licensure experience of vaccine developers. If this experience were assumed to translate to higher probability of success, investing in these projects could progress more epidemic infectious disease vaccines through to end of phase 2a.

Our analysis demonstrates that it is possible to use simulation-optimisation techniques to generate vaccine development cost estimates by combining pipeline and cost information, subject to multiple objectives against a range of constraints. In doing so, this study meaningfully combines up-to-date evidence on research and development pipelines and project costs with rigorous analytical methods to demonstrate investment needs under alternative scenarios. Moreover, we have done this study with the consideration of research and development cost drivers and uncertainty in both costs and probability of success informing the analysis.

Evidence on the cost of pharmaceutical research and development has been made available since at least the 1950s;[19] however, this has been limited to mainly chemical drug products.[20] Whereas the Di Masi and colleagues publications[17,21–23] have provided the foundations on which numerous analyses or critiques of pharmaceutical research and development costs have since been conducted,[16,19,20,24–33] evidence on vaccine-specific research and development costs for epidemic infectious diseases has been scarce for several reasons. First, the process of vaccine development might differ substantially from that of drug development, with implications for scale and intensity of resource use and associated costs by research and development phase.[34] Second, the complexity of the platform technologies used to develop vaccines might influence research and development costs.[3,20,35,36] The literature assumes that new technologies with no licensure track-record will induce higher research and development costs than well-established technologies. Third, the complexity of the pathogen against which vaccines are developed might affect research and development costs,[3,20,35,36] with vaccines against pathogens for which licensed vaccines already exist assumed to cost less.

The handful of articles published on vaccine research and development costs to date are either too descriptive or based on expert opinions with little data input to validate those claims,[16,28,35] focusing on single pathogens[15] or only on clinical research and development phases.[15,28] Studies[3,36]—one drawing on source data and assumptions from the other—have attempted to overcome several of the above limitations, focusing their analyses on either poverty diseases or epidemic infectious diseases, which are both characterised by poor commercial potential, as well as differentiating more systematically between costs associated with incremental versus breakthrough innovations.[3,36]

Our study attempts to overcome some of the limitations identified in previous vaccine research and development cost analyses and tries to deviate from recent studies focused on epidemic infectious disease vaccine research and development in several ways. First, although we draw our probability of success estimates from published evidence specific to vaccine research and development,[3,6,12–16] we consider probability of success distributions instead of point estimates, acknowledging uncertainties in research and development that cannot be attributed to specific explanatory factors, as our regression analyses have shown. Second, we draw our cost data from both historically incurred and projected cost estimates in infectious disease vaccine research and development, as reported by vaccine developers who are active specifically in the field of epidemic infectious diseases. This gives us confidence that the baseline cost estimates informing our models can provide a more accurate reflection of total investments needed for epidemic infectious disease vaccine development.

Third, our collected data suggest that costs associated with new technologies do not differ substantially from costs associated with well-established technologies—a finding that is contradictory to the prevailing assumptions made in the literature to date. This may be because of the compounding complexities of certain pathogens that make it difficult to disassociate pathogen-specific from technology-specific cost drivers, unless one has access to more granular cost data. However, a more plausible explanation perhaps is that cost variations are strongly associated with business models, rather than the technologies themselves, by which the various vaccine developers in epidemic infectious diseases are operating in the industry or non-industry sector.[35] Our statistical analysis suggests that platform technologies are not a substantial explanatory factor for average vaccine development project costs, even if we control for the assumption that the data may be nested with respect to the individual pathogens. Instead, it is indirect costs and variations in costs associated with different levels of experience in the organisations developing these products that drive cost estimates upward.

Our study has several limitations. First, the average vaccine development project cost estimates, from which our simulation-optimisation approach draws, are based on self-reported data by vaccine developers. Despite the statistical analyses and our consistency checks with CEPI and literature sources to minimise bias, such bias is likely to persist in any self-reported cost projections. This implies a certain price for innovation that vaccine developers are willing to accept in order to engage in research and development, which may differ across sectors and organisations operating with different business models and internal cost structures.[39] However, in practice, project costs in areas of relatively low commercial potential are more likely to be established by payer–developer negotiations around risk and benefit sharing, which balances payer constraints with the developers' appetite for financial risk exposure. Coupled with unexpected circumstances, such as unforeseen regulatory requirements, or technological spillovers from other research and development activities, such factors may well drive realised vaccine research and development expenditures either way, downwards or upwards, compared with the estimates provided in this study.

Second, the assumption that higher probability of success is associated with more experienced vaccine developers, and vice versa, is based on common sense and insights shared by vaccine developers during the survey process. However, clear evidence in the literature does not exist to indisputably substantiate such claims. The implications for epidemic infectious disease vaccine research and development cost estimates could be considerable. On one hand, higher probability of success associated with less experienced vaccine developers could well mean that the portfolio costs of achieving at least one phase 2a outcome per priority epidemic infectious disease would be lower than our analysis suggests. On the other hand, lower probability of success manifested in experienced vaccine developer efforts would suggest much higher portfolio costs than has been reported in this study.

Third, the numbers of vaccine candidates and associated portfolio costs reported in this study do not guarantee with full certainty that one phase 2a outcome per epidemic infectious disease would be achieved, under any probability of success and cost scenario. Given the confidence intervals applied, there is a small chance that the suggested vaccine candidates and costs would fail to meet such clinical development targets. Increasing the confidence intervals in the analysis would improve the certainty of phase 2a outcomes. However, given the variance in reported costs and probability of success estimates, the lower and upper limits of vaccine candidates required and associated portfolio costs would increase substantially in the model.

Fourth, our analysis is limited in scope to 11 priority epidemic infectious diseases. There are many other infectious diseases of epidemic potential that deserve attention according to different priority lists[11] and experts'

perspectives.[8] Our estimates of costs draw on contemporaneous information made available on vaccine research and development pipelines for more than just the 11 epidemic infectious diseases, and provide an overall price tag for bringing vaccines against the 11 epidemic infectious diseases successfully through to phase 2. Further pipeline data collection work would be needed to increase the number of diseases included in the cost analysis.

Fifth, our study does not report or estimate funding flows to epidemic infectious disease vaccine research and development, which other surveys do, at least for other neglected disease areas, and more recently, Ebola.[7] Different vaccine developers will probably have different capacities to access internal or external financing, which suggests that the funding gaps to support epidemic infectious disease vaccine research and development may be, overall, smaller than the cost estimates reported in this study as well as varying between sectors and types of organisations researching and developing epidemic infectious disease vaccines. This may also suggest that, in practice, transition probability of success between development phases is also likely to vary between organisations not only for technical reasons but also because of access to finance bottlenecks. It would be a plausible assumption to make that those organisations with previous licensure experience (and marketed vaccines) also have better access to finance, and are therefore, for financial reasons, likely to face higher probability of success in the vaccine research and development programmes (as captured by our high probability of success to high cost scenario).

Sixth, the hierarchical clustering analysis highlighted the possibility of marginal differences in costs between industry versus non-industry actors of different sizes. Our data sample was not sufficiently large to confidently label observations as smaller versus larger industry actors, nor was the composition of the partnerships developing these vaccines clearcut between sectors, subsectors, or geographical regions. These variables, in addition to the definitional challenges of what constitutes smaller or larger industry actors, suggest that more research would be needed to understand, and to report with greater certainty, any significant differences in costs associated with size, sectoral affiliation, and geographical location of vaccine developers.

Seventh, the study estimates costs for only a small part of a much bigger picture in epidemic infectious disease vaccine research and development preparedness. The research and development scope of our analysis is restricted to preclinical, phase 1, and phase 2a. It excludes costs associated with phase 2b–3 trials, stockpiles of phase 2b–3 ready material, regulatory, and delivery activities (including for having in-country infrastructure to support emergency response activities)—all critical elements of vaccine research and development preparedness needs in response to public health emergencies. Issues pertaining to clinical trial design, locations, and target populations of clinical studies, are some of the many factors that are likely to drive clinical development costs but which have not been explicitly considered in our study. These issues, together with factors pertaining to stockpile strategies and phase 2b–3 trial complexities under different disease outbreak scenarios, clinical trial designs, and regulatory requirements, deserve special attention and a separate analysis, which we hope a future study will provide.

Eighth, our simulation–optimisation framework assumes that one phase 2b–3 ready vaccine candidate expected per disease is a sufficient research and development preparedness target for efficacy testing in response to an epidemic. This assumption might not be the case if historical probability of success for phase 3 in the literature is considered.[6] However, unique clinical trial designs and speedy launches of these might be required to mitigate against waning disease outbreaks,[40] which might require different thresholds for clinical and regulatory success during public health emergencies. Moreover, as experience with Ebola and other recent epidemic infectious disease outbreaks has shown, interest of funders in supporting vaccine research and development in response to outbreaks withers together with the waning of epidemics. Any additional phase 2b–3 ready vaccine candidate would not only require an additional multimillion investment just in case, but also a substantial new investment in phase 2b–3 testing and emergency response. Whether more than one phase 2b–3-ready vaccine candidates can be supported for a particular epidemic infectious disease is therefore also an issue for consideration by funders and decision makers in the epidemic infectious disease vaccine research and development space.

Vaccines for epidemic infectious diseases need the world's attention and investment efforts if we are to respond effectively to potential future epidemics and avert humanitarian crises. Our study offers a comprehensive set of epidemic infectious disease vaccine research and development pipeline and cost findings and a reproducible methodology for identifying optimal research and development portfolios and associated investment needs across several of these diseases. More broadly, we demonstrate that a better understanding of disease-specific product research and development pipelines and associated costs through rigorous analyses can benefit any assessment of investment needs in global health research and development, improving the credibility of claims around funding requirements and of portfolio planning.

Contributors

DG led the model design, data collection, analysis and interpretation, and Article writing. TTL and KH co-led the vaccine pipeline and cost data collection and contributed to the analysis and interpretation of the article findings. AK co-led the statistical analysis, supervised overall methods design, data analysis, and interpretation of findings. TD and NCH contributed to the vaccine pipeline data collection, analysis, and interpretation of findings. JMR and PMH contributed to methods validation, analysis, and interpretation of findings. J-AR supervised the

overall methods design, contributed to data analysis and interpretation of findings.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

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Supplementary Materials

This document provides supplementary information on data, methods and results for our study on estimating the cost of vaccine development against epidemic infectious diseases. The supplement is comprised of five appendices, which are critical companions of the main article shedding light on methods, assumptions and data sources across all stages of analysis. The appendices include:

- Appendix 1: Acknowledgements
- Appendix 2: EID vaccine R&D pipeline and cost research methods
- Appendix 3: Statistical analysis methods and results for estimating vaccine development project costs and their explanatory factors
- Appendix 4: Monte Carlo Simulations for determining R&D costs associated with current vaccine pipeline structures for 11 EIDs
- Appendix 5: Stochastic optimization methods and sensitivity analysis

Appendix 1: Acknowledgements

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- Institut Pasteur
- Integrated Biotherapeutics
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- Karolinska Institutet
- Leaf expression systems
- LiteVax B.V.
- Medigen, Inc.
- Moderna Therapeutics
- MonitorCRO
- Najit Technologies, Inc
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- New York Blood Center
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- Vaccine and Infectious Disease Organization-International Vaccine Centre (VIDO-InterVac)

- Valneva SE
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- Wageningen Bioveterinary Research
- Undisclosed survey respondent
- Undisclosed survey respondent
- Undisclosed survey respondent
- Undisclosed survey respondent
- Undisclosed survey respondent

Appendix 2: EID vaccine R&D pipeline and cost data collection methods and additional results

In this appendix we present the details of our EID vaccine R&D pipeline and cost data collection methodology, including the presentation of some additional findings underpinning assumptions behind our simulation and stochastic optimization methods explained in other appendices of this supplement.

We begin with a discussion of the search methods and assumptions underlying the pipeline research process, including sources and strategies used to clean and validate the collected data. We then turn to the steps undertaken to collect cost information associated with EID vaccine R&D pipelines, providing details of the raw data findings and the assumptions behind these.

Step 1: Pipeline research

Our pipeline research comprised of a two stepped process:

- Step 1: a literature search
- Step 2: a survey-based validation process of the literature findings (and in some cases the identification of new candidates not available through public sources).

The final EID vaccine R&D pipeline included in this study is the outcome of these two sequential steps and is constrained by the following key assumptions that served as screening criteria in the pipeline compilation process:

- A vaccine candidate would need to be directed towards human use
- A vaccine candidate would need to classify as such if it followed the typology on vaccine technologies provided in the literature[1]
- Candidates demonstrating purely a passive immunization (e.g monoclonal antibodies) would not be considered as vaccines
- Vaccine candidates would only be considered if:
    - They had shown, as a minimum, some immunogenicity data in an animal model. If only in vitro studies and/or computational studies were available, candidates would be disregarded.
    - They had generated efficacy data, and showed complete protection. If candidates demonstrated efficacy data but did not show complete protection they would be disregarded.
    - They had not been terminated for safety reasons.
    - They were not duplicate entries with other candidates identified through different literature sources or survey respondents, on the basis of whether: (1) the candidates targeted the same antigen (and hence the same disease); (2) the candidates used the same platform technology; (3) developers of these vaccine candidates were the same. If vaccine candidates differed on one or more of these three criteria, and were reported as such by survey respondents also, they were considered as different vaccine candidates.
    - They had demonstrated some R&D activity, through published or other sources, during the past 10 years and no earlier than 2006.

Step 1.1: literature search

From April to July 2016 we collected data on vaccine R&D pipelines from preclinical through Phase III for 11 pathogens deemed by the WHO as likely to cause severe outbreaks in the near future. The original dataset was largely based on: a report by the Norwegian Institute of Public Health;[2] additional expert inputs from CEPI task teams (listed in the CEPI preliminary business plan 2017–2021);[3] mining of key academic literature,[3–11] clinicaltrials.gov; the NIH project reporter database; and other publicly available sources (e.g. numerous other funder websites and individual researcher and developer websites) for vaccine pipeline information on vaccines within the WHO scope. Depending on source searching, search terms were based on [pathogen name], [vaccine candidate name], [developer name], 'vaccine' and combinations of these. Searches were limited to the last 11 years (2006 onwards).

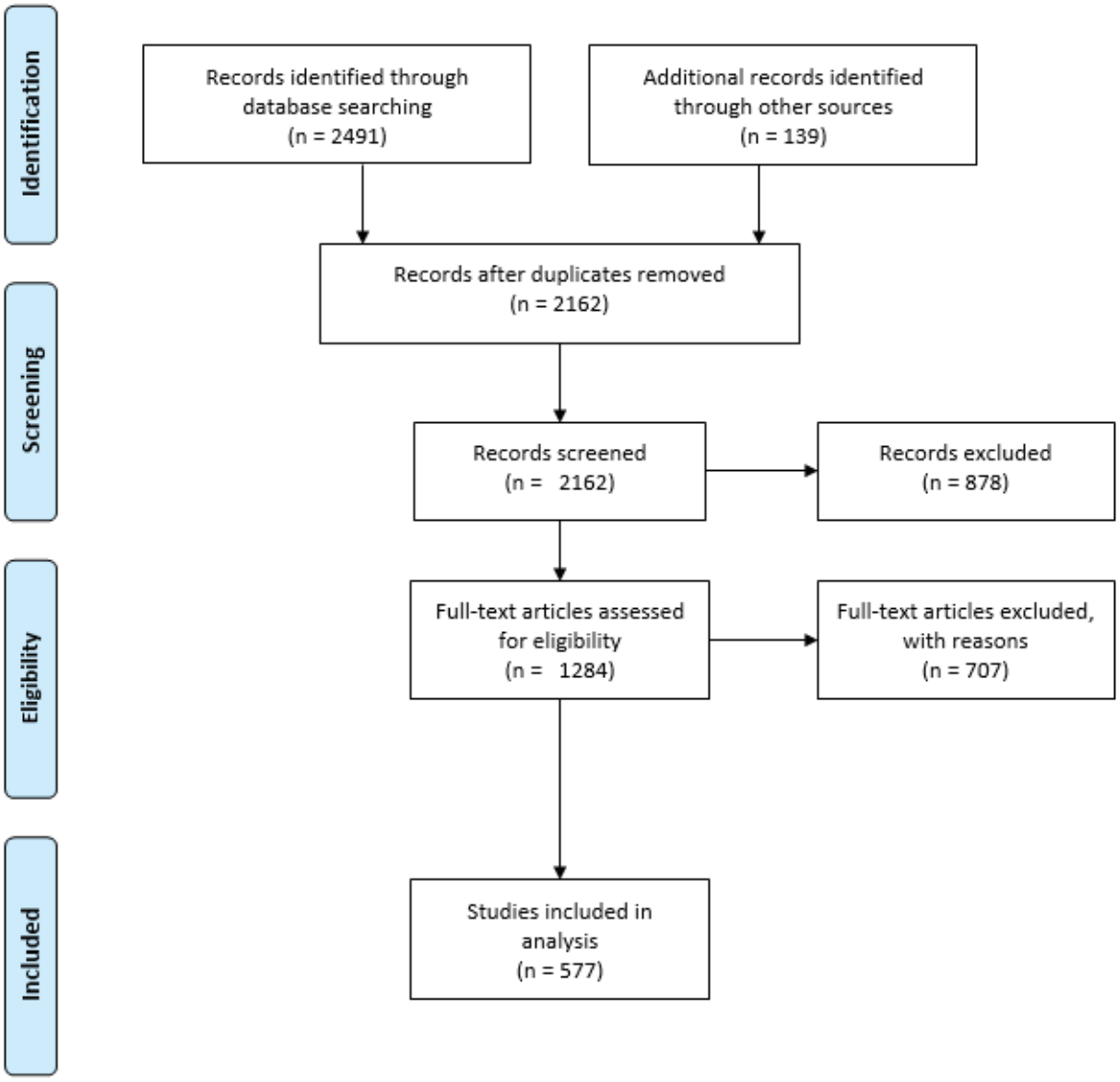
From January 2017 to September 2017 the original pipeline database was updated. Specifically, we applied different search strategies on the following sources:

- **Pubmed**: First, we searched using a combination of two search options: "All field" for term "vaccine" and "Meshterm" for name of the disease. Second, we searched by name of each EID under "Abstract".
- **Google & Google Scholar**: We searched by EID name and keyword "vaccine".
- **Clinicaltrial.gov**: We searched by EID name under search field 'condition' and by keyword "vaccine" under search field 'intervention'.
- **ICTRP and country level trial registries**: We searched by EID name under search field 'condition' and by keyword "vaccine" under search field 'intervention'.
- **NIH reporter**: We searched by EID name and keyword "vaccine" using text Search (Logic) under search fields 'Search in: Project and FY: Active Projects'
- **WHO pipeline tracker**: We searched for EID vaccines without specific search terms using this publically available dataset.

In order to ensure completeness of our search efforts, we also searched for pipeline information more freely in websites and press releases of organizations identified as vaccine development partners in our previous literature searches. We scanned the reference lists of identified articles in the literature for any missed vaccine candidates from previous searches. And we circulated lists of vaccine candidates including literature references to members of CEPI's Scientific Advisory Committee and other experts, for confirmation, addition to, or modification of our previous literature findings where more up to date information was made available on any particular candidate.

From an original volume of ~2,500 articles identified through the various sources and search strategies described above, we identified ~600 articles, press releases and online material as in scope and associated with a potential total number of 262 vaccine candidates from preclinical through phase III against the 11 EIDs. (See references for these at the end of the appendix)

Appendix figure 2.1: PRISMA flow diagram



Step 1.2: survey validation

We acknowledge that the definition of current product pipelines is challenging as there are a number of limitations to information gathering, including: not all information is publically available as developers may wish to keep information confidential, not all information is updated regularly on the publically available sources, the status of product development is dynamic, including partners involved and development status. In order to address these limitations we conducted a survey validation step.

Specifically, from September 2017 to January 2018 we validated the previously collated EID vaccine R&D pipeline data, through a survey sent to 414 organizations identified as directly or indirectly (e.g. as funders or collaborating partners of vaccine project owners) relevant to EID vaccine R&D in previous literature searches (covering the 262 vaccine candidates identified in Step 1). The survey aimed to:

- capture the current status of development of the various vaccine candidates identified in the literature

- identify potentially new vaccine candidates for which information had not been previously made publicly available in the literature
- clarify information on vaccine candidates related to: disease focus; platform technology used; product development partners; sources of funding; time spent and timelines projected for bringing candidates from preclinical through phase II stages of development; costs realized and costs projected for bringing candidates from preclinical through phase II stages of development; drivers of costs, timelines and risks associated with vaccine candidate development programmes.

We received survey responses from 64 organizations, covering 314 vaccine candidates for EIDs in total. Out of these, 121 were confirmations of active, not yet started or on hold vaccine candidates due to lack of funding previously identified through the literature review. 193 were newly reported vaccine candidates, out of which 97 vaccine candidates concerned infectious diseases of epidemic potential outside the scope of the WHO priority list.[1]

From the original set of 262 vaccine candidates identified in the literature for the 11 WHO priority EIDs, 104 remained unspecified due to lack of responses at the end of the survey, 44 were confirmed as terminated, on hold due to technical reason or were not confirmed at all as active projects by survey respondents, and 114 were confirmed as active, not yet started, or on hold due to lack of funding or other reasons not related to technical failures.

Appendix tables 2.1 to 2.11 below presents the validated list of vaccine candidates currently active, not yet started, or on hold due to lack of funding or other reasons not associated with technical failures, for 11 WHO priority EIDs. The table provides information on a total number of 210 candidates (including: survey validated candidates identified initially through the literature; new candidates reported by survey respondents not available in the literature; and excluding candidates from CEPI's own database of projects for which no evidence had been generated either through literature or survey). This table is based on the data collection and validation process outlined above and is limited, to our best of effort, and reflection of the current status of the vaccine development pipelines as at 30th January 2018.

Vaccine R&D pipelines for 11 priority EIDs (as of 30th January 2018), including two phase IIb/III ready vaccine candidates for Ebola, are presented in appendix tables 2.1 to 2.11 below.

[1] Anaplasmosis; Argentinian Haemorrhagic Fever; Avian Influenza Type H7; Babesia, atypical; Bolivian Haemorrhagic Fever; Bordetella pertussis; Borrelia miyamotoi; Campylobacter jejuni; Coxiella Burnetti (Q Fever); Cytomegalovirus; Dengue; Dobrava virus; East Equine Encephalitis; Ehlrichiosis; Enteroxinogenic Escherishia Coli (ETEC) diarrhoeal disease; Guanarito; Hantavirus Cardiopulmonar; Hepatitis E; Herpes Zoster; HPV; Human metapneumovirus and parainfluenza combinations; Human monkeypox; Influenza universal; Japanese Encephalitis; Junin; Lyme borreliosis; Machupo; Measles; Neisseria meningitidis; Norovirus; O'nyong'nyong virus; Pandemic H1N1; Pandemic H10N8; Pandemic H7N9; Paratyphoid; Plague; Puumala virus; Respiratory syncytial virus; Sabia; Schmallenberg disease; Seoul virus; Shigella; Smallpox, Variola major and other related pox viruses; Tickborne Encephalitis Complex Flaviviruses; Tuberculosis; Typhoid fever; Venezuelan Equine Encephalitis; Venezuelan Haemorrhagic fever; West Equine Encephalitis; West Nile Virus; Yellow Fever.

Appendix Table 2.1: Chikungunya vaccine R&D pipeline, preclinical through phase II

Disease	Vaccine candidate	R&D phase	Development Partners
Chikungunya	VRC-CHKVLP059-00-VP (37997)	Phase II	National Institute of Allergy and Infectious Diseases (NIAID); The EMMES Corporation; Leidos; FHI 360; PaxVax
Chikungunya	MV-CHIK recombinant measles virus vaccine expressing Chikungunya virus antigens	Phase II	Themis Bioscience GmbH; Institut Pasteur; In cooperation: National Institute of Allergy and Infectious Diseases (NIAID); Walter Reed Army Institute of Research (WRAIR)
Chikungunya	CHIKV- 5nsP3	Phase I	Karolinska Institute; EU research Council; Swedish research Council; Valneva SE
Chikungunya	mRNA-1388	Phase I	Moderna Therapeutics
Chikungunya	BBV87 (Inactivated whole virion CHIKV vaccine)	Phase I	Bharat Biotech International
Chikungunya	Formalin inactivated CHIKV181/25	Phase I	Indian Immunologicals Ltd., US Army Medical Research and Material Command (USAMRMC)
Chikungunya	AGS-v, a Universal Mosquito-Borne Disease Vaccine	Phase I	SEEK; National Institute of Allergy and Infectious Diseases (NIAID); Imutex; Innovate UK and the UK Department of Health and Social Care
Chikungunya	Vaccinia [Ankara]-Vectored (MVA-CHIKV E1E26KE3)	Preclinical	CSIC Madrid; Karolinska Institutet
Chikungunya	Vaccinia vectored (MVA-CHIKV E2E3)	Preclinical	University of Wisconsin- Madison
Chikungunya	p181/25-7CHIKV iDNA	Preclinical	Medigen, Inc.; University of Texas Medical Branch (UTMB); National Institute of Allergy and Infectious Diseases (NIAID)
Chikungunya	SCV-CHIKV (SCV305), SCV viral vectored vaccine	Preclinical	Sementis Ltd
Chikungunya	Plasmid DNA 'DREP-env' encoding the CHIKV replicase and envelope proteins (but lacking the capsid encoding gene	Preclinical	Karolinska Institutet; University of Tartu; Institute of Emerging Diseases and Innovative Therapies - IMETI; University Paris-Sud XI
Chikungunya	EILV/CHIKV	Preclinical	University of Texas Medical Branch (UTMB); University of Alabama at Birmingham; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Chikungunya	Recombinant Modified Vaccinia Ankara (MVA) expressing E3E2, 6KE1, or the entire CHIKV envelope polyprotein E3E26KE1 cassette.	Preclinical	Erasmus Medical Center; University of Munich LMU; Erasmus Medical Center Laboratory Animal Science Center (EDC); Artemis One Health
Chikungunya	Inactivated CHIKV	Preclinical	Najit Technologies, Inc; National Institute of Allergy and Infectious Diseases (NIAID)
Chikungunya	PODS Chik 1	Preclinical	Cell Guidance Systems; Imperial College London; Department of Health - UK; University of Cambridge
Chikungunya	Name yet to be assigned as early stage research	Preclinical	Leaf Expression Systems; Department of Health-UK
Chikungunya	Undisclosed	Preclinical	Undisclosed
Chikungunya	Infectious DNA (iDNA); Plasmid DNA-launched full-length attenuated RNA of CHIKV	Preclinical	Karolinska Institutet, Swedish Research Council
Chikungunya	Infectious RNA (iRNA); In vitro produced full-length attenuated genomic RNA of CHIKV	Preclinical	Karolinska Institutet, Swedish Research Council
Chikungunya	E2EP3 (long peptide)	Preclinical	Singapore Immunology Network
Chikungunya	SCV-CHIKV+ZIKV+YF, SCV viral vectored vaccine	Preclinical	Sementis Ltd
Chikungunya	SCV-CHIKV+ZIKV (SCV1002), SCV viral vectored vaccine	Preclinical	Sementis Ltd
Chikungunya	CHIKV live attenuated virus, a genetically stabilized virus vaccine	Preclinical	Medigen, Inc.
Chikungunya	CHIKV pMCE321 is a DNA plasmid that encodes CHIKV capsid, envelope E1 and E2 proteins	Preclinical	Inovio Pharmaceuticals; VGXTM Animal Health; University of Pennsylvania; University of South Florida Morsani College of Medicine
Chikungunya	ChAdOx1 CHIK	Preclinical	University of Oxford
Chikungunya	CHIKV-IRES (v1/v2)	Preclinical	Takeda Pharmaceuticals, Vaccines Business Unit; University of Texas Medical Branch (UTMB); Center for Disease Control and Prevention (CDC); Tulane National Primate Research Center; University of Alabama at Birmingham (UAB)

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Appendix Table 2.2: CCHF vaccine R&D pipeline, preclinical through phase I

Disease	Vaccine candidate	R&D phase	Development Partners
Crimean Congo Haemorrhagic Fever (CCHF)	KIRIM-KONGO-VAX Prepared in Cell Culture and Inactivated With Formalin	Phase I	Tubitak; Ministry of Health of Turkey; Monitor CRO; Aydin Erenmemisoglu; Erciyes University
Crimean Congo Haemorrhagic Fever (CCHF)	ChAdOx1 CCHF	Preclinical	University of Oxford
Crimean Congo Haemorrhagic Fever (CCHF)	ChAdOx2 CCHF	Preclinical	University of Oxford
Crimean Congo Haemorrhagic Fever (CCHF)	recombinant MVA expressing CCHFv glycoprotein	Preclinical	Department of Health-UK; Pirbright Institute; University of Oxford; Microbiology Services Research, Public Health England
Crimean Congo Haemorrhagic Fever (CCHF)	DNA CCHFv M segment	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Crimean Congo Haemorrhagic Fever (CCHF)	Gc-e Subunit vaccine	Preclinical	Wageningen Bioveterinary Research
Crimean Congo Haemorrhagic Fever (CCHF)	Undisclosed	Preclinical	Undisclosed

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Appendix Table 2.3: Ebola vaccine R&D pipeline, preclinical through phase III

Disease	Vaccine candidate	R&D phase	Development Partners
Ebola	VSV-ZEBOV GP	Phase III	Public Health Agency of Canada; Merck Sharp & Dohme Corp.,; World Health Organization (WHO); Wellcome Trust; Institute of Tropical Medicine; University of Tuebingen; Albert Schweitzer Hospital; Philipps University Marburg Medical Center; Universitätsklinikum Hamburg-Eppendorf University Hospital; National Institute of Allergy and Infectious Diseases (NIAID); Centers for Disease Control and Prevention; University of Sierra Leone; Ministry of Health and Sanitation - Sierra Leone; Department of Health and Human Services - eHealth Africa; University of Texas Medical Branch; Boston University School of Medicine; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Ebola	Ad26.ZEBOV + MVA-BN-Filo	Phase III	Janssen Vaccines & Prevention B.V.; Bavarian Nordic GmbH; National Institute of Allergy and Infectious Diseases (NIAID); BARDA; Walter Reed Army Institute of Research (WRAIR); EBOVAC 1 and 2 Consortia (IMI): London School of Hygiene and Tropical Medicine (LSHTM); Institut National de la Santé Et de la Recherche Médicale (INSERM), University of Oxford
Ebola	ChAd3 EBOZ - A chimpanzee adenovirus 3–vectored vaccine encoding the surface glycoprotein of Ebolavirus Zaire	Phase II	GlaxoSmithKline; Okairos; University of Maryland; National Institute of Allergy and Infectious Diseases Vaccine Research Center (in collaboration with University of Oxford; Centre Hospitalier Universitaire Vaudois; Infectious Disease Service, CHUV, Lausanne; Policlinique Médicale Universitaire; University of Lausanne Hospitals; Swiss Tropical & Public Health Institute; World Health Organization; Immunology and Allergy Service, CHUV, Lausanne; Bernhard Nocht Institute for Tropical Medicine)
Ebola	EBOV GP	Phase I	Novavax, Inc.
Ebola	rVSVN4CT1-EBOVGP1 (VesiculoVax)	Phase I	Profectus BioSciences Inc; Yale University; University of Texas Medical Branch (UTMB); United States Department of Defense (US DOD); Joint Vaccine Acquisition Program (JVAP); BARDA
Ebola	Multivalent Filovirus vaccine (heterologous prime boost with Ad26.Filo and MVA-BN-Filo)	Phase I	Janssen Vaccines & Prevention B.V.; Bavarian Nordic GmbH; National Institute of Allergy and Infectious Diseases (NIAID)
Ebola	INO-4201 is a DNA plasmid that encodes the full-length Ebola virus glycoprotein	Phase I	Inovio Pharmaceuticals Inc.; GeneOne Life Science, Inc.; Public Health Agency of Canada; University of Pennsylvania; University of Manitoba; The University of Texas at Austin
Ebola	Undisclosed	Preclinical	Undisclosed
Ebola	Marv VLPs; EBOV VLP; SUDV VLPs (Blended)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Integrated Biotherapeutics, Inc; Protein Expression Laboratory; Science Applications International Corporation (SAIC)–Frederick, National Cancer Institute, Frederick, Maryland
Ebola	VRP SUDV GP + VRP EBOV GP	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Ebola	Undisclosed	Preclinical	Undisclosed
Ebola	CAdVax-filo GP + NP CAdVax-EBOV M7 + M8	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Medical University of South Carolina
Ebola	Ad-CAGoptZGP + Ad-IFNα	Preclinical	Public Health Agency of Canada; University of Manitoba
Ebola	inact. BNSP333-coEBOV/SUD/MARV/LASVGP + adjuvants (FILORAB1, FILORAB2, FILORAB3, LASSARAB)	Preclinical	Thomas Jefferson University; Exxell BIO, Inc.; National Institute of Allergy and Infectious Diseases (NIAID); United States Army Medical Research Institute of Infectious Diseases (USAMRIID); IDT Biologika GmbH; Infectious disease research institute (IDRI)
Ebola	VSV-EBOV GP, VSV-SUDV GP, VSV-MARV GP	Preclinical	Public Health Agency of Canada; Boston University School of Medicine; United States Army Medical Research Institute of Infectious Diseases (USAMRIID); University of Manitoba; National Institute of Allergy and Infectious Diseases(NIAID); National Emerging Infectious Diseases Laboratories Institute
Ebola	DNA EBOV GP + rAd5-EBOV GP	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); National Institute of Allergy and Infectious Diseases (NIAID); Centers for Disease Control and Prevention
Ebola	CAdVax-EBOV M7 + M8	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Medical University of South Carolina
Ebola	Undisclosed	Preclinical	Undisclosed

Ebola	MVA-VLP-TV vaccine (Haemorrhagic Fever Vaccine (Ebola, Sudan, Marburg, Lassa))	Preclinical	GeoVax; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Ebola	PODS Ebola 1	Preclinical	Cell Guidance Systems; University of Cambridge; Imperial College London; Department of Health - UK
Ebola	Undisclosed	Preclinical	Undisclosed
Ebola	Undisclosed	Preclinical	Undisclosed
Ebola	DNA pWRG/EBOV-GP(opt)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Ichor Medical Systems
Ebola	DNA pWRG/SUDV-GP(opt)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Ichor Medical Systems
Ebola	GEO-EM03	Preclinical	Geovax
Ebola	MV-EBOV recombinant measles virus vaccine expressing EBOV antigens	Preclinical	Institut Pasteur
Ebola	NI.LV-EBO	Preclinical	Institut Pasteur; Theravectys
Ebola	Structuraly designed Pan-ebolavirus vaccine	Preclinical	Integrated Biotherapeutics
Ebola	DREP-GP: DNA plasmid expressing an alphavirus replicase and the glycoprotein of Ebola	Preclinical	Karolinska Institutet, Swedish Research Council
Ebola	Ebola RNA-Moderna	Preclinical	Moderna Therapeutics
Ebola	rVSVN4CT1-SUDVGP1 (VesiculoVax™ Vesicular Stomatitis Virus Vector)	Preclinical	Profectus; Yale University; University of Texas Medical Branch (UTMB); National Institute of Allergy and Infectious Diseases (NIAID); Joint Vaccine Acquisition Program (JVAP)
Ebola	rVSVN4CT1-EBOV/SUDV/MARV/LASV Quadra-valent (VesiculoVax™ Vesicular Stomatitis Virus Vector)	Preclinical	Profectus; Yale University; University of Texas Medical Branch (UTMB); National Institute of Allergy and Infectious Diseases (NIAID)
Ebola	ChAdOX1 triFilo(2A)	Preclinical	University of Oxford
Ebola	ChAdOx1-biEBOV	Preclinical	University of Oxford
Ebola	Ebola GP VLP	Preclinical	Vaxine Pty Ltd, Australia; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Ebola	RREP-GP: DNA plasmid expressing an alphavirus replicase and the glycoprotein of Ebola; In vitro RNA transcript of the template.	Preclinical	Karolinska Institutet, Swedish Research Council
Ebola	DIOS-panEbola	Preclinical	Department of Health - UK; University of Cambridge; University of Oxford
Ebola	Undisclosed	Preclinical	Undisclosed
Ebola	Ebola GPclamp	Preclinical	The University of Queensland; Australian Government - National Health and Medical Research Council (NHMRC)
Ebola	GEO-EM01	Preclinical	Geovax
Ebola	DNA pWRG/EBOV-Z76(opt); Mayina	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet
Ebola	DNA pWRG/SUDV-BON(opt); Boniface	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet
Ebola	DNA pWRG/EBOV-BUN(opt); Bundibugyo	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet
Ebola	DNA pWRG/EBOV-Z14(opt); Guinea	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet

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Appendix Table 2.4: Lassa vaccine R&D pipeline, preclinical

Disease	Vaccine candidate	R&D phase	Development Partners
Lassa fever	rVSVN4CT1-LASV (VesiculoVax™ Vesicular Stomatitis Virus Vector)	Preclinical	Profectus Biosciences; Yale University; University of Texas Medical Branch (UTMB)
Lassa fever	ML29 L-AttV, rLCMV(IGR/S-S)	Preclinical	The Scripps Research Institute (TSRI), USA
Lassa fever	ML29 virus - reassortant encodes major immunogenic proteins, GPC and NP, from LASV and RNA polymerase and Z protein from MOPV.	Preclinical	Medigen, Inc.(technology licensed from the University of Maryland); National Institute of Allergy and Infectious Diseases (NIAID)
Lassa fever	Live attentuated rLCMV/CD	Preclinical	University of Rochester; The Scripps Research Institute
Lassa fever	GPC441-449 subunit	Preclinical	University of Vermont College of Medicine; The Scripps Research Institute; MWH Laboratories; University of North Carolina; PaxVax, Inc.,; University of California
Lassa fever	LASV VLP	Preclinical	Tulane University Health Sciences Center; Autoimmune Technologies, LLC; Corgenix Medical Corporation; Vybion, Inc.,; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Lassa fever	RABV based on chemically inactivated rabies virus containing Lassa Virus coGPC (LASSARAB)	Preclinical	Thomas Jefferson University; National Institute of Allergy and Infectious Diseases (NIAID); The Geneva Foundation; United States Army Medical Research Institute of Infectious Diseases (USAMRIID); IDT Biologika GmbH; Infectious disease research institute (IDRI)
Lassa fever	PODS Lassa 1	Preclinical	Cell Guidance Systems; University of Cambridge; Imperial College London; Department of Health - UK
Lassa fever	MV-LASV recombinant measles virus vaccine expressing Lassa virus antigens	Preclinical	Institut Pasteur; Themis Bioscience GmbH
Lassa fever	MOPEVAC (Modified Mopeia virus expressing antigens of pathogenic arenaviruses)	Preclinical	Institut Pasteur
Lassa fever	Alphavirus replicon encoding LASV genes	Preclinical	Medigen, Inc.; University of Louisville, United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Lassa fever	Undisclosed	Preclinical	Undisclosed
Lassa fever	Lassa GPCclamp	Preclinical	The University of Queensland; Australian Government - National Health and Medical Research Council (NHMRC)
Lassa fever	ChAdOx1 Lassa	Preclinical	University of Oxford
Lassa fever	MVA Lassa	Preclinical	University of Oxford
Lassa fever	ChAdOx1-biLAMA	Preclinical	University of Oxford
Lassa fever	Viral genome rearrangement for the development of live-attenuated arenavirus vaccines	Preclinical	University of Rochester; The Scripps Research Institute
Lassa fever	Single cycle infectious viruses as live attenuated arenavirus vaccines	Preclinical	University of Rochester; The Scripps Research Institute
Lassa fever	Undisclosed	Preclinical	Undisclosed
Lassa fever	GEO-LM01	Preclinical	GeoVax; The Scripps Research Institute; University of Maryland
Lassa fever	pLASV-GPC is a DNA plasmid vaccine that encodes the LASV glycoprotein precursor gene (GPC)	Preclinical	Inovio Pharmaceuticals; United States Army Medical Research Institute for Infectious Diseases (USAMRIID)
Lassa fever	MVA-VLP-TV vaccine (Haemorrhagic Fever Vaccine (Ebola, Sudan, Marburg, Lassa))	Preclinical	GeoVax; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)

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Appendix Table 2.5: Marburg vaccine R&D pipeline, preclinical through phase I

Disease	Vaccine candidate	R&D phase	Development Partners
Marburg	Ebola DNA and Marburg DNA - prime boost	Phase I	National Institute of Allergy and Infectious Diseases (NIAID); Makerere University; Makerere University Walter Reed Project (MUWRP) clinic; Walter Reed Army Institute of Research (WRAIR)
Marburg	DNA	Phase I	AgilVax; Integrated Biotherapeutics; National Institute of Allergy and Infectious Diseases (NIAID); Visterra; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	MARV VLPs	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Integrated Biotherapeutics, Inc.
Marburg	Undisclosed	Preclinical	Undisclosed
Marburg	VEE replicon particles (VRP) expressed GP from MARV	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	Trimeric hybrid GPs (VLPs)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	complex adenovirus (CAdVax) five different filoviruses	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	MARV VP40 and GP (VLPs)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	MVA-VLP-TV vaccine (Haemorrhagic Fever Vaccine (Ebola, Sudan, Marburg, Lassa))	Preclinical	GeoVax; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	Undisclosed	Preclinical	Undisclosed
Marburg	DNA pWRG/MARV-GP(opt)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Ichor Medical Systems
Marburg	Marburg RNA-Moderna	Preclinical	Moderna Therapeutics
Marburg	ChAdOx1-biLAMA	Preclinical	University of Oxford
Marburg	Undisclosed	Preclinical	Undisclosed
Marburg	GEO-EM05	Preclinical	GeoVax
Marburg	DNA pWRG/MARV-ANG(opt); Angola	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet
Marburg	ChAdOX1 triFilo(2A)	Preclinical	University of Oxford
Marburg	rVSVN4CT1-MARVGP1 (VesiculoVax™ Vesicular Stomatitis Virus Vector)	Preclinical	Profectus BioSciences Inc; Yale University; University of Texas Medical Branch (UTMB); National Institute of Allergy and Infectious Diseases (NIAID); Joint Vaccine Acquisition Program (JVAP)
Marburg	pMARV is a DNA plasmid that encodes Marburg virus glycoprotein	Preclinical	Inovio Pharmaceuticals; Public Health Agency of Canada
Marburg	Attenuate VSV vector	Preclinical	National Institute of Allergy and Infectious Diseases (NIAID); Public Health Agency of Canada; United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Marburg	RABV based on chemically inactivated rabies virus virions containing MARV glycoprotein (GP) (FILORAB3)	Preclinical	Thomas Jefferson University; National Institute of Allergy and Infectious Diseases (NIAID); The Geneva Foundation; United States Army Medical Research Institute of Infectious Diseases (USAMRIID); IDT Biologika GmbH; Infectious disease research institute (IDRI)

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Appendix Table 2.6: MERS-CoV vaccine R&D pipeline, preclinical through phase I

Disease	Vaccine candidate	R&D phase	Development Partners
MERS-CoV	MVA-MERS-S	Phase I	University of Munich LMU; Erasmus Medical Center; University of Marburg; German Centre for Infection Research (DZIF)
MERS-CoV	ChAdOx1 MERS	Phase I	University of Oxford; Department of Health - UK; MRC Human Immunology Unit; UK Medical Research Council
MERS-CoV	GLS-5300 is a DNA plasmid vaccine that encodes the MERS CoV spike (S) glycoprotein	Phase I	Inovio Pharmaceuticals; GeneOne Life Science; International Vaccine Institute (IVI); Public Health Agency of Canada; University of Laval; University of Manitoba; University of Pennsylvania; University of Washington; University of South Florida Morsani College of Medicine
MERS-CoV	RABV-MERS RABV contains spike protein of the MERS-CoV S1 domain fused to the RABV G protein C terminus (BNSP333-S1). Live and deactivated irons	Preclinical	Thomas Jefferson University; IDT Biologika GmbH; National Institute of Allergy and Infectious Diseases (NIAID); University of Maryland; University of North Carolina; University of Colorado
MERS-CoV	RBD fused with human Fc/ Mersmab1	Preclinical	New York Blood Center; Baylor College Medicine; University of Texas Medical Branch (UTMB)
MERS-CoV	Full length S trimers/ nanoparticle	Preclinical	Novavax, Inc.
MERS-CoV	Venezuelan equine encephalitis replicons (VRP) expressing nucleocapsid proteins	Preclinical	University of Iowa; The First Affiliated Hospital of Guangzhou Medical University; University of North Carolina; Mayo Clinic
MERS-CoV	VRP expressing spike protein	Preclinical	University of Iowa; University of North Carolina at Chapel Hill
MERS-CoV	Live-attenuated recombinant MERS-CoVs	Preclinical	University of Iowa; German Centre for Infection Research (DZIF); King Abdullah International Medical Research Center; University of Kent; University of Marburg; CNB-CSIC
MERS-CoV	MERS RNA	Preclinical	Moderna Therapeutics
MERS-CoV	MERS Sclamp	Preclinical	The University of Queensland; Australian Government - National Health and Medical Research Council (NHMRC)
MERS-CoV	mammalian subunit with triadjuvant	Preclinical	Vaccine and Infectious Disease Organization-International Vaccine Centre (VIDO-InterVac); King Saud bin Abdulaziz University for Health Sciences
MERS-CoV	replication defective Ad5 vectored	Preclinical	Vaccine and Infectious Disease Organization-International Vaccine Centre (VIDO-InterVac); King Saud bin Abdulaziz University for Health Sciences
MERS-CoV	live attenuated camelpox (Ducapox) vectored	Preclinical	Vaccine and Infectious Disease Organization-International Vaccine Centre (VIDO-InterVac); Central Veterinary Research Lab, Dubai, UAE
MERS-CoV	MERS vaccine	Preclinical	Vaxine Pty Ltd, Australia
MERS-CoV	DNA pWRG/MERScoV(opt)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet
MERS-CoV	Measles S recombinant measles virus expressing the spike glycoprotein	Preclinical	Themis Bioscience GmbH

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Appendix Table 2.7: Nipah vaccine R&D pipeline, preclinical

Disease	Vaccine candidate	R&D phase	Development Partners
Nipah	HeV sG (Hendra virus soluble G protein)	Preclinical	Zoetis Inc.; Uniformed Services University of the Health Sciences (USU); Commonwealth Scientific and Industrial Research Organisation (CSIRO); Duke-NUS Graduate Medical School; Profectus Biosciences; University of Manitoba
Nipah	rMV-NiV-G	Preclinical	University of Tokyo; National Institute of Infectious Diseases, Japan; Themis Bioscience GmbH
Nipah	VLP: pCAGGS- G, F, and M protein	Preclinical	University of Texas Medical Branch (UTMB); Commonwealth Scientific and Industrial Research Organisation (CSIRO); Mount Sinai School of Medicine
Nipah	NiV soluble molecular clamp stabilised F protein	Preclinical	Department of Health - UK; The Pirbright Institute; University of Oxford; University of Queensland; CSIRO Health and Biosecurity; Australian Government - National Health and Medical Research Council (NHMRC); University of Malaya; Assam Agricultural University; Monash University Malaysia; Zoetis Inc.
Nipah	ChAdOx1 Nipah (Chimpanzee adenoviral vectored NiV G protein)	Preclinical	Department of Health - UK; The Pirbright Institute; University of Oxford; University of Queensland; CSIRO Health and Biosecurity; University of Malaya; Assam Agricultural University; Monash University Malaysia; Zoetis Inc.
Nipah	Undisclosed	Preclinical	Undisclosed
Nipah	Undisclosed	Preclinical	Undisclosed
Nipah	Undisclosed	Preclinical	Undisclosed
Nipah	NiV soluble G protein subunit	Preclinical	Department of Health - UK; The Pirbright Institute; University of Oxford; University of Queensland; CSIRO Health and Biosecurity; University of Malaya; Assam Agricultural University; Monash University Malaysia; Zoetis Inc.
Nipah	VSV-HeV sG recombinant vesicular stomatitis virus (VSV), expressing either the codon-optimized or the wild-type (wt) HeV glycoprotein (G) gene or Nipah (codon optimized)	Preclinical	Thomas Jefferson University; National Institute of Allergy and Infectious Diseases (NIAID); Rocky Mountain Laboratories
Nipah	RABV-HeV G recombinant rabies virus, expressing either the codon-optimized or the wild-type (wt) HeV glycoprotein (G) gene or Nipah G (codon optimized)	Preclinical	Thomas Jefferson University; National Institute of Allergy and Infectious Diseases (NIAID); Rocky Mountain Laboratories

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Appendix Table 2.8: Rilf Valley fever vaccine R&D pipeline, preclinical through phase II

Disease	Vaccine candidate	R&D phase	Development Partners
Rift Valley fever	TSI-GSD 200	Phase II	U.S. Army Medical Research and Materiel Command; Salk Institute
Rift Valley fever	RVF MP-12	Phase II	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); Salk Institute
Rift Valley fever	DNA vaccine pCMV-Ub-N	Preclinical	Centro de Investigación en Sanidad Animal, INIA, Valdeolmos, Madrid, Spain
Rift Valley fever	DNA Vaccine, pCMV-M4 encoding mature GnGc glycoproteins	Preclinical	Centro de Investigación en Sanidad Animal, INIA, Valdeolmos, Madrid, Spain
Rift Valley fever	NDFL-GnGc, vector based	Preclinical	Wageningen Bioveterinary Research
Rift Valley fever	- Gn-e Subunit Protein - Gn/Gc VLP with/without Adjuvant (Stimune)	Preclinical	Wageningen Bioveterinary Research; Utrecht University
Rift Valley fever	Undisclosed	Preclinical	Undisclosed
Rift Valley fever	RVF - Bovine Herpesvirus-4 (attenuated)	Preclinical	Plymouth University; Department of Health - UK; Defence Science and Technology Laboratory (Dstl); Kansas State University; University of Liege
Rift Valley fever	Name yet to be assigned as early stage research	Preclinical	Leaf Expression Systems; Department of Health - UK
Rift Valley fever	ChAdOx1 RVF	Preclinical	University of Oxford; Department of Health - UK; MRC Uganda Virus Research Institute; Pirbright Institute
Rift Valley fever	NI.LV-RIFT	Preclinical	Institut Pasteur; Institut Pasteur de Dakar; Theravectys
Rift Valley fever	Gn and Gc expressed in LSDV	Preclinical	Vaccine and Infectious Disease Organization-International Vaccine Centre (VIDO-InterVac); University of Alberta; The National Centre for Foreign Animal Disease (NCFAD), Canada; Onderstepoort Veterinary Institute, South Africa
Rift Valley fever	4-segmented RVFV	Preclinical	Wageningen Bioveterinary Research; BunyaVax B.V.
Rift Valley fever	MVA Expressing GnGc Glycoproteins	Preclinical	University of Oxford; Centro de Investigacio´n en Sanidad Animal, INIA, Valdeolmos, Madrid, Spain
Rift Valley fever	DNA based, baculovirus expressed M segments	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID)
Rift Valley fever	RNA particles (RRP/NSR)	Preclinical	Wageningen Bioveterinary Research; BunyaVax B.V.
Rift Valley fever	RNA particles (NSR-Gn)	Preclinical	Wageningen Bioveterinary Research; Utrecht University; BunyaVax B.V.

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Appendix Table 2.9: SARS vaccine R&D pipeline, preclinical

Disease	Vaccine candidate	R&D phase	Development Partners
SARS	receptor binding domain (RBD) of the SARS- CoV spike (S) protein	Preclinical	Baylor College Medicine; BCM-Sabin; New York Blood Center (NYBC); University of Texas Medical Branch (UTMB); Walter Reed Army Institute of Research (WRAIR); National Institute of Allergy and Infectious Diseases (NIAID)
SARS	rSARSCoV-E*	Preclinical	CNB-CSIC; University of Iowa
SARS	SARS VLPs S protein and inflenza M1 protein	Preclinical	Novavax
SARS	ChAdOX1 SARS	Preclinical	University of Oxford
SARS	MV-SARS recombinant measles virus vaccine expressing SARS CoV antigen	Preclinical	Institut Pasteur
SARS	SARS recombinant spike protein	Preclinical	Vaxine Pty Ltd, Australia

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Appendix Table 2.10: SFTS vaccine R&D pipeline, preclinical

Disease	Vaccine candidate	R&D phase	Development Partners
SFTS	DNA Vaccine	Preclinical	GeneOne Life Science; Graduate school of Medical Science and Engineering, KAIST; College of Medicine, Chungbuk National University

References related to the SFTS vaccine R&D pipeline:

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Appendix Table 2.11: Zika vaccine R&D pipeline, preclinical through phase II

Disease	Vaccine candidate	R&D phase	Development Partners
Zika	VRC-ZKADNA090-00-VP	Phase II	Paxvax; National Institute of Allergy and Infectious Diseases (NIAID)
Zika	GLS-5700 is a DNA plasmid encoding for pre-membrane and envelope (prME) proteins of the Zika virus	Phase I	Inovio Pharmaceuticals; GeneOne Life Science, Inc.
Zika	AGS-v	Phase I	SEEK; National Institute of Allergy and Infectious Diseases (NIAID); Imutex; Innovate UK and the UK Department of Healt and Social Care
Zika	mRNA-1325	Phase I	Moderna Therapeutics
Zika	MV-Zika based on measles vector platform	Phase I	Themis Bioscience GmbH; Institut Pasteur
Zika	VRC ZIKV DNA	Phase I	National Institute of Allergy and Infectious Diseases (NIAID)
Zika	ZIKV PIV	Phase I	Walter Reed Army Institute of Research (WRAIR); Beth Israel Deaconess Medical Center (BIDMC); Harvard University; National Institute of Allergy and Infectious Diseases (NIAID); Sanofi Pasteur
Zika	BBV121 (Inactivated whole virion ZIKV vaccine)	Phase I	Bharat Biotech International
Zika	UOL- Zika vaccine	Phase I	University of Liverpool; Department of Health - UK
Zika	GEO-ZM02	Preclinical	GeoVax; University of Georgia; Center for Disease Control and Prevention (CDC)
Zika	NI.LV-ZIK	Preclinical	Institut Pasteur
Zika	ChAdOx1 Zika	Preclinical	University of Oxford
Zika	Undisclosed	Preclinical	Undisclosed
Zika	SCV-CHIKV+ZIKV+YF, SCV viral vectored vaccine	Preclinical	Sementis Ltd
Zika	SCV-CHIKV+ZIKV (SCV1002), SCV viral vectored vaccine	Preclinical	Sementis Ltd
Zika	SCV-ZIKV (SCV1003), SCV viral vectored vaccine	Preclinical	Sementis Ltd
Zika	Inactivated whole target organism	Preclinical	Takeda Pharmaceuticals, Vaccines Business Unit
Zika	VLA1601 (Inactivated whole target organism)	Preclinical	Emergent BioSolutions; Valneva SE
Zika	Paxvax VLP	Preclinical	Paxvax; Center for Disease Control and Prevention (CDC)
Zika	Single cell infectious ZIKV (SCIrZIKV) Live attentuated vaccine	Preclinical	University of Rochester; Centro Nacional de Biotecnología, Spain
Zika	mRNA-1706	Preclinical	Moderna Therapeutics
Zika	Undisclosed	Preclinical	Undisclosed
Zika	PODS Zika 1	Preclinical	Cell Guidance Systems; University of Cambridge; Imperial College London; Department of Health - UK
Zika	Undisclosed	Preclinical	Undisclosed
Zika	Undisclosed	Preclinical	Undisclosed
Zika	Undisclosed	Preclinical	Undisclosed
Zika	Undisclosed	Preclinical	Undisclosed
Zika	ZIKV iDNA, a DNA vaccine encoding genetically stable, live-attenuated chimeric flavivirus encoding ZIKV genes	Preclinical	Medigen, Inc.
Zika	Inactivated ZIKV	Preclinical	Najit Technologies, Inc; National Institute of Allergy and Infectious Diseases (NIAID)
Zika	rISFVN4CTΔ25-ZIKV (VesiculoVax™ Isfahan Virus Vector)	Preclinical	Profectus Biosciences; Yale University; University of Texas Medical Branch (UTMB)
Zika	ZIKA DIII	Preclinical	Singapore Immunology Network
Zika	Adeno virus based	Preclinical	CanSino Biologics Inc.
Zika	Zika PrME vaccine	Preclinical	Vaxine Pty Ltd, Australia ; Protein Sciences
Zika	Codon deoptimization for the development of ZIKV live attenuated vaccines	Preclinical	University of Rochester
Zika	Undisclosed	Preclinical	Undisclosed
Zika	DNA pWRG/ZIKA-JE-prME(opt)	Preclinical	United States Army Medical Research Institute of Infectious Diseases (USAMRIID); PharmaJet
Zika	Subunit vaccine based on critical neutralizing fragment in ZIKV EDIII	Preclinical	New York Blood Center

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Step 2: Cost research

The vaccine EID R&D cost data informing our regression, simulation, and stochastic optimization analyses was collected through the same survey process that we employed to validate the EID R&D pipeline data, described in step 1: Pipeline research above.

From September 2017 to January 2018 we launched a cost data collection process as part of the same survey described in the previous section. A copy of the survey can be accessed in the following weblink, under heading 'CEPI vaccine R&D pipeline and cost tracking survey': http://cepi.net/news.

Out of the 313 vaccine candidates confirmed through the survey responses, 113 vaccine candidates were reported with full R&D costs by R&D phase. Our definition of full R&D costs included whether reported costs covered all or most critical non-clinical, clinical, chemistry, manufacturing and control (CMC) and regulatory activities associated with each R&D phase, as classified in an R&D scope checklist that was used to assess completeness of cost estimates by R&D phase. (See Appendix table 1.2 for more details)

Based on this criterion, we compiled an initial set of 113 vaccine candidate cost entries. Following on several statistical tests which we describe in more detail in appendix 3, we merged this dataset with additional CEPI data on vaccine project costs to generate a total set of 138 unique vaccine development project cost entries, including information by: R&D phase, platform technology and disease, indirect costs, sectoral affiliation (industry *versus* non-industry) and geographical location of product developers.

Cost estimates reported in this study do not include:

- Basic laboratory research activities (e.g. basic epidemiology and pathogen biology studies; studies for antigen detection, expression, genetic construct, development of new animal models to assist in vaccine design, in-vitro studies, development of functional, neutralization or other assays / immunoassays, etc.)
- Activities associated with Phase IIb/III efficacy testing, CMC, regulatory and delivery
- Activities associated with stockpiles of investigational material for phase IIb/III studies
- Activities associated with manufacturing capacity building or maintenance to support phase IIb/III studies or scale up production in response to public health emergencies

Appendix table 2.12: R&D scope checklist to support survey-based reporting and quality checking of completeness of EID vaccine R&D costs by R&D phase

R&D Phase	Activities
Preclinical	- Safety & Immunogenicity: Dosing and safety studies in animal models; Toxicology or equivalent studies; Immunogenicity and protective efficacy studies in animal models - Chemistry, Manufacturing and Control (CMC): Establishment of seed lot; Establishment of Good Laboratory Practice (GLP) production / Pilot lot production planning; Potency demonstration/ Identity/ Sterility/ Purity studies; Good Manufacturing Practices (GMP) production consistency studies - Regulatory: Investigational New Drug (IND) or equivalent regulatory advice and application procedures
Phase I	- Safety: Phase Ia studies assessing safety, dosing and adverse events in humans - Immunogenicity: Evaluation of immuno-assays for correlates of immunity and risk in clinical studies; Phase Ia studies assessing immunogenicity in humans - Chemistry, Manufacturing and Control (CMC): Stability studies; Product quality control and quality assurance validation studies; Clinical lot consistency studies - Regulatory: Regulatory planning and clinical trial protocol development
Phase II	- Safety: Phase IIa studies assessing safety, dosing and common short-term side effects in humans - Immunogenicity: Phase IIa studies assessing immune responses in target populations - Chemistry, Manufacturing and Control (CMC): Clinical lot consistency studies and GMP product formulation - Regulatory: Development and finalization of clinical development and regulatory pathway strategy

Appendix 2 references

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Appendix 3: Statistical methods and results for estimating vaccine development project costs and their explanatory factors

In this appendix we present the details of our statistical tests and regression analysis to determine average vaccine development project cost estimates by R&D phase. We begin with a discussion of the variables considered and the rationale behind these. We then turn to a description of the statistical tests conducted and rationale for performing these, including how their results impacted the final selection of explanatory variables informing the average vaccine development project cost functions.

Consistency checking

Prior to determining what variables are likely to determine average vaccine development project costs, we checked for consistency of the survey data with CEPI's own database of vaccine R&D budgets. Based on a Student's T-test conducted between the two samples we found no significant inconsistency in the survey data, for both one-tailed and two-tailed tests (see Appendix table 3.1).

Appendix table 3.1: t-Test: Two-Sample Assuming Unequal Variances

	CEPI data	Survey data
Observations	57	113
Hypothesized Mean Difference	0	
Df	123	
t Stat	1·008532207	
P(T<=t) one-tail	0·157589464	
t Critical one-tail	1·657336397	
P(T<=t) two-tail	0·315178928	
t Critical two-tail	1·979438685	

These results allowed us to merge the two samples into a new set of 138 unique cost data entries (some of the CEPI cost data was later reported by survey respondents independently, we therefore removed a total of 32 duplicate entries from the final dataset). This check allowed to us to minimize the risk of skewing or increasing the reporting bias of the baseline data used to determine average vaccine development project costs.

Variables

Based on the data made available to us, we constructed the following variables which we assumed may have an explanatory role in the determination of average vaccine project development costs by R&D phase:

- R&D timelines (#years)
- Indirect cost (%) (Such costs may include: (1) In-kind R&D contributions (e.g. training of developing country scientists, sharing of compounds); (2) Overhead costs including, but not limited to, building running costs and general administrative and management costs).
- Product Developer licensure track-record (YES=1/NO=0)
- Industry (YES=1/NO=0)
- Platform technology licensure track-record against any disease (YES=1/NO=0)
- Vaccine licensure track-record against the disease (YES/NO)

All above listed variables are clearly identified as drivers of pharmaceutical R&D costs in numerous literature sources.[1-21] Moreover, in a discussion of cost drivers by R&D phase, survey respondents commonly cited Non-Human Primate studies, toxicology studies, analytical testing and manufacturing/ process development, project management, salaries, consumables, equipment, clinical trial costs associated with numbers of enrolees and locations of studies among several of common reasons for escalation of costs. Other reasons, such as unforeseen regulatory requirements, were also argued to drive vaccine development project costs, but which we could not translate into quantifiable variables due to lack of sufficient information collected via the survey.

It is worth noting that we did not consider geographical location of product developers as a variable, although we do recognize that this can have a more or less substantial effect on R&D costs, for two reasons. First, almost all reported vaccine R&D projects included partners from multiple countries and regions, making it difficult to quantify the relationship between geographical location and cost. Second, our sample size was not large enough to accurately differentiate between geographies and therefore provide significant statistical inferences for our model (only 5 out of 138 vaccine project cost entries were clearly attributed to Low and Middle Income Country organizations).

Descriptive statistics

Prior to assessing the statistical significance of the constructed variables that would allow us to conclude whether to consider these or not as explanatory factors of average vaccine development projects in our model, we ran some descriptive statistics to assess averages and distributions of the reported data by variable. Appendix table 3.2 summarizes these statistics for the two continuous variables (timelines and indirect cost share) and Appendix table 3.3 summarizes the breakdown of self-reported costs in the survey by data clusters and explanatory variables considered in the regression (for clustering analysis see below) Appendix box plots 3.1 to 3.4 summarize the ranges for the four dichotomous variables (product developer licensure track-record, industry/non-industry, platform technology licensure track-record, disease track-record of licensed vaccines).

As Appendix table 3.2 demonstrates, the average timeline for bringing EID vaccine development projects from preclinical through end of phase II is 6 to 7 years (+/- 2 years) and can arguably range from 4 to 15 years. The average share of indirect costs out of total vaccine development project costs from preclinical through end of phase II is 20-23% (+/- 18%) and can arguably range from 0% to 79%.

Appendix table 3.2: Descriptive statistics for timelines (#years) and indirect costs (%) from preclinical through phase II (N=138)

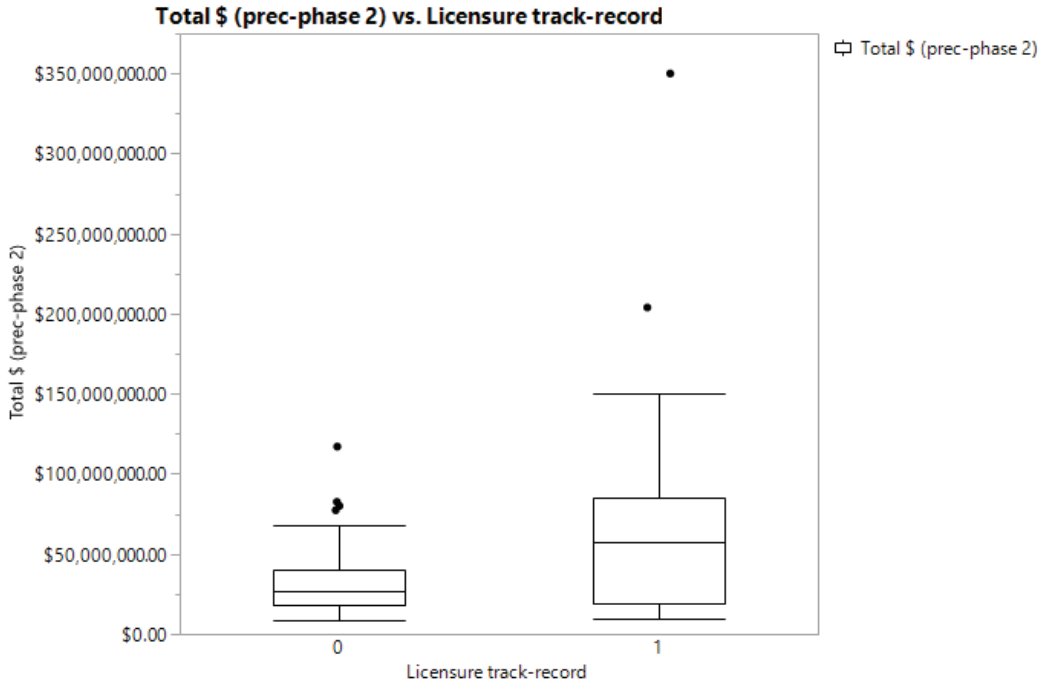
Descriptive Statistic	R&D timeline preclinical through phase II (# years)	Indirect cost share preclinical through phase II (%)
Mean	~7 years	~23%
Standard Deviation	+/-2 years	+/-18%
Median	6 years	20%
Maximum	4 years	79%
Minimum	15 years	0%

Appendix table 3.3: Self-reported data through survey, by data clusters and explanatory variables considered in regression

	Data clusters			Product Developer licensure track-record		Licensed product for disease already exists		Industrial sector affiliation of lead developer		Licensed products on this platform technology exist	
	Cluster 1	Cluster 2	Cluster 3	(YES =1)	(NO =0)	(YES=1)	(NO=0)	(YES=1)	(NO=0)	(YES =1)	(NO =0)
Observations											
Total (#)	103	21	14	33	105	10	128	105	33	56	82
PD track-record (YES=1) (% of total)	19%	19%	64%	100%	0%	40%	23%	22%	30%	23%	24%
Industry (YES=1) (% of total)	76%	86%	64%	70%	78%	70%	77%	100%	0%	77%	76%
Licensed disease (YES=1) (% total)	9%	5%	0%	12%	6%	100%	0%	7%	9%	5%	9%
Licensed tech (YES=1) (% total)	42%	52%	14%	39%	41%	30%	41%	41%	39%	100%	0%

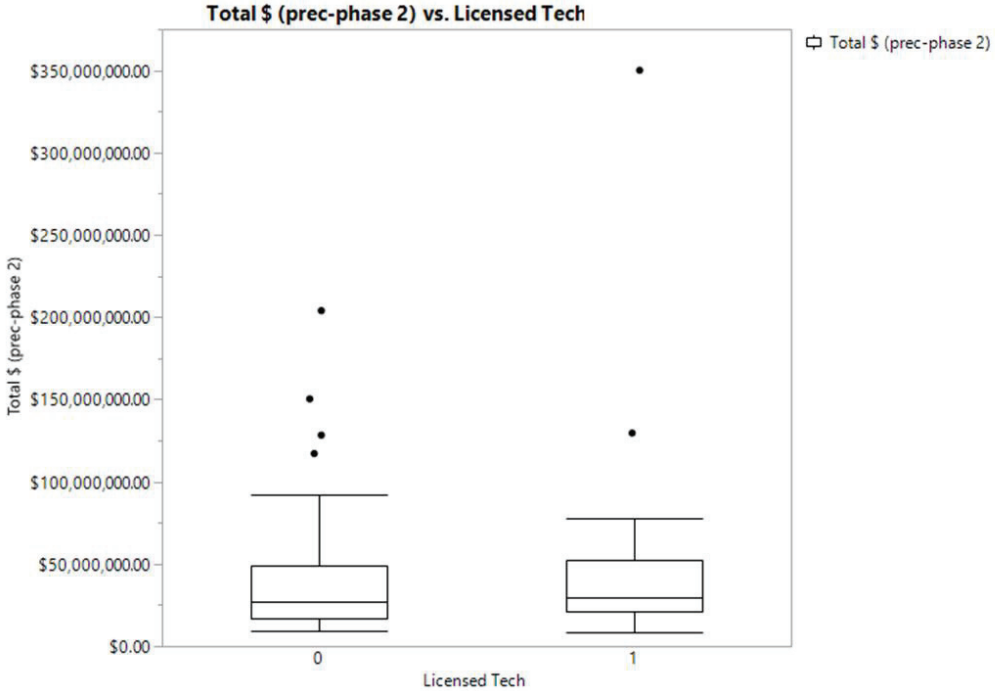
As Appendix box plots 3.1 to 3.4 below demonstrate, the distribution of reported costs from preclinical through phase II is skewed more upwards for vaccine developers with previous vaccine licensure track-record than those without (box plot 1), whereas they are relatively the same for technologies for which there are licensed vaccines in other disease settings in comparison to those for which no licensed vaccines exist (box plot 2). In contrast, reported costs from preclinical through phase II are distributed towards the lower end for diseases where licensed vaccines exist than those for which there is licensed vaccine at the time of R&D (box plot 3). Industry reported costs are distributed in a similar manner to non-industry reported estimates, however industry reported costs include significant outliers at the higher end of the reported cost range.

Appendix box plot 3.1: Total preclinical-phase 2 cost estimates reported by Product Developers, with or without licensure track-record



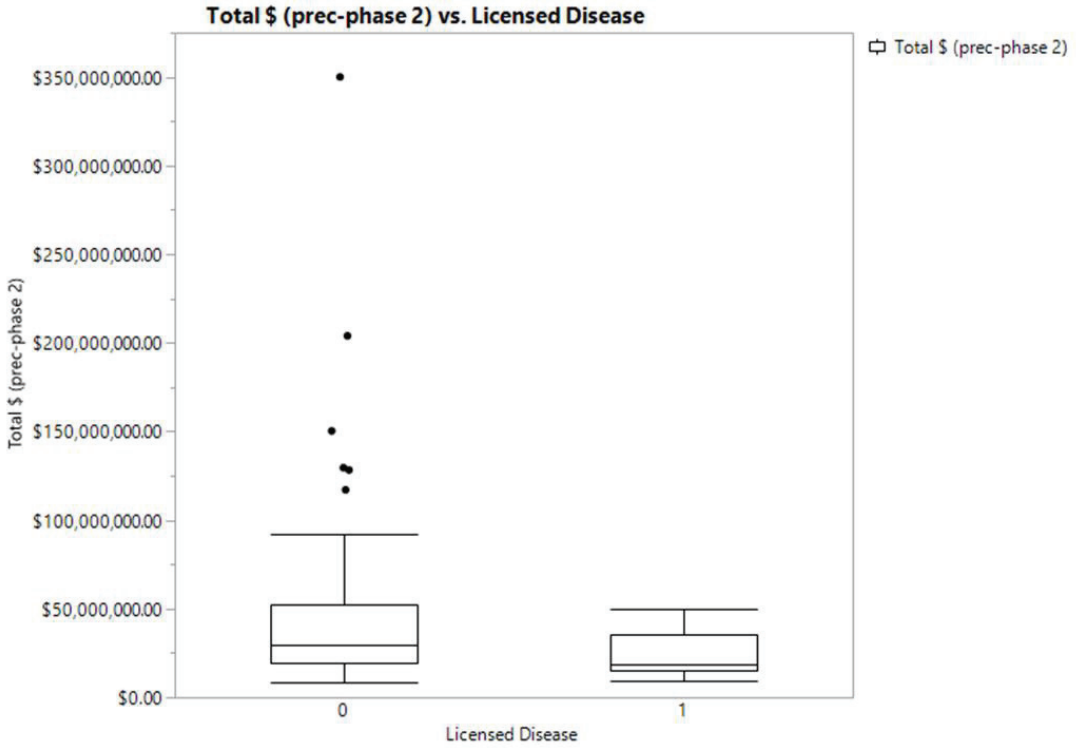
**Number of observations for licensure track-record (=1) = 33*
***Number of observations for no licensure track-record (=0) = 105*

Appendix box plot 3.2: Total preclinical-phase 2 cost estimates reported by Product Developers, with or without platform technologies with licensure track-record



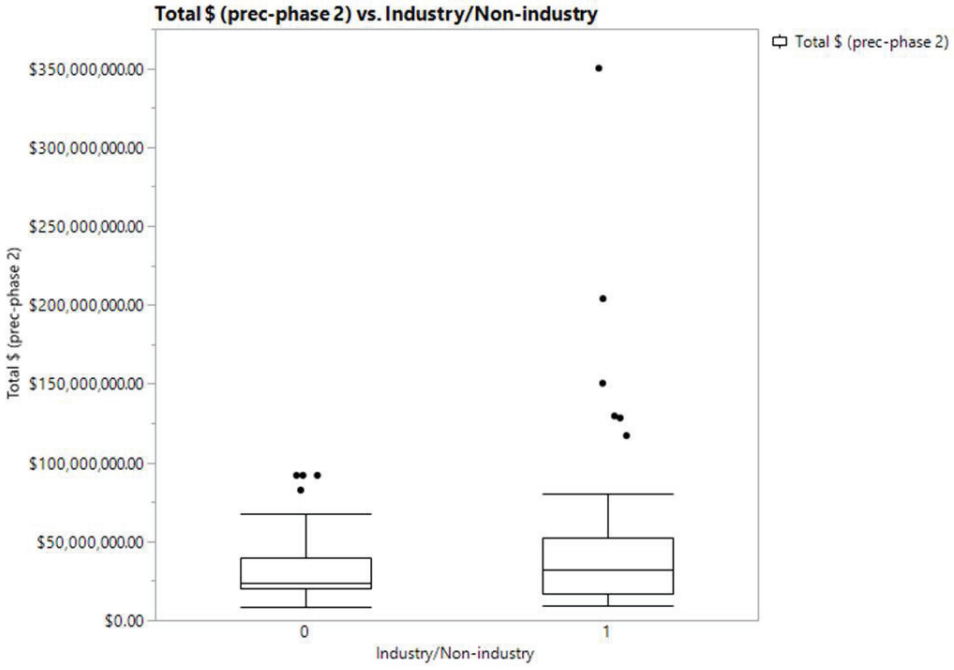
**Number of observations for licensure track-record (=1) = 56*
***Number of observations for no licensure track-record (=0) = 82*
****Platform technologies with licensure track-record include: attenuated virus- based technologies; inactivated pathogen- based technologies; Sub-Unit Protein- based technologies*
Platform technologies with no licensure track-record include: Nucleic acid- based technologies; Peptide-based technologies; Viral vector- based technologies

Appendix box plot 3.3: Total preclinical-phase 2 cost estimates reported by Product Developers, against diseases with licensed or not licensed vaccines at the time of R&D being conducted



**Number of observations for licensure track-record (=1) = 10*
***Number of observations for no licensure track-record (=0) = 128*
****Diseases with licensed vaccines at the time of R&D being conducted include: Hendra; Hepatitis E; IPV; Japanese Encephalitis; Measles; Yellow Fever*
Diseases with no licensed vaccines at the time of R&D being conducted include: Cambylobacter Jejuni; Chagas; Chikungunya; Cytomegalovirus; Dengue; East Equine Encephalitis; Ebola; ETEC; Human Metapneumovirus; Influenza (universal); Lassa; Marburg; MERS; Nipah; Other Arenaviruses; Pandemic H10N8; Pandemic H7N9; Respiratory Syncytial Virus; Rift Valley Fever; SARS; Venezuelan Equine Encephalitis; West Equine Encephalitis; West Nile Virus; Zika

Appendix box plot 3.4: Total preclinical-phase 2 cost estimates reported by industry or non-industry Product Developers



**Number of observations for industry respondents (=1) = 105*
***Number of observations for non-industry respondents (=0) = 33*

Correlation testing

Our next step was to run a correlation test to determine how strongly the considered variables are related to each other. As Appendix table 3.4 demonstrates, there is a weak negative correlation between timelines and product developer licensure track-record (~-0.24) and a weak positive correlation between timelines and platform technology licensure track-record (~0.29). These findings suggest that timelines are likely to be somewhat affected by the level of experience of the product developer undertaking the vaccine R&D project, as well as by the type of platform technology used to develop the vaccine. No other significant relationships between variables were found (correlation coefficient values close to zero).

Appendix table 3.4: Correlation findings

	Timelines	Indirect cost (%)	PD track-record YES=1/NO=0)	Industry (YES=1/NO=0)	Licensed tech (YES=1/NO=0)	Licensed disease (YES/NO)
Timelines	1					
Indirect cost (%)	0·129486684	1				
PD track-record YES=1/NO=0)	-0·239877069	0·084900437	1			
Industry (YES=1/NO=0)	0·086187148	-0·052764841	-0·083982684	1		
Licensed tech (YES=1/NO=0)	0·293382573	0·161873462	-0·013537585	0·013537585	1	
Licensed disease (YES/NO)	0·026287447	0·006986613	0·105413533	-0·039886202	-0·060220857	1

Regression analysis

In order to determine whether the considered variables are statistically significant explanatory factors of average vaccine development projects by R&D phase, we ran several regressions to identify consistently significant values of these (95% confidence interval). Although there are various types of regression models that can potentially be used, we present below the findings of linear regressions using Ordinary Least Squares (OLS) estimators of the explanatory variables. As we demonstrate below, the coefficient of determination (R squared) is low – i.e. the proportion of the variance in average vaccine development project costs by R&D phase that can be predicted from the explanatory variables in the regression models. This coefficient does not improve when running non-linear (e.g. logarithmic or exponential) regressions, which we also tested. However, the coefficient improves when hierarchically clustering the data. We therefore opted for OLS, which are well-established methods with robust (Best Linear Unbiased Estimator) properties. And we conducted a hierarchical clustering analysis to determine to what extent the predicted cost ranges in our model failed to capture the proportion of the variance in average vaccine development project costs by R&D phase not predicted from the explanatory variables in the regression model.

The general linear multiple regression function for our analytical purposes can be expressed as follows:

Y = intercept + Sum(biXi) + Sum(biDi) + Sum(ei)

Where

Y = dependent variable capturing the mean vaccine development project cost by R&D phase

Intercept = Average constant cost of vaccine development by R&D phase at chosen values of explanatory variables

Xi= explanatory variable i that is continuous (e.g. in our case: timelines, indirect cost)

Di=explanatory variable i that is dichotomous i.e. it takes either a 0 or 1 value (e.g. in our care: product developer licensure track-record, platform technology licensure track-record, disease track-record of licensed vaccine, industry/non-industry)

bi = coefficient parameter of variable Xi, which estimates the change in the mean cost of vaccine development per explanatory variable value change, all other explanatory variables held constant

ei = residual, i.e. the cost of vaccine development by R&D phase that cannot be explained by the intercept and explanatory variables included in the cost function

For our six variables previously described, we ran regressions on average vaccine development project costs by R&D phase. As Appendix tables 3.5 to 3.8 demonstrate, only two variables (indirect cost, product developer licensure track-record) are consistently statistically significant across R&D phases (p values for these variables are less than 0.05, suggesting significance within a 95% confidence interval).

Appendix table 3.5: Exploratory regression statistics for six considered variables, preclinical phase

	Multiple R	R Square	Adjusted R Square	Standard Error	Observations
	0·5676	0·3222	0·2911	14,000,053	138
	df	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	6·00	12,204,961,821,826,900	2,034,160,303,637,820	10·378290325	0·000000002
Residual	131·00	25,676,194,386,044,700	196,001,483,862,936		
Total	137·00	37,881,156,207,871,600			
	Coefficients	**Standard Error**	**t Stat**	**P-value**	
Intercept	- 118,824	3,897,262	- 0·030	0·976	
Timelines	- 188,077	453,041	- 0·415	0·679	
Indirect cost (%)	18,741,986	6,799,654	2·756	0·007	
PD track-record YES=1/NO=0)	18,694,704	2,927,244	6·386	0·000	
Industry (YES=1/NO=0)	7,231,687	2,816,865	2·567	0·011	
Licensed tech (YES=1/NO=0)	212,515	2,571,289	0·083	0·934	
Licensed disease (YES/NO)	- 9,992,501	4,646,705	- 2·150	0·033	

Appendix table 3.6: Exploratory regression statistics for six considered variables, phase I

	Multiple R	R Square	Adjusted R Square	Standard Error	Observations
	0·4587	0·2104	0·1742	8,588,765	138
	df	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	6·00	2,574,550,353,103,880	429,091,725,517,314	5·816860566	0·000021237
Residual	131·00	9,663,462,859,623,110	73,766,892,058,192		
Total	137·00	12,238,013,212,727,000			
	Coefficients	**Standard Error**	**t Stat**	**P-value**	
Intercept	448,660	2,390,896	0·188	0·851	
Timelines	429,070	277,932	1·544	0·125	
Indirect cost (%)	11,766,596	4,171,458	2·821	0·006	
PD track-record YES=1/NO=0)	8,164,516	1,795,808	4·546	0·000	
Industry (YES=1/NO=0)	1,932,689	1,728,093	1·118	0·265	
Licensed tech (YES=1/NO=0)	- 588,972	1,577,436	- 0·373	0·709	
Licensed disease (YES/NO)	- 5,281,677	2,850,665	- 1·853	0·066	

Appendix table 3.7: Exploratory regression statistics for six considered variables, phase II

	Multiple R	R Square	Adjusted R Square	Standard Error	Observations
	0·4142	0·1716	0·1336	15,225,809	138
	df	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	6·00	6,289,010,935,437,650	1,048,168,489,239,610	4·521372976	0·000337977
Residual	131·00	30,369,109,743,942,500	231,825,265,220,935		
Total	137·00	36,658,120,679,380,200			
	Coefficients	**Standard Error**	**t Stat**	**P-value**	
Intercept	7,594,841	4,238,482	1·792	0·075	
Timelines	741,523	492,706	1·505	0·135	
Indirect cost (%)	20,425,013	7,394,989	2·762	0·007	
PD track-record YES=1/NO=0)	12,311,901	3,183,535	3·867	0·000	
Industry (YES=1/NO=0)	1,736,393	3,063,492	0·567	0·572	
Licensed tech (YES=1/NO=0)	- 2,566,669	2,796,414	- 0·918	0·360	
Licensed disease (YES/NO)	- 8,027,628	5,053,541	- 1·589	0·115	

Appendix table 3.8: Exploratory regression statistics for six considered variables, Total preclinical - phase II

	Multiple R	R Square	Adjusted R Square	Standard Error	Observations
	0·5010	0·2510	0·2167	35,366,432	138
	df	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	6·00	54,916,978,260,331,200	9,152,829,710,055,210	7·317671173	0·000000927
Residual	131·00	163,852,770,054,642,000	1,250,784,504,233,910		
Total	137·00	218,769,748,314,973,000			
	Coefficients	**Standard Error**	**t Stat**	**P-value**	
Intercept	7,924,667	9,845,123	0·805	0·422	
Timelines	982,517	1,144,456	0·859	0·392	
Indirect cost (%)	50,933,579	17,177,042	2·965	0·004	
PD track-record YES=1/NO=0)	39,171,132	7,394,698	5·297	0·000	
Industry (YES=1/NO=0)	10,900,759	7,115,863	1·532	0·128	
Licensed tech (YES=1/NO=0)	- 2,943,114	6,495,497	- 0·453	0·651	
Licensed disease (YES/NO)	- 23,301,799	11,738,340	- 1·985	0·049	

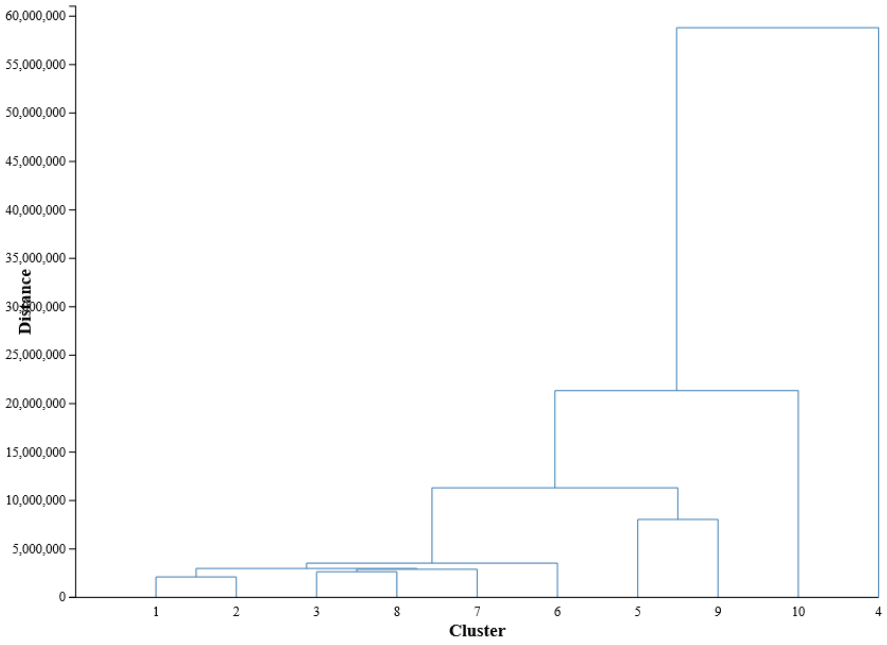
Hierarchical clustering analysis

It is worth noting that for all regressions the outputs of which are presented in Appendix tables 3.5 to 3.8 above, the results are reliable (given that Significance F is less than 0.05 in all regressions), however there is a great deal of variation in average cost estimates that is not sufficiently explained by any standalone or combinations of the considered explanatory variables (R Squared is less than 0.28 in all regression; Multiple R Squared is less than 0.48 in all regressions; and there are large residual values).

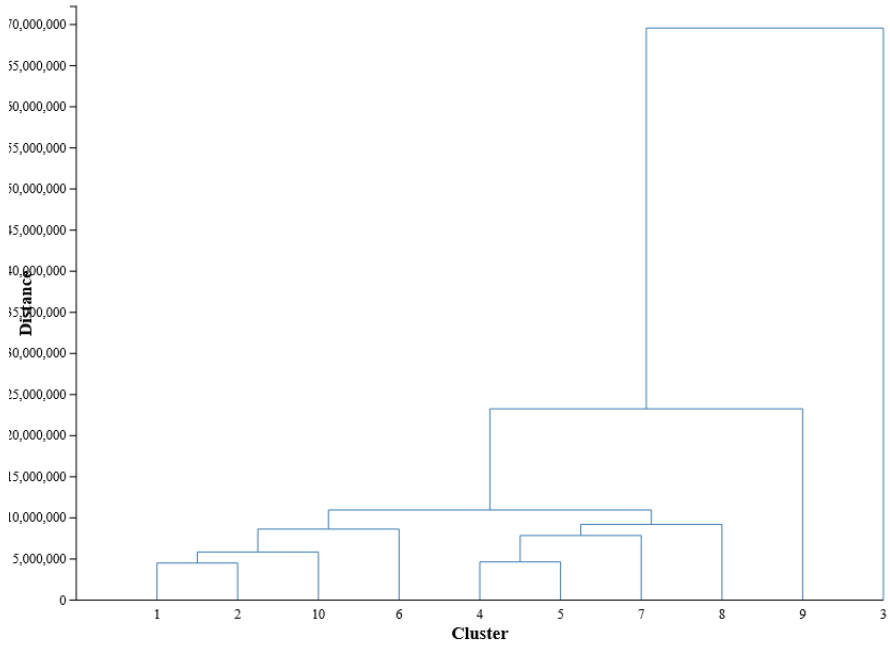
We therefore ran a hierarchical clustering analysis to identify potential clusters of cost estimates in our sample and associated cost drivers not captured in the tested variables above which could improve the explanatory power of the model. We did this by computing the distance between clusters using a Euclidean metric as the similarity measure for our data. The results are presented in appendix dendrograms 3.1 and 3.2 and appendix table 3.9 below.

As the vertical distances between sub-clusters in the dendrograms show, no strong clustering effect becomes immediately apparent. When testing for clusters at the preclinical cost level (appendix dendrogram 3.1), sub-clusters 5 and 9 contain only 4 out of 138 observations. Sub-cluster 10 is a single observation, and so is sub-cluster 4. All other observations are contained in the remaining sub-clusters, whose distance in cost terms is very small. Similarly, when testing for clusters at the clinical cost level (appendix dendrogram 3.2), sub-clusters 3 and 9 each concern single observations, whereas all other observations are contained in the remaining sub-clusters, whose distance in cost terms is again very small.

Appendix dendrogram 3.1.: Dendrogram of cost data clusters, preclinical phase



Appendix figure 3.2.: Dendrogram of cost data clusters, clinical phases I & II



Looking at the total number of cost observations per cluster for the preclinical phase, 119 are contained in sub-cluster 1 and and the remaining observations are distributed in very small numbers between 1 and 5 across sub-clusters 2 and 10. However, at the clinical phase, sub-cluster 1 reduces its total number of observations to 103, and sub-cluster 2 increases its observations to 21. All other observations are distributed in small numbers between 1 and 5 across sub-clusters 3 to 10. When grouping together the clinical phase sub-clusters into three main clusters 1, 2, and 3 (this includes sub-clusters 3 to 10), we identified:

- One cluster (cluster 3 - comprised of sub-clusters 1 to 3) concerning cost estimates reported by vaccine developers with previous licensure experience, representing both industry and non-industry sectors, concerning costs for diseases where no vaccine had been previously licensed at the time of R&D, and representing both well-established and less established platform technologies.
- A second cluster (cluster 2) concerning cost estimates reported by vaccine developers with limited licensure experience, representing predominantly industry, concerning costs for diseases where no vaccine had been previously licensed at the time of R&D, and representing both well-established and less established platform technologies.
- The remaining sample observations excluded from clusters 2 and 3 (cluster 1), concerning cost estimates reported by vaccine developers with limited licensure experience, representing both industry and non-industry sectors, concerning costs for diseases where no vaccine had been previously licensed at the time of R&D, and representing both well-established and less established platform technologies.

Appendix table 3.9: Concentration of cost sample observations by cluster, by explanatory variable considered in the regression

Observations	Cluster 1	Cluster 2	Cluster 3
Total (#)	103	21	14
PD track-record (YES=1) (% of total)	19%	19%	64%
Industry (YES=1) (% of total)	76%	86%	64%
Licensed disease (YES=1) (% total)	9%	5%	0%
Licensed tech (YES=1) (% total)	42%	52%	14%

Applying this clustering to the regression model and removing all other variables improves the coefficient of determination, at least for the clinical development phases, as demonstrated by the increased R square in Appendix table 3.10 below. This finding, in combination with the above, may suggest that increased R&D costs, particularly at clinical R&D phases, may potentially be associated with increased industrial sector affiliation but that the greatest increase in costs is associated with previous licensure track-record. However, as the same table suggests, the modes and boundaries of the estimated R&D cost distributions per R&D phase remain very close between the regression model that accounts for this clustering effect and the regression model that accounts for the statistically significant explanatory variables presented in the previous section.

Appendix table 3.10: Exploratory regression statistics for six considered variables of vaccine R&D cost, preclinical through end of phase IIa

	6 variables considered			*3 variables considered*			*Clusters only considered*		
	Preclinical	***Phase I***	***Phase II***	***Preclinical***	***Phase I***	***Phase II***	***Preclinical***	***Phase I***	***Phase II***
Observations	138	138	138	138	138	138	138	138	138
	0·5676	0·4587	0·4142	0·5365	0·4092	0·3728	0·5912	0·7772	0.8123
R Square	0·3222	0·2104	0·1716	0.2878	0.1675	0.1390	0.3495	0.6041	0.6598
Adjusted R Square	0·2911	0·1742	0·1336	0.2719	0.1551	0.1263	0.3399	0.5982	0.6548
Standard Error	$14m	$9m	$15m	$14m	$9m	$15m	$14m	$6m	$10m
Significance F	0·000	0·000	0·000	0.000	0.000	0.000	0.000	0.000	0.000
P–values									
Intercept	0·976	0·851	0·075	0.024	0.001	0.000	0.000	0.000	0.000
Timelines (#years)	0·679	0·125	0·135	NA	NA	NA	NA	NA	NA
Indirect cost (%)	0·007	0·006	0·007	0.010	0.003	0.005	NA	NA	NA
PD track-record (dichotomous)	0·0000	0·0000	0·0000	0.000	0.000	0.001	NA	NA	NA
Industry (dichotomous)	0·011	0·265	0·572	NA	NA	NA	NA	NA	NA
Licensed tech (dichotomous)	0·934	0·709	0·36	NA	NA	NA	NA	NA	NA
Licensed disease (dichotomous)	0·033	0·066	0·115	0.027	0.006	0.1	NA	NA	NA
Cluster 2	NA	NA	NA	NA	NA	NA	0.1	0.000	0.000
Cluster 3	NA	NA	NA	NA	NA	NA	0.000	0.000	0.000

Analysis of Variance (ANOVA) testing

We ran an ANOVA to test whether the average vaccine development project cost estimates by R&D phase are statistically equal across explanatory variables included in the model. As Appendix tables 3.11 to 3.13 demonstrate, there is a significant source of variation in cost estimates between product developers with licensure track-record and all other variables. Results from both one-tailed and two-tailed t-tests are also provided in tables 3.11 to 3.13 below.

Appendix table 3.11: ANOVA single factor and t-Test two-sample assuming unequal variances, preclinical

Anova: Single Factor

Groups	Count	Sum	Average	Variance
PD track-record YES=1	33	867,401,039	26,284,880	803,483,567,916,375
PD track-record NO=0	105	825,990,434	7,866,576	35,115,003,439,485
Industry YES=1	105	1,423,567,211	13,557,783	337,789,373,741,060
Industry NO=0	33	269,824,261	8,176,493	63,248,643,525,856
Licensed tech YES=1	56	726,536,692	12,973,869	428,865,418,267,238
Licensed tech NO=0	82	966,854,780	11,790,912	175,888,802,991,404
Licensed disease YES=1	10	55,806,500	5,580,650	16,704,012,558,333
Licensed disease NO=0	128	1,637,584,972	12,793,633	293,293,304,928,347

Source of Variation	Sum Square	df	Mean Square	F	P-value	F crit
Between Groups	9,773,961,952,630,980	7	1,396,280,278,947,280	5·358539 1	0·000006	2·02640
Within Groups	141,750,662,878,855,000	544	260,571,071,468,483			
Total	151,524,624,831,486,000	551				

t-Test: Two-Sample Assuming Unequal Variances (PD track-record YES=1 versus other variables)

	PD track-record NO=0	Industry YES=1	Industry NO=0	Licensed tech YES=1	Licensed tech NO=0	Licensed disease YES=1	Licensed disease NO=0
Df	33	41	37	52	38	36	38
t Stat	3·707	2·424	3·533	2·353	2·816	4·059	2·614
P(T<=t) one-tail	0·000	0·010	0·001	0·011	0·004	0·000	0·006
t Critical one-tail	1·692	1·683	1·687	1·675	1·686	1·688	1·686
P(T<=t) two-tail	0·001	0·020	0·001	0·022	0·008	0·000	0·013
t Critical two-tail	2·035	2·020	2·026	2·007	2·024	2·028	2·024

Appendix table 3.12: ANOVA single factor and t-Test two-sample assuming unequal variances, phase I

Anova: Single Factor

Groups	Count	Sum	Average	Variance
PD track-record YES=1	33	468,833,200	14,207,067	233,033,295,881,201
PD track-record NO=0	105	714,691,672	6,806,587	32,748,244,738,700
Industry YES=1	105	934,490,529	8,899,910	100,599,773,071,757
Industry NO=0	33	249,034,343	7,546,495	54,051,388,658,770
Licensed tech YES=1	56	511,536,402	9,134,579	104,547,774,615,255
Licensed tech NO=0	82	671,988,470	8,194,981	79,734,675,155,287
Licensed disease YES=1	10	51,042,500	5,104,250	15,044,365,402,778
Licensed disease NO=0	128	1,132,482,372	8,847,519	94,272,811,001,822

Source of Variation	Sum Square	df	Mean Square	F	P-value	F crit
Between Groups	1,580,466,516,067,730	7	25,780,930,866,818	2·5927953	0·012266	2·02640
Within Groups	47,371,586,334,840,200	544	7,080,121,939,045			
Total	48,952,052,850,907,900	551				

t-Test: Two-Sample Assuming Unequal Variances (PD track-record YES=1 versus other variables)

	PD track-record NO=0	Industry YES=1	Industry NO=0	Licensed tech YES=1	Licensed tech NO=0	Licensed disease YES=1	Licensed disease NO=0
Df	35	41	46	49	41	41	39
t Stat	2·725	1·874	2·258	1·698	2·121	3·110	1·919
P(T<=t) one-tail	0·005	0·034	0·014	0·048	0·020	0·002	0·031
t Critical one-tail	1·690	1·683	1·679	1·677	1·683	1·683	1·685
P(T<=t) two-tail	0·010	0·068	0·029	0·096	0·040	0·003	0·062
t Critical two-tail	2·030	2·020	2·013	2·010	2·020	2·020	2·023

Appendix table 3.13: ANOVA single factor and t-Test two-sample assuming unequal variances, phase II

Anova: Single Factor

Groups	Count	Sum	Average	Variance
PD track-record YES=1	33	924,078,219	28,002,370	687,821,296,459,282
PD track-record NO=0	95	651,777,596	6,860,817	111,122,022,648,137
Industry YES=1	105	2,064,475,820	19,661,674	315,250,134,797,915
Industry NO=0	33	621,330,168	18,828,187	120,458,237,847,132
Licensed tech YES=1	56	1,091,477,869	19,490,676	356,658,345,530,359
Licensed tech NO=0	82	1,594,328,118	19,443,026	210,393,038,536,530
Licensed disease YES=1	10	144,551,000	14,455,100	37,308,432,544,444
Licensed disease NO=0	128	2,541,254,988	19,853,555	283,874,252,037,103

Source of Variation	Sum Square	df	Mean Square	F	P-value	F crit
Between Groups	16,234,682,363,794,800	7	2,319,240,337,684,980	8·7129202	0·000000	2·02672
Within Groups	142,142,280,272,954,000	534	266,184,045,454,970			
Total	158,376,962,636,749,000	541				

t-Test: Two-Sample Assuming Unequal Variances (PD track-record YES=1 versus other variables)

	PD track-record NO=0	Industry YES=1	Industry NO=0	Licensed tech YES=1	Licensed tech NO=0	Licensed disease YES=1	Licensed disease NO=0
Df	40	42	43	52	40	40	39
t Stat	2·410	1·708	1·854	1·632	1·769	2·733	1·697
P(T<=t) one-tail	0·010	0·048	0·035	0·054	0·042	0·005	0·049
t Critical one-tail	1·684	1·682	1·681	1·675	1·684	1·684	1·685
P(T<=t) two-tail	0·021	0·095	0·071	0·109	0·085	0·009	0·098
t Critical two-tail	2·021	2·018	2·017	2·007	2·021	2·021	2·023

Implications

Based on the findings presented in this appendix, product developer licensure track-record and indirect costs are significant explanatory factors of R&D costs. However, there is a substantial variation in self reported cost estimates that cannot be adequately explained by clustering or explanatory variables considered in the regression.

Appendix 3 references

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Appendix 4: Monte Carlo Simulations for determining R&D costs associated with current vaccine pipeline structures for 11 EIDs

In this appendix we present the details of our Monte Carlo simulation methodology and scenario analysis to determine the expected total cost for bringing a portfolio of vaccines through end of phase IIa, out of initial investments in 194 preclinical, 24 clinical phase I, and 6 phase II vaccine candidates for 11 EIDs, accounting for risk of failure.

We begin with a discussion of the parameters and assumptions underlying the simulation, including how we constructed the cost and PoS distributions defining the different simulation scenarios. We then turn to the steps undertaken from random sampling to estimating total expected vaccine R&D costs from preclinical through phase II.

Simulation parameters

The estimation of total vaccine R&D costs from preclinical phase through clinical phase II is dependent on the number of preclinical and clinical EID vaccine candidates currently available in the R&D pipeline and their combination with two sets of randomized input parameters to generate expected phase II and associated R&D cost outputs:

- Cost by R&D phase
- PoS by R&D phase

In setting our cost by R&D phase parameters, we relied on the self-reported cost estimates provided by vaccine developers through the survey (appendix 2) categorized in two groups: a lower bound group with cost estimates based on product developers with no previous licensure track-record; and an upper bound group with cost estimates based on product developers with licensure track-record. For each of these groups, we took the self-reported cost estimates and created ranges of costs; range boundaries being defined by the lowest and highest reported cost estimates for each respective group. We assigned equal probabilities to these costs, to construct discrete distributions of costs by R&D phase.

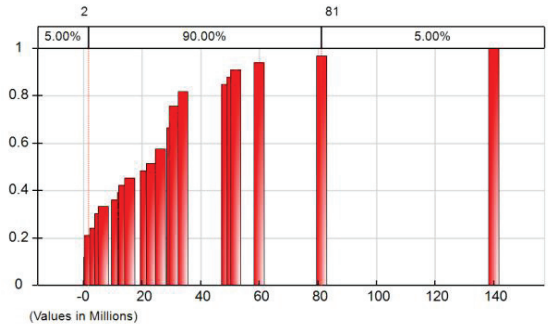
The figures below present the cumulative distribution functions for the lower and upper bounds of vaccine R&D costs by R&D phase. These figures demonstrate that vaccine project costs used for the simulation scenarios fall between:

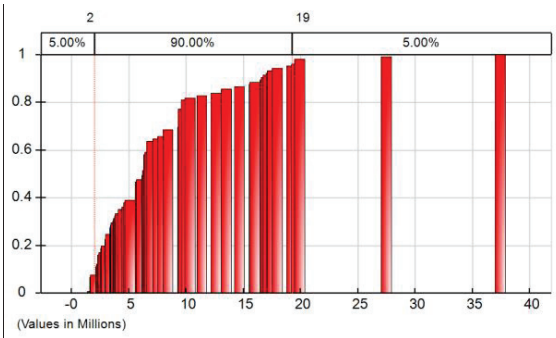
- US$ 1.7m – US$ 140m (upper bound) and US$ 1.8m – US$ 37.4m (lower bound) for preclinical
- US$ 1.9m – US$ 70m (upper bound) and US$ 1m – US$ 30.2m (lower bound) for phase I
- US$ 3.8m – US$ 140m (upper bound) and US$ 4.4m – US$ 54.5m (lower bound) for phase II

Figures 4.1 to 4.3.: Upper bound cumulative cost distributions by R&D phase, based on product developers with previous vaccine licensure track-record

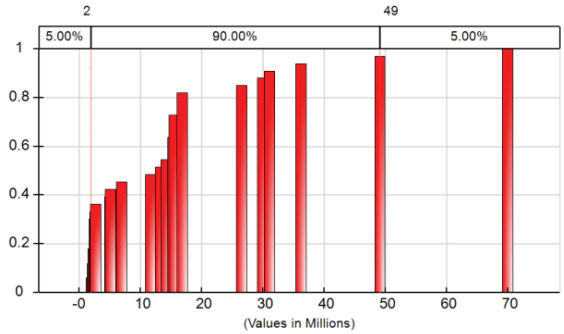
Figures 4.4. to 4.6.: Lower bound cumulative cost distributions by R&D phase, based on product developers with no vaccine licensure track-record

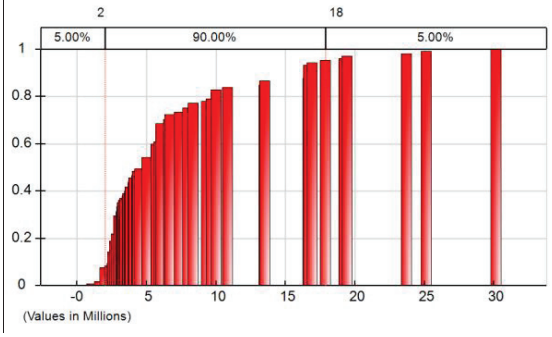
Preclinical phase



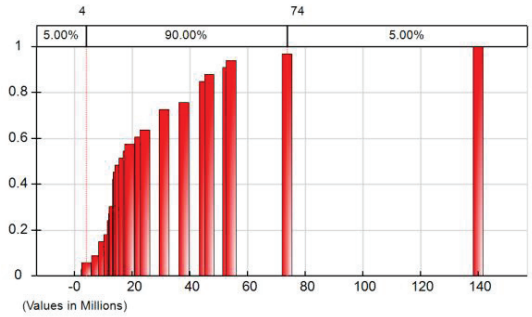


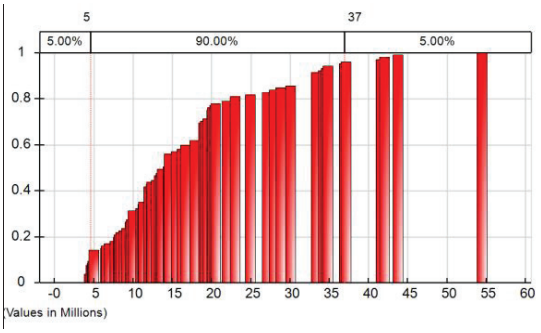
Phase I





Phase II





**X axis shows the self-reported cost estimates; Y axis shows their cumulative frequency*

In setting our PoS by R&D phase parameters, we relied on published evidence of estimates of vaccine R&D PoS by R&D phase in the literature and a number of key assumptions. The literature sources and their associated estimates of vaccine R&D PoS by R&D phase are listed in table 1 of the main article. As that table demonstrates, the literature on vaccine R&D PoS is not consistent, with variable estimates of PoS by R&D phase suggested by different sources. To capture this variability in previously published vaccine R&D PoS estimates, we assumed three PoS distribution scenarios, whereby:

- The lower PoS scenario is defined for each R&D phase by lower and upper bounds equivalent to the lowest and highest PoS estimates in the literature, and a modal value equivalent to the lowest published estimate of PoS
- The higher PoS scenario is defined for each R&D phase by lower and upper bounds equivalent to the lowest and highest PoS estimates in the literature, and a modal value equivalent to the highest published estimate of PoS
- The base case PoS scenario is defined for each R&D phase by lower and upper bounds equivalent to the lowest and highest PoS estimates in the literature, and a modal value equivalent to Pronker's estimates,[1] acknowledging that this research provides one of the most comprehensive and recently updated sources of PoS estimates on vaccine R&D.

The figures below present the frequency and cumulative distribution functions for the PoS associated with lower bound, base case, and upper bound scenarios by R&D phase, from preclinical through phase II.

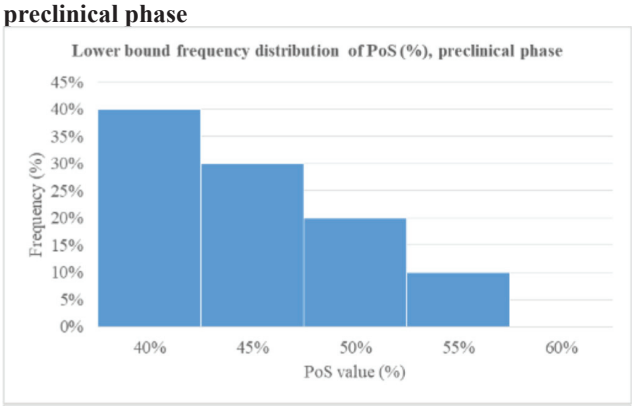
The figures for preclinical phase demonstrate that PoS:

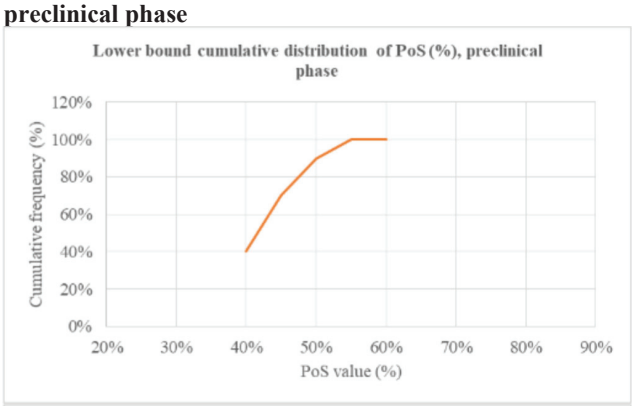
- Has in the *lower bound* scenario a modal value of 40%, and it ranges from 40% to 60%, with over two-thirds of the PoS % value falling between 40% and 45%
- Has in the *base case* scenario the same modal value, ranges and frequency distribution with the lower bound scenario
- Has in the *upper bound* scenario a modal value of 60%, and it ranges from 40% to 60%, with half of the PoS % value falling between 40% and 50%

Figures 4.7 to 4.8: Frequency distributions of PoS (%), preclinical phase

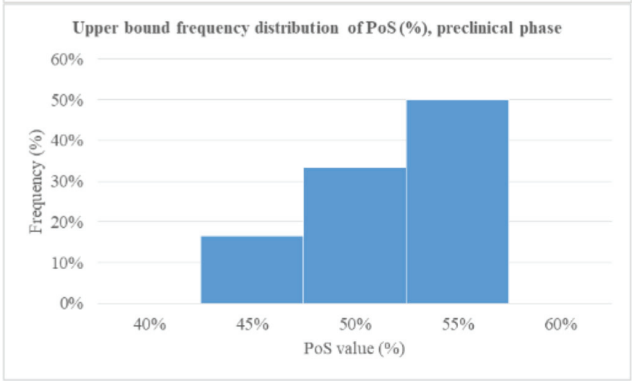
Figures 4.9 to 4.10: Cumulative distributions of PoS (%), preclinical phase

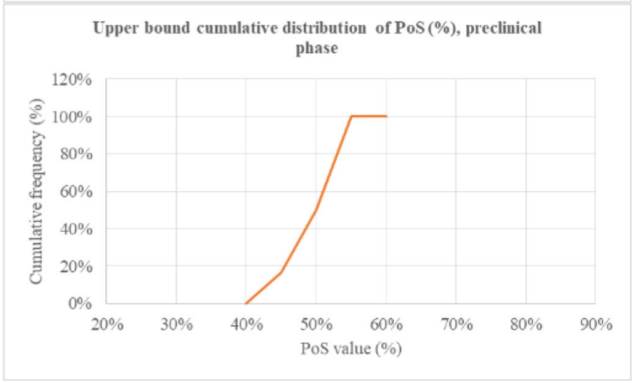
Lower bound





Upper bound





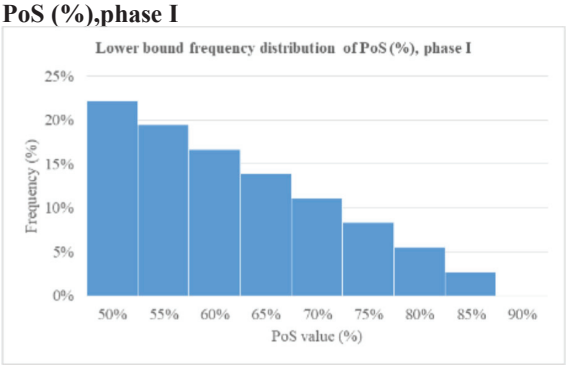
The figures for phase I demonstrate that PoS:

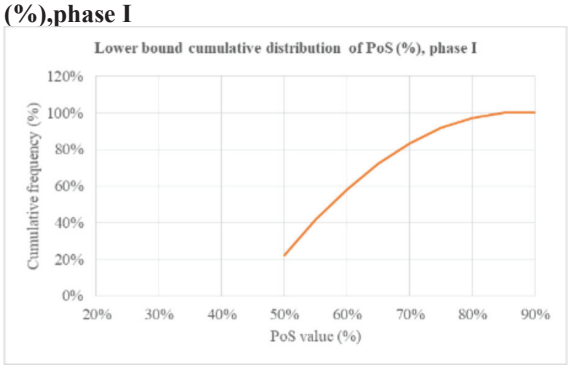
- Has in the *lower bound* scenario a modal value of 50%, and it ranges from 50% to 90%, with half of the PoS % value falling between 50% and 60%
- Has in the *base case* scenario a modal value of 80%, and it ranges from 50% to 90%, with over half of the PoS % value falling between 50% and 75%
- Has in the *upper bound* scenario a modal value of 90%, and it ranges from 50% to 90%, with half of the PoS % value falling between 50% and 80%

Figures 4.11 to 4.12: Frequency distributions of PoS (%),phase I

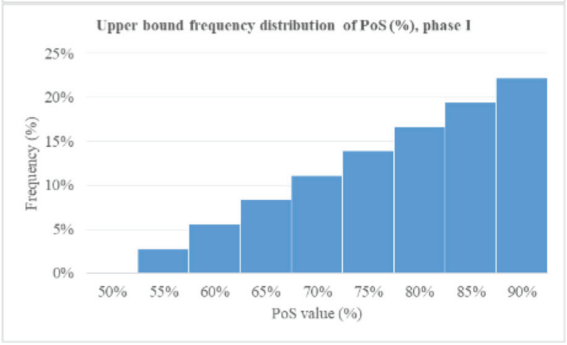
Figures 4.13 to 4.14: Cumulative distributions of PoS (%),phase I

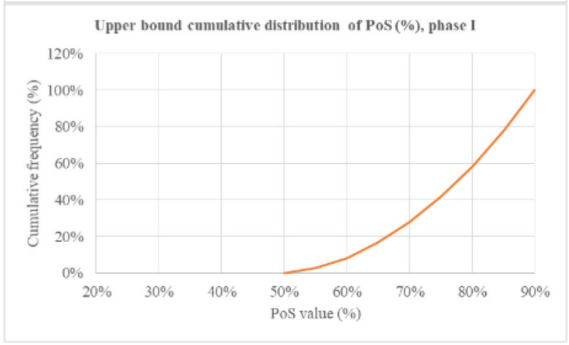
Lower bound





Upper bound





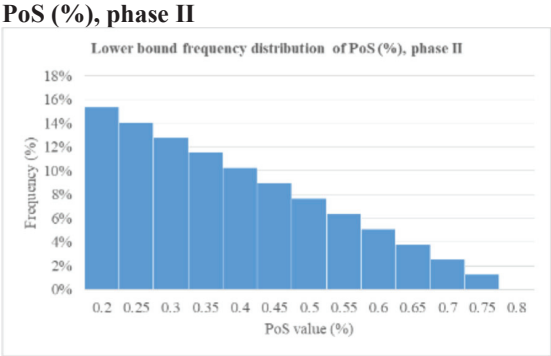
The figures for phase II demonstrate that PoS:

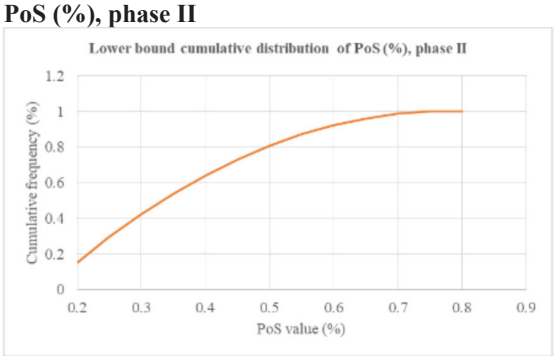
- Has in the *lower bound* scenario a modal value of 20%, and it ranges from 20% to 80%, with half of the PoS % value falling between 20% and 35%
- Has in the *base case* scenario a modal value of 30%, and it ranges from 20% to 80%, with half of the PoS % value falling between 25% and 40%
- Has in the *upper bound* scenario a modal value of 80%, and it ranges from 20% to 80%, with half of the PoS % value falling between 20% and 65%

Figures 4.15 to 4.16: Frequency distributions of PoS (%), phase II

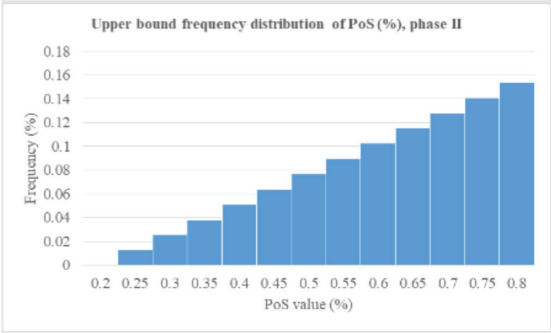
Figures 4.17 to 4.18: Cumulative distributions of PoS (%), phase II

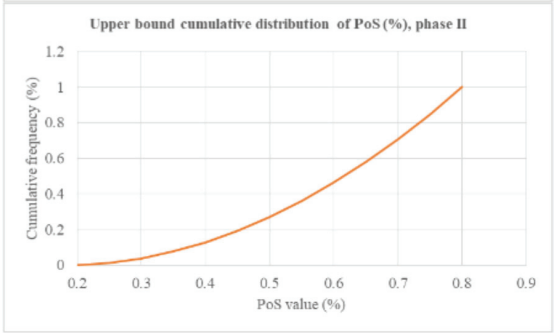
Lower bound





Upper bound





Our final assumption based on which we ran the simulation is that of statistical independence between parameters. The PoS by R&D phase parameters were drawn from different datasets identified in our literature review. Their independence from cost parameters is therefore likely. We assumed no further correlation between PoS by R&D phase and other possibly significant variables to which PoS may relate, namely: targeted disease; and type of technology used. Given no prophylactic vaccine and no standardized regulatory pathway exists for any of the 11 EIDs, disease-specific failure risks are assumed to be the same across all diseases. Moreover, R&D failures due to platform technology issues between preclinical and phase II are assumed not to spill over to other vaccine candidates even when these are being developed by the same organization. However, if phase III and licensure were to be included in the analysis, this assumption would no longer hold, and PoS correlation coefficients between vaccine candidates making use of the same platform technology would have to be calculated and integrated explicitly in the simulation analysis.

Simulating total vaccine R&D project costs given EID vaccine R&D pipelines are known

Our methodology for calculating total vaccine R&D costs is based on the combination of EID vaccine R&D pipeline data and our simulation parameters in a step-wise manner:

- Step 1: Specify values for the number of vaccine candidates by R&D phase (preclinical, phase I, phase II) available
- Step 2: Specify distributions for cost and PoS by R&D phase to define simulation scenarios. As per our clarifications on distributions in the previous section, we have six different simulation scenarios:
    - Scenario 1: Simulation with random sampling from base case PoS and lower bound cost distributions
    - Scenario 2: Simulation with random sampling from base case PoS and higher bound cost distributions
    - Scenario 3: Simulation with random sampling from lower bound PoS and lower bound cost distributions
    - Scenario 4: Simulation with random sampling from lower bound PoS and higher bound cost distributions
    - Scenario 5: Simulation with random sampling from higher bound PoS and lower bound cost distributions
    - Scenario 6: Simulation with random sampling from higher bound PoS and higher bound cost distributions
- Step 3: For each scenario, draw randomly (10,000 iterations) from a range of cost US$ values for which the distribution function is known, to determine the base cost associated with bringing the current number of EID vaccine candidates through the next phase of development (call it Stage Gate 1) – i.e. phase I for vaccine candidates currently at preclinical phase of development; phase II for vaccine candidates currently at phase I; and phase III for vaccine candidates currently at phase II.
- Step 4: For each scenario, draw randomly (10,000 iterations) from a range of PoS % values for which the triangular cumulative distribution function is known, to determine the probability of successful advancement of the current number of EID vaccine candidates through the next phase of development (Stage Gate 1).
- Step 5: For each scenario, estimate the integer value of the number of EID vaccine candidates advancing through the next phase of development (Stage Gate 1) by adjusting the values in step 1 according to the PoS % values in step 4.
- Step 6: For each scenario, repeat step 3 above using the cost US$ value distributions associated with bringing the number of Stage Gate 1 EID vaccine candidates through the next phase of development (Stage Gate 2) - i.e. phase II for vaccine candidates at phase I of development under Stage Gate 1; phase III for vaccine candidates at phase II under Stage Gate 2.
- Step 7: For each scenario, repeat step 4 above using the PoS % value distributions associated with bringing the number of Stage Gate 1 EID vaccine candidates through Stage Gate 2; then repeat steps 5 and 6 to calculate integer values and associated costs of the number of EID vaccine candidates advancing through Stage Gate 3 – i.e. phase III for vaccine candidates that were at phase II in Stage Gate 2.

The above steps, and the data and assumptions supporting the simulation parameters that we described above, allow us to estimate through this simulation model the number of successful phase II outcomes expected from investing in the current vaccine R&D pipelines by EID; and the associated total portfolio costs for achieving those phase II outcomes, given current EID vaccine R&D pipelines are known.

Appendix 4 references

1. Pronker ES, Weenen TC, Commandeur H, Claassen EH, Osterhaus AD. Risk in vaccine research and development quantified. *PLoS One* 2013; 8(3):e57755

Appendix 5: Stochastic optimization of EID vaccine R&D portfolios and associated costs

In this appendix we present a more detailed overview of the rationale and design of our stochastic optimization methodology. We begin with a descriptive formulation of the model and then turn to a discussion of solution methods. We conclude with a presentation of our probabilistic sensitivity analysis findings associated with the different stages of the model.

Section 5.1. Model formulation

Rationale

Whereas simulation-based scenario analyses can provide analytical depth to highlighted scenarios, they have limited capacity to demonstrate optimal solutions on their own, such as how to minimize or optimize objectives in EID vaccine R&D. Optimization techniques can provide insights on how to prioritize R&D investments through the minimization or maximization of objective functions subject to analytical constraints that cannot be exceeded.[1] Moreover, the simultaneous consideration of multiple candidate projects is a key aspect in managing a new product development pipeline.[2]

In pharmaceutical R&D management, several stochastic modelling approaches have been proposed to address a variety problems. A multistage simulation-optimization model identified the optimal number of projects required to deliver pharmaceutical R&D outputs that maximize economic value.[3] Discrete-event simulation was combined with mixed integer linear programming for the optimal structuring of, and ordering of activities within pharmaceutical R&D portfolios.[4] Mixed integer linear programming using simulation and real options valuation was employed to determine the optimal size and structuring of pharmaceutical R&D portfolios.[5] Discrete-event simulation was combined with genetic algorithm based optimization procedures for the optimal selection and ordering of pharmaceutical R&D projects to maximize economic value and to minimize the probability of economic losses.[6] In other approaches discrete-event simulation was combined with efficient frontier analysis to identify optimal pharmaceutical R&D portfolios at different levels of risk and budget constraints.[7, 8] Simulation-optimization techniques have been proposed that incorporate mixed integer linear programming for the optimal scheduling and allocation of resources for pharmaceutical R&D pipelines.[9] Other related approaches were proposed for clinical trial scheduling and value maximization in pharmaceuticals.[10–12] An event stochastic simulation model used multi-objective genetic algorithms for the optimal structuring and sequencing of pharmaceutical R&D portfolios to minimize time, minimize risk and maximize economic value of R&D.[2] Others used multistage stochastic programming with knapsack decomposition algorithms for the optimal structuring of pharmaceutical R&D pipelines,[13] and multi-range robust optimization techniques for pharmaceutical R&D project selection.[14]

A number of simulation-optimization techniques for simultaneous portfolio management and manufacturing capacity planning are summarized in the literature.[15] So are several other simulation-optimization techniques for time dependent optimization of new product development pipeline schedules.[2] And programming techniques have recently been reviewed using chance constrained optimization for the optimization of pharmaceutical development processes under uncertainty.[16]

This literature demonstrates that stochastic optimization can provide meaningful prioritization insights for new product development in the presence of uncertainty. Given the inherently risky nature of vaccine R&D, stochastic modelling approaches are likely to represent realistic reflections of the uncertain expectations from the pharmaceutical R&D process. However, this evidence predominantly provides theoretical approaches to hypothetical, yet challenging and sophisticated problems may relate to, but do not directly address real-life situations. This is a common limitation of this literature that our study attempts to overcome.

Problem description

Our optimization model can be described as a stochastic non-smooth mixed integer programming (SNP/MIP) problem. The key parameters of the model are provided in the main part of the study, table 2. Here, we provide some definitions and elaborate on several assumptions we have undertaken.

Mixed integer problems concern optimization problems where at least some of these variables are restricted to be integers, introducing discontinuities in the objective function and in the search space of feasible solutions. Non-smooth optimization means optimization of a problem where derivative information on the objective and variables cannot be used to determine the direction in which the objective function is increasing or decreasing, creating a non-convex space of many potentially feasible solutions.

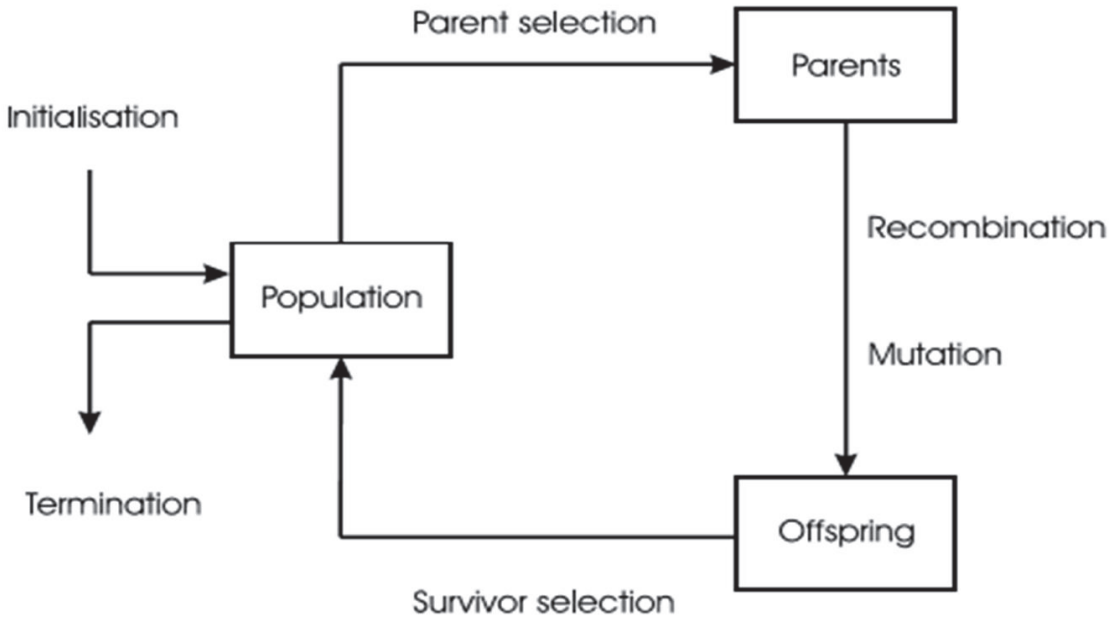
Given the nature of SNP/MIP problems it is unlikely that all possible solutions can be calculated or a globally optimal solution found. In SNP/MIP problems, traditional optimization techniques – such as linear or non-linear convex programming – break down, either due to the irregular structure of the search space or because the search becomes computationally intractable.[17] In such cases, evolutionary computation approaches can offer robust and flexible alternatives to optimization problem solving,[17] where solutions are no longer deterministic (i.e. single point estimates representing global optimum solutions without uncertainty) but probabilistic (i.e. range estimates representing multiple likely optimal solutions with uncertainty).

A general introduction to evolutionary algorithms and an overview of genetic algorithms for modelling and optimization can be found elsewhere in the literature.[17, 18] Although genetic and evolutionary algorithms developed independently since the 1960s,[19, 20] they share the same overall approach to generating candidate solutions to some problem via random selection and evolution of solutions to near-optimal solutions through a series of fitness-based evolutionary steps (see figure 5.1 for an illustration). Despite

small differences in technical details[2], genetic and evolutionary algorithms are generally treated as part of the same family of evolutionary computation methods.

As figure 5.1 illustrates, an evolutionary algorithm starts by randomly drawing from a population of candidate solutions. The algorithm learns and adapts its search for even better optima in relation to a current solution, as the composition of the population of candidate solutions changes. This adaptation is supported by random changes (mutations) to the original (the parent) population of candidate solutions, yielding new candidate solutions (the children) – which may or may not be an improvement to previous solutions. Throughout this process, an evolutionary algorithm selects the 'fittest' and eliminates the 'least fit' members of the population of candidate solutions.

Figure 5.1: The general scheme of an evolutionary algorithm as a flow-chart[18]



An evolutionary algorithm will continue to drive towards ever-better, or at least ever-new, solutions in comparison to previously generated solutions, only to be constrained by rules designed to serve as stopping conditions in the computation process. These include: (1) the maximum computation time allowed; (2) the number of 'fitness' iterations allowed; (3) the maximum time allowed for fitness iterations to take place without improving on the current solutions; (4) and the minimization of differences between new *versus* previous sets of solutions.[18] The latter condition, also known as convergence, is a critical indication of whether optimal or near-optimal solutions have been met. However, premature convergence – the loss of diversity between sets of solutions too quickly in the search process – can lead to solutions that are not near-optimal. To avoid this, the number of optimization runs permitted in any given optimization problem making use of evolutionary algorithms needs to be substantial. Although a good practice, there is no agreement on the minimum threshold for the number of optimization runs required for evolutionary algorithms to reach convergent, or near optimal solutions.[18] In our study, we ran between 10 and 100 optimizations on the same problem, for each stage of the model. We assumed that a minimum of 10 optimizations would be sufficient to minimize the risk of early convergence on the problem for each stage of the model. If differences between model parameters were consistently zero or close to zero on their 5th and 95th percentile values after 5 consecutive optimizations, beyond and above the 10 minimum runs, we then assumed that a convergent solution had been found.

Evolutionary programming is increasingly being employed to solve stochastic optimization problems through simulation-optimization techniques in pharmaceutical R&D management problems, as demonstrated by evidence also referenced earlier in this appendix. [2,6,12,13,15,21–23] The basic idea behind simulation optimization is that for each set of values for the decision variables considered by the model, we perform one simulation of 10,000 iterations for the constraints and objective that depend on uncertainty. The model uses these measures to decide what set of values it should try next for the decision variables – and the process is repeated with a new simulation conducted at each step of the optimization. The overall benefit of simulation-optimization is the treatment of optimization outcomes as probabilistic outcomes accounting for uncertainty. A significant limitation associated with such techniques is the number of computational steps required to derive solutions, which can grow exponentially with the number of variables and constraints included in the optimization problem. For instance, the cumulative computational time for solutions across all stages of our model was over 20 hours in total.

[2] E.g. an evolutionary algorithm may make a sequence of mutations of an original solution, whereas a genetic algorithm may make a recombination of two original solutions to generate new solutions. Both mutation and recombination operators are stochastic and are applied so as to randomly draw from populations of multiple original solutions.

Although the theory behind evolutionary computation is limited in scope and applicability to special cases,[17] the literature on pharmaceutical R&D management problems demonstrates that evolutionary algorithms provide acceptable means of coping with large and discontinuous search spaces (such as non-smooth mixed integer problems) and robust ways of dealing with problems where there is significant uncertainty associated with key parameters of the problems (such as PoS in pharmaceutical R&D optimization problems).

Section 5.2. Probabilistic sensitivity analysis

Here we assess the robustness of our results, by analysing the expected outcome probabilities associated with the lowest and highest PoS/Cost scenarios and by examining the degree of correlation between the variance in outcomes and the uncertain parameters of the model. To do this we are employing a probabilistic sensitivity analysis approach, inherent in Monte Carlo simulations[24] and simulation-optimization methods,[25] whereby probability distributions are defined for the uncertain parameters of the model: cost and PoS by R&D phase. By simulating the consequences of random drawings from these distributions, we are able to determine the likelihood that different outcomes will occur and to identify the most significant sources of variation in our model's outcomes.

In stage 1, we asked how many vaccine candidates would ideally need to enter into preclinical, or phase I, or phase II, to achieve at least one phase IIa outcome by EID. The probabilities associated with the occurrence of at least one phase IIa outcome due to vaccine candidates entering different phases of the R&D pipeline by disease are presented in table 5.1 for the low PoS/ low cost scenario and in table 5.2 for the high PoS/ high cost scenario, respectively. Here we find that the probability of zero phase IIa outcomes remains consistently below 5% across scenarios. For each EID, the probability of one vaccine progressing through end of phase IIa is higher than the respective probability of two or more phase IIa outcomes in the low PoS/Cost scenario (see table 5.1). In the high PoS/Cost scenario two phase IIa outcomes per EID are more likely for all EIDs, except for RVF (see table 5.2).

Table 5.1: Probabilistic Sensitivity Analysis under low PoS/ low cost scenario, stage 1 of stochastic optimization model

	0 phase IIb/III ready candidates	1 phase IIb/III ready candidate	2 phase IIb/III ready candidates	3 phase IIb/III ready candidates	4 phase IIb/III ready candidates	5 phase IIb/III ready candidates
RVF	4%	52%	32%	11%	1%	0%
Chikungunya	0%	50%	34%	14%	2%	0%
CCHF	5%	49%	32%	11%	3%	0%
Marburg	5%	49%	32%	11%	3%	0%
MERS	4%	49%	32%	12%	3%	0%
SARS	4%	48%	31%	13%	3%	1%
SFTS	4%	47%	32%	13%	3%	1%
Lassa	4%	47%	32%	13%	4%	0%
Nipah	4%	47%	32%	13%	4%	0%
Zika	0%	46%	34%	16%	4%	0%
Starting from phase II	0%	56%	33%	11%	0%	0%
Starting from preclinical	1%	37%	34%	19%	7%	2%
Starting from phase I	0%	36%	35%	20%	7%	2%

Table 5.2: Probabilistic Sensitivity Analysis under high PoS/ high cost scenario, stage 1 of stochastic optimization model

	0 phase IIb/III ready candidates	1 phase IIb/III ready candidate	2 phase IIb/III ready candidates	3 phase IIb/III ready candidates	4 phase IIb/III ready candidates
Chikungunya	1%	30%	55%	14%	0%
Zika	2%	37%	51%	10%	0%
RVF	5%	55%	40%	0%	0%
MERS	4%	43%	46%	7%	0%
Marburg	4%	38%	46%	12%	0%
CCHF	4%	37%	45%	14%	0%
SARS	3%	37%	45%	15%	0%
Lassa	3%	37%	45%	15%	0%
SFTS	4%	36%	45%	15%	0%
Nipah	4%	36%	45%	15%	0%
Starting from phase II	1%	24%	59%	16%	0%
Starting from phase I	0%	17%	43%	37%	3%
Starting from preclinical	1%	19%	44%	32%	4%

In stage 2, we asked how much investment would be needed to progress at least one vaccine through end of phase IIa by EID, given current and new preclinical vaccine candidates are made available. As table 5.3 demonstrates, the probabilities associated with at least one phase IIa outcome per EID at a total cost of less than US$ 4 billion or more than US$ 7 billion are less than 2% across scenarios. The most likely cost range for achieving the minimum phase IIa targets for all 10 EIDs is US$5 – 6 billion, followed by the US$4 – 5 billion range and the US$6 – 7 billion range, respectively.

Table 5.3: Probabilistic Sensitivity Analysis across PoS/cost scenarios, stage 2 of stochastic optimization model

Scenario	<$1bn	$1–2bn	$2–3bn	$3–4bn	$4-5bn	$5-6bn	$6-7bn	$7-8bn	$8-9bn	$9-10bn	>$10bn
Low PoS/cost	2%	28%	33%	22%	10%	4%	0.5%	0.5%	0%	0%	0%
High PoS/cost	4%	18%	19%	26%	14%	9%	4%	3%	2%	1%	0%

Finally, as table 5.4 demonstrates, the variance in expected phase IIa outcomes is strongly correlated with the variance in PoS by R&D phase, and in particular with PoS in phase II. The variance in associated portfolio costs is positively correlated with both costs and PoS by R&D phase. However, the variance in expected costs is most sensitive to preclinical and phase II costs, followed by PoS by R&D phase.

Table 5.4: Correlations between variance in stochastic optimization outcomes and uncertain parameters in the model

	Cost		Phase IIa outcomes	
	Low	High	Low	High
Preclinical $	72%	82%	N/A	N/A
Phase I $	40%	32%	N/A	N/A
Phase II $	53%	46%	N/A	N/A
Preclinical PoS	10%	6%	21%	20%
Phase I PoS	11%	4%	32%	36%
Phase II PoS	N/A	N/A	86%	82%

This sensitivity analysis demonstrates that whereas zero phase II outcomes are unlikely, expected phase II outcomes above and beyond one phase IIb/III ready candidate are dependent on the PoS. Moreover, whereas the likelihood of portfolio costs below US$ 1 billion or above US$8 billion to achieve minimum preparedness R&D targets for the EIDs of interest is close to zero, the likely cost below or above this range will depend on the relationship of the PoS by R&D phase and the cost associated with experience and indirect costs of the vaccine developers. For instance, in a scenario where low costs were associated with high PoS distributions the same numbers of vaccine candidates would need to be funded as per the high PoS/high Cost scenario, but the overall portfolio cost would drop to US$ 1.6 billion (US$715 million – 2.9 billion range); whereas in a scenario where high costs were associated with low PoS distributions, the same numbers of vaccine candidates would need to be funded as per the low PoS/low Cost scenario, however the portfolio cost would increase to US$ 6.8 billion (US$1.5 – 15.1 billion range).

Table 5.5: Minimum R&D portfolios and costs for progressing at least one vaccine candidate through end of phase IIa, per EID, under extreme scenarios

	#preclinical candidates (High PoS/ Low Cost to Low PoS/ High Cost scenario)		#phase I candidates High PoS/ Low Cost to Low PoS/ High Cost scenario)	#phase II candidates (High PoS/ Low Cost to Low PoS/ High Cost scenario)	Expected US$ cost, preclinical through phase IIa (95% CI)		Expected number of phase IIb/III ready vaccine candidates (95% CI)	
Pathogen	**# currently available candidates**	**# new candidates needed**	**# currently available candidates**	**# currently available candidates**	**High PoS/ Low Cost scenario**	**Low PoS/ High Cost scenario**	**High PoS/ Low Cost scenario**	**Low PoS/ High Cost scenario**
Chikungunya	0 to 3	-	2 to 5	2	$64 m ($21–131 m)	$314 m ($99–684 m)	1 (1 to 3)	1 (1 to 2)
Zika	-	-	4 to 8	1	$88 m ($31–177 m)	$271 m ($75–662 m)	1 (1 to 3)	1 (1 to 3)
Rift Valley Fever	5 to 13	-	-	2	$103 m ($46–185 m)	$562 m ($122 m–1·3 bn)	1 (1 to 3)	1 (1 to 2)
MERS	3 to 12	-	4	-	$114 m ($50–208 m)	$592 m ($135 m–1·3 bn)	1 (1 to 3)	1 (1 to 3)
Marburg	7 to 16	-	2	-	$150 m ($66–274 m)	$693 m ($144 m–1·6 bn)	1 (1 to 3)	1 (1 to 3)
Lassa	11 to 21	-	-	-	$185 m ($80–341 m)	$835 m ($157 m–1·9 bn)	1 (1 to 3)	1 (1 to 3)
CCHF	6	3 to 12	1	-	$168 m ($74–309 m)	$744 m ($147 m–1·7 bn)	1 (1 to 3)	1 (1 to 3)
Nipah	11 to 13	0 to 8	-	-	$185 m ($80–341 m)	$835 m ($157 m–1·9 bn)	1 (1 to 3)	1 (1 to 3)
SARS	6	5 to 15	-	-	$185 m ($80–341 m)	$835 m ($157 m–1·9 bn)	1 (1 to 3)	1 (1 to 3)
SFTS	1	10 to 20	-	-	$185 m ($80–341 m)	$835 m ($157 m–1·9 bn)	1 (1 to 3)	1 (1 to 3)
Total	**50 to 91**	**18 to 55**	**13 to 20**	**5**	**$1·6 bn ($0·7–2·9 bn)**	**$6·8 bn ($1·5–15·1 bn)**	**10 (10 to 30)**	**10 (10 to 29)**

Section 5.3. Quantifying uncertainty in analytical measurements

As explained in appendix 4, statistical independence has been assumed between cost and PoS distributions by R&D phase. Moreover, it is assumed that self-reported cost estimates are statistically independent from numbers of vaccine candidates identified in the R&D pipeline. As per section 5.2, the variance in portfolio costs associated with phase IIa outcomes is positively correlated with cost and PoS distributions by R&D phase. Given that this variance is likely to be amplified from the variance observed in the reported cost and pipeline data, we quantified the uncertainty associated with the simulation-optimization analysis to determine to what extent the variation in the observed data was amplified in the analytical process. We did this by:

- Estimating the variance of the product of the following two variables: (1) number of vaccine candidates per R&D phase; (2) self-reported cost estimates per R&D phase, using the following formula:

$$Var(XY) = E(X^2)E(Y^2) - [E(X)]^2[E(Y)]^2$$

Where

X = number of candidates in the pipeline considered

Y = self-reported cost estimates

- Comparing the standard deviation of the above with the standard deviation associated with the PoS-adjusted cost estimates in the simulation-optimization.

As per table 3 in the main article, the standard deviation of the cost of a single vaccine candidate advancing through end of phase IIa in the simulation model assuming 100% PoS is lower than the standard deviation observed in the self-reported cost data. The standard deviation of the cost of one vaccine candidate successfully advancing through end of phase IIa in the simulation-optimization deviates increasingly from the standard deviation observed in the self-reported data as the number of vaccine candidates considered start from earlier phases of development and PoS distributions by R&D phase are taken into account (for comparison of standard deviations see Appendix table 5.6 below). In line with the sensitivity analysis above, this suggests that the amplification of uncertainty in the measurement of EID vaccine R&D costs is solely based on the objective function of the simulation-optimization model (minimum 1 phase IIa outcome) and the impact of PoS distributions by R&D phase on the numbers of vaccine candidates required per R&D phase to achieve this objective. There are no other sources of uncertainty amplification in the analysis in relation to the variation observed in the self-reported cost data.

Table 5.6: Comparison of standard deviations of cost estimates between simulation-optimization and self-reported data

	Simulation assuming 100% PoS vs self-reported data				**Simulation-optimization of PoS-adjusted cost vs self-reported data**		
High Cost/ High PoS scenario							
	Preclinical	**Phase I**	**Phase II**	**Total**	**Starting from phase 2**	**Starting from phase 1**	**Starting from preclinical**
SD self-reported	28,345,786	15,265,428	26,226,347	67,747,184	92,045,406	76,707,607	260,839,556
SD simulation-optimization	27,914,228	15,032,372	25,826,057	40,849,928	103,304,711	142,019,505	332,532,567
Low Cost/ Low PoS scenario							
SD self-reported	5,925,791	5,722,608	10,508,552	18,975,332	55,916,750	52,726,261	120,381,555
SD simulation-optimization	5,895,823	5,694,263	10,458,030	13,377,017	52,306,472	86,375,514	150,096,592

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PAPER III

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RESEARCH ARTICLE

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Prioritizing investments in new vaccines against epidemic infectious diseases: A multi-criteria decision analysis

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Abstract

Background: In 2016, the Coalition for Epidemic Preparedness Innovations (CEPI) launched a call for proposals (CfP) for vaccine development against Lassa, MERS, and Nipah. CEPI is faced with complex decisions that involve confronting trade-offs between multiple objectives, diverse stakeholder perspectives, and uncertainty in vaccine performance.

Objective: This study reports on a multi-criteria decision analysis (MCDA) and its testing on CEPI decisions.

Methods: Consultations with CEPI's Scientific Advisory Committee (SAC) and document reviews helped identify and structure the criteria against which to evaluate proposals. Forty four subject-matter experts assessed performance of 18 proposals on multiple criteria. SAC preferences were elicited via a survey employing an adapted swing-weighting technique and were incorporated into measures of value and cost-to-value. A Monte Carlo simulation estimated overall value and ranking probabilities by value and by cost-to-value for each proposal.

Results: Reviewer assessments and SAC preferences varied significantly. Despite this uncertainty, 14 preferred proposals emerged from the analysis and SAC recommendations on the basis of value and cost-to-value. In some cases, SAC recommendations deviated from the analysis because of: less emphasis on cost-to-value if budgets seemed underestimated by applicants, more emphasis on the likelihood of generating vaccines for target pathogens versus platform potential against unknown pathogens, and emphasis on funding a diversity of platforms per pathogen.

Conclusions: Despite vaccine performance uncertainty and stakeholder preference heterogeneity, MCDA distinguished between options in a way that broadly corresponded to decisions. Divergence between the MCDA and the SAC point to potential updates needed to the model such as platform diversity trade-offs.

KEYWORDS

CEPI, epidemic infectious diseases, health research priority setting, multi-criteria decision analysis, research and development, vaccines

1 | INTRODUCTION

Following the successful vaccine research and development (R&D) response to the 2014 West-African Ebola epidemic (Grobusch & Goorhuis, 2017), the World Health Organization (WHO) prioritized 11 epidemic infectious diseases (EIDs) most likely to cause severe outbreaks in the near future (WHO, 2016). Vaccines can prevent EID outbreaks from becoming humanitarian crises (CEPI, 2016a; Kieny et al., 2016). However, market incentives have failed to sustain R&D efforts in this area (Plotkin, 2016). A new entity, the Coalition of Epidemic Preparedness Innovations (CEPI), was set up in 2016 with a US$1 billion investment target to support the development of vaccines, contributing to the world's preparedness for EID outbreaks (CEPI, 2016a).

One of CEPI's first business plan targets was to advance the development of two to three vaccine candidates against priority EIDs from preclinical through to end of early clinical safety and immunogenicity testing (Phase IIa) by 2022 (CEPI, 2016a). By doing so, CEPI aimed to address the "just-in-case" R&D preparedness gap associated with lack of Phase IIb/III-ready EID vaccines in advance of epidemic outbreaks.

Just like any funder of pharmaceutical R&D, CEPI is faced with the challenge of prioritizing limited resources in order to meet inherently risky R&D targets (Aurentz, Kirschbaum, & Thunecke, 2011). Evidence suggests that the average probability of successfully advancing a vaccine candidate from preclinical through to end of Phase II is less than 10% (Pronker, Weenen, Commandeur, Claassen, & Osterhaus, 2013). In addition, the large costs (DiMasi, Grabowski, & Hansen, 2016; Gouglas et al., 2018) and long timelines (Russell & Gronwall, 2012) involved in developing vaccines make investment decisions in this space tremendously complex. This complexity is compounded by the fact that where commercial objectives are lacking, such as in the field of EID vaccines, commercial value alone is an insufficient criterion to making pharmaceutical R&D investment decisions (Antonijevic, 2015; Cioffe, 2011; Perez-Escobedo, Azzaro-Pantel, & Pibouleau, 2012; Phillips & Bana e Costa, 2007).

To address its business plan targets in line with mission and scope, CEPI launched a competitive call for proposals (CfP) in late January 2017 to support the development of vaccine R&D in three priority EIDs: Lassa Virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and Nipah virus. The rationale was to invest in vaccine R&D projects that would improve the likelihood of generating vaccines relevant for use in response to these EIDs; as well as improve the likelihood that the platform technologies supporting these vaccines would be suitable for use in vaccine development against newly or unexpectedly emerging EIDs.

Evaluating proposals received in response to the call faces several challenges. First, pharmaceutical R&D portfolio management involves considering multiple criteria, including organizational capabilities, technical and manufacturing feasibility, development timelines and costs, and alignment with target product profiles (TPPs; Aurentz et al., 2011; Bode-Greuel & Nickisch, 2008; Seget, 2005). For instance, the WHO has been advocating for use of ideal TPPs, or preferred product characteristics (PPCs) tailored to EID outbreak preparedness needs, to determine use potential of vaccines and to guide R&D priorities in the field (WHO, 2018).

Second, stakeholder opinions varied on the relative importance of different objectives. CEPI's Board has the ultimate decision-making authority on all CEPI R&D investments. An independent, multi-member Scientific Advisory Committee (SAC) advises the CEPI Board and Secretariat on R&D investments and makes technical recommendations for project funding. The composition of the SAC is diverse, and at the time of the deliberations described here included nine representatives of governments and regulators, seven industry members, eight academics, and four representatives of non-profit R&D organizations (CEPI, 2016b).

In this context of multiple trade-offs and heterogeneous stakeholder perspectives, multi-criteria decision analysis (MCDA) has the potential to improve the quality of decision making (Marsh et al., 2016; Viergever, Gouglas, & Tromp, 2017). MCDA has become increasingly popular in health valuation (Marsh et al., 2017; Thokala et al., 2016) and its applications are numerous across a variety of areas in health (Adunlin, Diaby, & Xiao, 2015) and associated decision problems (Drake, de Hart, Monleon, Toro, & Valentim, 2017; Marsh et al., 2017; Thokala et al., 2016). MCDA can offer a rational and transparent approach to priority setting, simultaneously considering all relevant criteria to avoid ad hoc decisions (Baltussen & Niessen, 2006). Where there are multiple stakeholders with diverse perspectives, MCDA can make relevant conflicts explicit, helping decision makers understand them and consider their impact on decisions (Phillips & Bana e Costa, 2007; Timmis, Black, & Rappuoli, 2017).

The use of MCDA has been increasingly advocated in vaccine R&D (Barrochi, Black, & Rappuoli, 2016; Timmis et al., 2017). However, to our knowledge, only one other MCDA framework has been applied to support the prioritization of vaccine R&D (see for instance Phelps et al., 2014; Kloeber, 2011; Madhavan et al., 2012; Madhavan et al., 2013; Madhavan et al., 2015). This framework places emphasis on different attributes of burden of disease, which are difficult to apply in the CEPI context, given the sporadic and unpredictable nature of EIDs. Moreover, it does not lend itself easily to the estimation of value of vaccine R&D, which is adjusted for the probability of success (PoS) of early stage, risky vaccine candidates; nor does it assume sources of preference and constraints that are relevant to the CEPI decision context.

An MCDA framework was developed in accordance with ISPOR Good Practice guidelines (Marsh et al., 2016) to inform the prioritization of EID vaccine R&D proposals and support CEPI CfP decisions and was tested against the SAC recommendations. This study reports on the application of the MCDA framework. Results are anonymized because of confidentiality restrictions associated with ongoing contract negotiations between CEPI and developers of selected proposals for funding.

2 | METHODS

The analysis focused on 18 full proposals that were selected by the CEPI SAC for an extended review following on an initial review of 33

preliminary proposals (CEPI, 2017a). The 18 proposals had a combined budget of over US$700 million and were reviewed by CEPI between March and May 2018. Seventeen proposals were at the preclinical development phase and one proposal was at clinical phase 1, with the aim that CEPI funding would advance them to the end of clinical phase 2. Proposals covered three different types of diseases: Lassa, MERS, and Nipah. Proposal budgets ranged from US$22 million to US$68 million, with a median cost of US$35 million. Proposal timeframes through to end of clinical phase 2 ranged from 4 to 6 years, with a median timeframe of 5 years. Due to confidentiality restrictions, individual proposal budgets and timeframes are not reported here; however, it is these budgets and timeframes that have been used to generate values in the framework presented below. Proposal names and disease classifications have been anonymized throughout the remainder of this manuscript. Proposals have been labelled as P1 to P18 and platform types are labelled 1–3. Seven proposals covered disease 1; seven proposals covered disease 2; and four proposals covered disease 3.

The goal was to undertake a quantitative valuation and ranking of the 18 proposals against criteria that were of interest to the SAC. It was assumed that not more than 14 proposals could be funded, given the resources available. The remainder of this section provides a step-by-step overview of the modelling approach adopted (more details provided in Data S1).

Step 1. Value framework

Between October 2016 and December 2016, a long list of potential value criteria was initially generated via document reviews, including: the CEPI Business Plan (CEPI, 2016a); documents from CEPI consultations informing the business plan (Røttingen et al., 2017); CEPI policy documents on principles of equitable access, cost coverage, risk sharing, and management of intellectual property (CEPI, 2017b); the WHO Blueprint process (WHO, 2016); evaluation criteria used by other agencies of health R&D funding in Europe and the United States—such as Biomedical Advanced Research and Development Authority (BARDA, 2018), Innovative Medicines Initiative (IMI, 2018), Horizon 2020 (EC, 2018), and national aid agencies supporting Product Development Partnerships active in global health R&D (DFID, 2015; Gouglas & Plahte, 2015; NEA, 2018). Additional contributions to this list came from semi-structured interviews with 19 members of the SAC, which were conducted in parallel with the document review process.

To narrow down the list of criteria, and combine the criteria into a value framework, members of the SAC and CEPI secretariat staff were asked first in an email survey and then in a group discussion in January 2017 to determine: whether all factors relevant to CfP decisions had been captured by the criteria; the relationship between the criteria, and whether any of the criteria should be removed or re-grouped if overlapping, or irrelevant. Following this engagement, overall value (*Vi*) was estimated as described in Equation (1).

$$V_i = \frac{1}{(1+r)^{t_i}}.(W_{O1}.PV_{O1}.O1_i + W_{O2}.PV_{O2}.O2_i) \quad (1)$$

Where:

V_i = overall value of proposal i.

$O1_i$ = likelihood of generating a suitable vaccine for one of the CfP target pathogens.

$O2_i$ = likelihood that the platform technology will be suitable for vaccine development against new pathogens.

W_{O1} = weight given to likelihood of generating a suitable vaccine for one of the CfP1 target pathogens.

W_{O2} = weight given to likelihood that the platform technology will be suitable for vaccine development against new pathogens.

PV_{O1} = partial value function for likelihood of generating a suitable vaccine for one of the CfP1 target pathogens.

PV_{O2} = partial value function for likelihood that the platform technology will be suitable for vaccine development against new pathogens.

t_i = timeframe over which the proposal i will deliver.

r = discount rate.

A number of other criteria were identified as defining a proposal's performance against *O*1 and *O*2. Equations 2 and 3 describe how performance against these criteria were combined multiplicatively to estimate *O*1 and *O*2 for each proposal (*i*). Criteria C1 to C5 are defined in Table 1. Each of these criteria is defined as a probability on a measurement scale 0–100%.

$$O1_i = C1_i.C2_i.C3_i.C4_i \quad (2)$$

$$O2_i = C1_i.C2_i.C3_i.C5_i \quad (3)$$

where:

$C1_i$ = experience and track-record: Likelihood that the applicant is sufficiently competent to deliver on the proposed activities of the project, for a given proposal *i*.

$C2_i$ = feasibility: Likelihood that the development of the candidate vaccine through phase II is technically feasible, for a given proposal *i*.

$C3_i$ = manufacturing scalability and speed: Likelihood that the vaccine candidate is manufacturable and scalable in timeframes and volumes to respond to outbreaks, for a given proposal *i*.

$C4_i$ = use potential for CfP target pathogens: Should a vaccine candidate be successfully developed and manufactured, the likelihood that it will meet CEPI's Target Product Profile and will be relevant for use in an emergency, for a given proposal *i*.

$C5_i$ = use potential for new pathogens: Should a vaccine candidate be successfully developed and manufactured, the likelihood that the platform technology supporting the candidate vaccine will be suitable for use in vaccine development against newly emerging pathogens for a given proposal *i*.

The value framework presented in Equations 1–3 was presented to and approved by the SAC in February 2017, together with proposed criteria descriptions, measurement scales, and appraisal questions for reviewers (see Table 1).

TABLE 1 Criteria CfP vaccine development Lassa-MERS-Nipah

Criterion	Metric	Assessment informed by:
C1. Applicant competencies, experience & track-record	Overall likelihood that the applicant is sufficiently competent to deliver on the proposed activities of the project (0–100%)	• Technical competency/expertise of project staff • Experience in preclinical testing of vaccines • Experience in conduct of Phase I/II clinical vaccine trials • Experience in regulatory interactions with competent authorities and licensing of vaccines • Manufacturing capabilities and skills
C2. Technical feasibility	Overall likelihood that the development of the candidate vaccine through phase II is technically feasible (0–100%)	• Soundness of the theoretical concept/scientific rationale • Quality of the integrated product development plan • Current development status/technical readiness • Soundness of the clinical development and regulatory approach
C3. Manufacturing scalability & speed	Overall likelihood that the vaccine candidate is manufacturable and scalable in timeframes and volumes to respond to outbreaks (0–100%)	• Soundness/scientific rationale of manufacturing processes/technologies supporting the candidate vaccine • Current status/availability of manufacturing • Manufacturing capacity and yield • Time to produce/release sufficient quantities of vaccine for emergency use in response to a disease outbreak • Suitability of manufacturing processes/technologies for large scale production and delivery in an emergency
C4. Use potential for target pathogens	Overall likelihood that the candidate vaccine will meet CEPI's ideal Target Product Profile and, if not, that any deviations from this will be still relevant for use of the vaccine in emergency (0–100%)	• Suitability of the candidate vaccine for outbreak control • Suitability of the candidate vaccine for routine use
C5. Use potential for new pathogens	Overall likelihood that the platform technology supporting the candidate vaccine(s) will be suitable for use in vaccine development against newly emerging/unexpected pathogens (0–100%)	• Suitability of the technology platform for other pathogens of the WHO priority list of emerging infectious diseases • Suitability of the technology platform for other pathogens beyond the WHO priority list of emerging infectious diseases
O1. Likelihood of generating a suitable vaccine for one of the CfP target pathogens	Overall likelihood that the project will generate a vaccine that is relevant for use in response to one of the CfP target pathogens (0–100%)	• Probability of successful vaccine development from preclinical through phase II (criteria C1 to C3) times the probability of use for CfP target pathogens (C4)
O2. Likelihood that the platform technology will be suitable for vaccine development against new pathogens	Overall likelihood that the platform technology supporting the vaccine will be suitable for use in response to newly emerging and/or unexpected pathogens (0–100%)	• Probability of successful vaccine development from preclinical through phase II (criteria C1 to C3) times the probability of use for new pathogens (C5)

Criteria C1, C2, and C3 presented above relate to the probability that the vaccine candidate and the technology platform supporting its development can be successfully advanced through to end of clinical phase 2. Criteria C4 and C5 relate to the anticipated benefits from these proposals, if successfully developed through to end of clinical phase 2. Specifically, criterion C4 relates to the anticipated clinical and operational benefits of the vaccine candidate in response to an outbreak of the targeted disease, if the candidate vaccine was to be successfully developed through to end of clinical phase 2. Criterion C5 relates to the anticipated potential of the technology platform used to develop the candidate vaccine to support the development of other candidate vaccines against newly or unexpectedly emerging pathogen outbreaks, regardless of whether the development of the vaccine candidate against the currently targeted pathogen was successful or not.

Assuming a technology platform is successfully developed, the value of its potential to be used to develop a vaccine against a targeted pathogen (C4) is not dependent on its potential to be used to develop a vaccine against an unknown pathogen (C5) and vice versa—they are additively valuable. However, for either of these potentials to be realized, the platform needs to be successfully developed, which is reflected in criteria C1–C3. Moreover, there is no value in a platform being technically feasible (C2), if the vaccine developer does not have the competency to develop it (C1), vaccines cannot be manufactured to scale on this platform (C3) or the platform

does not have the potential to support vaccine development against a pathogen (C5)—so these criteria were combined multiplicatively.

Step 2. Measuring performance ($C1_i$,$C2_i$,$C3_i$,$C4_i$,$C5_i$)

Proposals were assessed against criteria C1 to C5 by 44 external reviewers with subject matter expertise on EID vaccine development and no conflicts of interest. Reviewers were selected through an open competitive process on the basis of demonstrable experience—including years of work experience—in non-clinical, clinical, chemistry, manufacturing, and control aspect of vaccine development. Each proposal was assessed by three to five reviewers. Reviewers received a manual and presentation providing detailed descriptions of criteria, scorecard templates, instructions, and examples for filling in these templates. Further assistance and clarifications were provided in response to specific questions over email and phone throughout the review process.

For each criterion C1–C5, reviewers were asked to define the most likely worst-case and best-case performance of proposals on a scale of 0–100% (see Data S1 for details). In order to determine the degree of homogeneity in the assessments provided by the different reviewers, an inter-reviewer assessment variability test was conducted. Specifically, for each criterion C1–C5, and for each performance estimate (worst-case, most likely, best-case), the following steps were undertaken. First, the performance mean across all reviewers assessing a given proposal was calculated. Second, the difference between this mean and each reviewer's performance estimate on the given proposal was calculated. Third, steps 1 and 2 were repeated for all proposals. Fourth, for each reviewer, the average deviation of his or her performance estimate from the performance mean across all of his or her assessed proposals was estimated. Fifth, on the basis of Cicchetti's (1994) classification, reviewer variability was determined as good if this average deviated less than 20% from the performance mean, and excellent if it deviated less than 10% from the performance mean across all of his or her assessed proposals. Seven of the 44 reviewers were found to have at least one average worst-case, most likely, or best-case performance estimate against C1–C5 that deviated more than 20% from the equivalent performance mean across all their assessed proposals. In total, the estimates for which such deviations were observed accounted for only 3% of the total number of worst-case, most likely, and best-case performance estimates collected. The impact of removing these results from the analysis was tested and found to not substantially change the performance of proposals.

Step 3. Estimating partial values (PV_{O1}, PV_{O2})

Partial value functions were elicited for *O*1 and *O*2 from each SAC member using an online survey (24 respondents out of 29 survey recipients). The functions were defined using a mid-value splitting method—a widely-used decomposed scaling technique also known as the bi-section method (Von Winterfeldt & Edwards, 1986)—by eliciting the value mid-point on a 10%–60% performance range (point a in Figure 1).

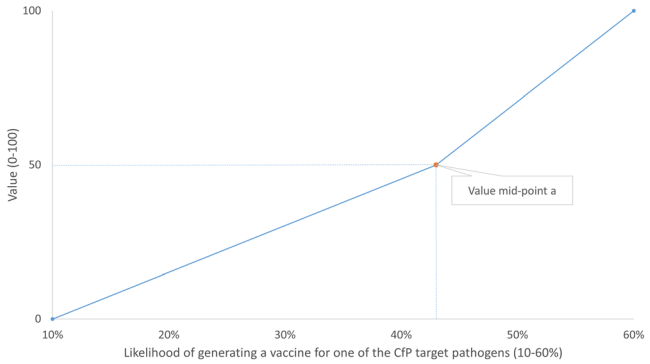

FIGURE 1 Partial value function of likelihood of generating a vaccine for one of the CfP target pathogens: an illustration

In the questioning procedure applied for the elicitation of partial values on each of *O*1 and *O*2, SAC members answered up to six pairwise choice questions that iteratively approached this value mid-point. For instance, for *O*1 the first question was:

"Consider the following two proposals, each with different starting likelihoods of generating a vaccine that will be relevant for use in response to one of the CfP target pathogens. Imagine you are given the opportunity to improve the performance of one of these proposals. Which of the following options would you prefer?

- Option A: Improve Proposal A so that the likelihood that it generates a vaccine that will be relevant for use in response to one of the CfP target pathogens increases from 10% to x%
- Option B: Improve Proposal B so that the likelihood that it generates a vaccine that will be relevant for use in response to one of the CfP target pathogens increases from x% to 60%
- Indifferent between options A and B"

In the first question, *x* was set as the mid-point in the performance range (35%). If a respondent was indifferent, the partial value function was considered linear, and no further questions were asked. If a respondent chose option A or option B, the value of *x* was updated according the logic defined in Section 2 of the Data S1.

The pairwise choice questions identified *a* to be within a range. It was assumed that *a* was the mid-point in this range, on the basis of which partial value functions could then be defined (see Section 2 of Data S1).

Step 4. Estimating weights (W_{O1}, W_{O2})

Weights were elicited for *O*1 and *O*2 using the trade-off method (von Winterfeldt and Edwards, 1986), in each case for a range of performance of 10%–60%, from each SAC member using an online survey (24 respondents out of 29 survey recipients). An iterative pairwise comparison was used to identify the value of *b*, such that respondents would be indifferent between improving *O*1 from 10% to *y*% and improving *O*2 from 10% to 60%. Specifically, the following question was asked via an online survey:

"Considering the following two proposals, which of these would you prefer?

- Proposal A
  - Likelihood of generating a vaccine that will be relevant for use in response to one of the CfP1 target pathogens = y%
  - Likelihood that the technology will be suitable for use in vaccine development against newly emerging/unexpected pathogens = 10%
- Proposal B
  - Likelihood of generating a vaccine that will be relevant for use in response to one of the CfP1 target pathogens = 10%
  - Likelihood that the technology will be suitable for use in vaccine development against newly emerging/unexpected pathogens = 60%"

The initial value of *y* was set at 35%, and varied depending on responses as defined in Section 2 of the Data S1. After six questions, the value of *b* was defined within a range defined in Section 2 of Data S1. It was assumed that the value of *b* was the mid-point in this range. Section 2 of the Data S1 provides more details on how b was used to estimate weights for *O*1 and *O*2.

Step 5. Eliciting time preference (r)

Time preference was estimated using a choice exercise designed to identify the value of *c*, such that SAC members were indifferent between a *z*% chance of successfully delivering a proposal within 5 years, and a 100% chance of doing so within 10 years. The following question format was implemented with SAC members in an online survey:

"Considering the following two proposals, which of these would you prefer?

- Proposal A
  - Time-to-completion = 5 years
  - Likelihood of successful completion = z%
- Proposal B
  - Time-to-completion = 10 years
  - Likelihood of successful completion = 100%"

The value of *z* in the first question was set at 55%, and then varied depending on responses in a manner described in Section 2 of Data S1. After up to six questions, the value of *c* was identified within a range described in Section 2 of Data S1. It was assumed that *c* took the value of the mid-point in this range. Section 2 of the Data S1 provides more details on how c was used to estimated to estimate the discount rate.

Step 6 Dealing with uncertainty

Both reviewer performance inputs and SAC preferences were subject to significant variations. This uncertainty was incorporated into the MCDA via Monte Carlo simulation. The model was run 10,000 times, each time drawing from the different inputs, as follows:

- Performance inputs: For criteria C1 to C5, each iteration randomly selected one reviewer and randomly selected a performance estimate from their performance distribution.
- SAC preferences: Each iteration randomly drew the partial value, weights, and time preference of a single SAC member's distributions.

The mean and 95% confidence intervals of performance on *C1–C5*, *O1*, *O2*, and *V* were estimated for each iteration of the simulation. Comparison of proposals within each iteration allowed a ranking of proposals, which, when analysed across all iterations, allowed the estimation of the rank probability of a proposal.

Step 7: Reporting the MCDA

Various iterations of the model were presented to the SAC over email and teleconferences for validation of its practical utility between December 2016 and July 2017. A detailed methodology document was shared in July 2017 and the model findings were presented during the SAC decision meeting in August 2017.

3 | RESULTS

Criteria performances of the 18 vaccine R&D proposals are presented in Table 2. The uncertainty in performance means that there is substantial overlap in the confidence intervals around most proposals' performance on: the likelihood of generating a suitable vaccine for one of the CfP target pathogens (*O1)* and on the likelihood that the platform technology will be suitable for vaccine development against new pathogens (*O2)*.

Table 3 presents the results of the preference elicitation survey. Greater weight was attached to performance on *O1* than *O2* by 92% of participants. The remaining participants gave equal weight to performance on *O1* and *O2*. Participants' discount rate was high, with 63% having a rate above 20%. Most participants' responses to the preference survey implied that the partial value function of both *O1* and *O2* was non-linear with increasing marginal returns (54% for *O1* and 78% for *O2*). Though a small proportion of participants' responses implied a linear function, 29% and 13% for *O1* and *O2*, respectively, or decreasing marginal returns, 17% and 8% for *O1* and *O2*, respectively.

Figure 2 presents the overall, discounted value and cost-to-value of the 18 proposals. Ranking of proposals was similar by overall value and cost-to-value, with the exception of a handful of proposals which had high budgets. Uncertainty in performance scores and preferences mean that there is substantial overlap in the confidence intervals around proposals' overall value. Over 90% of the variance observed in Figure 2 is explained by the variation in reviewer assessments of proposal performance.

TABLE 2 Proposal performances on criteria C1 to C5 (Mean, 95% CI)*^

		C1	C2	C3	C4	C5	O1	O2
Disease 1	**Proposal 13**	94% (90–100%)	87% (75–100%)	93% (75–100%)	81% (60–100%)	89% (80–100%)	62% (40–86%)	68% (51–90%)
	Proposal 1	92% (80–100%)	68% (25–95%)	88% (65–100%)	82% (50–100%)	81% (30–100%)	45% (14–81%)	45% (11–81%)
	Proposal 17	91% (85–100%)	73% (60–85%)	81% (60–100%)	81% (65–90%)	69% q(35–100%)	44% (24–65%)	37% (15–72%)
	Proposal 10	91% (80–100%)	76% (55–100%)	78%(45–100%)	82% (45–100%)	81% (35–100%)	39% (14–77%)	44% (16–81%)
	Proposal 16	77% (40–100%)	68% (30–100%)	78% (40–100%)	60% (15–100%)	86% (60–100%)	25% (3–77%)	35% (8–81%)
	Proposal 8	83% (55–100%)	58% (40–85%)	71% (50–95%)	68% (40–90%)	77% (45–100%)	23% (8–48%)	26% (9–54%)
	Proposal 5	78% (50–95%)	38% (20–55%)	65% (20–95%)	58% (15–90%)	78% (60–95%)	11% (2–29%)	15% (4–32%)
Disease 2	**Proposal 14**	93% (85–100%)	87% (70–100%)	93% (75–100%)	83% (60–100%)	89% (80–100%)	62% (39–86%)	66% (48–86%)
	Proposal 3	86% (70–95%)	73% (65–90%)	84% (60–100%)	66% (50–95%)	78% (65–95%)	35% (20–58%)	41% (25–61%)
	Proposal 6	83% (55–100%)	79% (50–100%)	71% (50–95%)	75% (65–90%)	77% (45–100%)	35% (15–61%)	35% (14–69%)
	Proposal 12	89% (65–100%)	81% (65–100%)	60% (40–90%)	71% (60–80%)	76% (60–95%)	31% (15–55%)	33% (16–61%)
	Proposal 2	83% (75–90%)	70% (50–85%)	67% (30–95%)	63% (35–95%)	73% (45–90%)	25% (7–51%)	28% (9–51%)
	Proposal 15	82% (65–90%)	61% (30–80%)	70% (45–95%)	62% (35–75%)	70% (40–90%)	22% (7–40%)	24% (9–46%)
	Proposal 11	69% (35–95%)	55% (20–75%)	77% (45–100%)	62% (40–100%)	69% (40–100%)	18% (4–47%)	20% (5–50%)
	Proposal 9	89% (70–100%)	81% (65–100%)	82% (55–100%)	83% (65–100%)	67% (50–90%)	49% (27–77%)	40% (21–68%)
	Proposal 18	91% (85–100%)	73% (40–100%)	76% (40–100%)	72% (40–95%)	62% (30–100%)	37% (9–81%)	32% (5–86%)
	Proposal 7	83% (55–100%)	72% (60–90%)	72% (55–95%)	76% (65–90%)	77% (45–100%)	32% (17–51%)	33% (15–58%)
	Proposal 4	78% (50–95%)	38% (20–55%)	66% (20–100%)	46% (25–65%)	78% (60–95%)	9% (2–22%)	15% (4–34%)

*Proposals listed in order by disease, by O1 mean performance.

^C1: Experience & track-record; C2: Feasibility; C3: Manufacturing scalability & speed; C4: Use potential for CfP target pathogens; C5: Use potential for new pathogens; O1: Likelihood of generating a suitable vaccine for one of the CfP target pathogens; O2: Likelihood that the platform technology will be suitable for vaccine development against new pathogens

TABLE 3 Preference elicitation findings*

	O1 weight	O2 weight	O1 value mid-point	O2 value mid-point	Time discount rate
Mean	0.72	0.28	0.40	0.43	0.22
Standard Deviation	0.13	0.13	0.12	0.09	0.11
Lowest estimate	0.50	0.10	0.17	0.22	0.04
Highest estimate	0.90	0.50	0.60	0.60	0.46

*O1: Likelihood of generating a suitable vaccine for one of the CfP target pathogens; O2: Likelihood that the platform technology will be suitable for vaccine development against new pathogens.

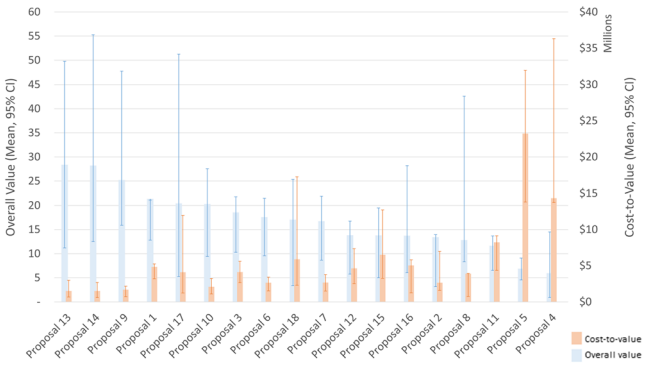

FIGURE 2 Proposal overall value and cost-to-value

Assuming that not more than 14 projects can be selected, Figure 3 plots the likelihoods of proposals ranking in the top 1–14, on the basis of discounted value versus cost-to-value. The consideration of budgets did not affect most of these ranking outputs in the analysis,

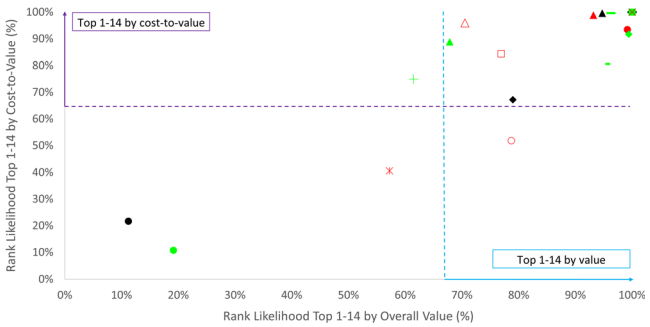

FIGURE 3 Top 1–14 ranking likelihood of proposals by overall value and by cost-to-value

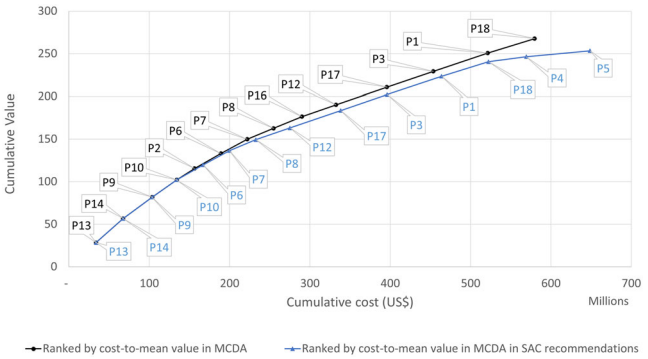

FIGURE 4 Efficiency frontier by different ranking methods

with the exception of two proposals that substituted each other in the top 1–14 depending on whether they were ranked by value or by cost-to-value (top 1–14 by value to the right of the blue dotted line; top 1–14 by cost-to-value to the top of the purple dotted line, in Figure 3).

Figure 3 demonstrates that despite the large uncertainty in criteria performance and stakeholder preferences, clear proposal rankings emerged through the consideration of top 14 ranking likelihoods. SAC recommendations marginally deviated from these rankings. In a face-to-face meeting in August 2017, the SAC was presented with the reviewer assessments of each proposal and the results of the MCDA. Following a deliberation, they recommended 14 proposals for funding (proposals 1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 17, and 18). Most of the recommended proposals had the highest probability of being ranked in the top 14 proposals by the MCDA on both value and cost-to-value. In some cases where SAC recommendations deviated from the analytical findings, the SAC's deliberation highlighted possible reasons for this divergence: A lower emphasis on cost-to-value as it was believed that some of the requested budgets were unrealistic and they could substantially increase during implementation; a lower emphasis placed on feasibility (*C2*) and manufacturing scalability and speed (*C3*) and a higher emphasis placed on use potential for new pathogens (*C5*). Additional considerations that contributed to the final selection recommendation included: a higher emphasis on target pathogens (*O1*) versus unknown pathogens (*O2*); and diversity consideration, in particular funding a diversity of platforms by CfP target pathogen.

Figure 4 plots the top 14 ranked proposals by cumulative value and cumulative cost. These are ranked in two different ways, by: (a) cost-to-mean value and (b) proposals recommended for funding by the SAC by cost-to-mean value.

4 | DISCUSSION AND CONCLUSIONS

This paper involved a number of innovations in the evaluation of early stage vaccine R&D candidates for EIDs, addressing gaps identified in previous literature. These included the explicit consideration of technical and operational feasibility of proposals using expert reviewer assessments of vaccine performance, in the absence of historical PoS data for these proposals; the multiplicative and additive combination of performance against a comprehensive list of criteria into an assessment of overall value of proposals, compliant with the theoretical properties required of a set of criteria in MCDA (Marsh et al., 2016) and applied as these properties have emerged in this particular decision context (Zeleny, 2011); the use of an adaptive swing weighting technique to elicit and incorporate stakeholder preferences into an assessment of overall value of proposals; and the use of Monte Carlo simulation to account for uncertainty in performance estimates and stakeholder preferences in proposal rankings.

CEPI's investment in EID vaccine R&D faced significant uncertainty in both the potential performance of proposed vaccine candidates—which were all in preclinical or early clinical phases of development—and stakeholder objectives. This is evident in both the MCDA model inputs and outputs, with substantial overlap in the confidence intervals on the overall value of proposals. Nevertheless, the use of a Monte Carlo Simulation reflected this uncertainty in rank probabilities that distinguished proposals, and that were broadly consistent with the SAC's recommendations.

During the SAC decision meeting in August 2017, MCDA findings informed deliberations on individual proposal performances and comparisons between proposals across diseases and platform technologies. The SAC's recommendations did not, however, correspond entirely with the MCDA. It was never the intention of the MCDA to remove the deliberative component of the decision-making process. However, the divergence in SAC recommendations and model outputs point to some lessons from the research and was also a way to validate the practical usefulness of the model.

First, the SAC's deliberation pointed to criteria that could have been added to the MCDA, such as distributional considerations—spreading investment across proposals that employ different platforms. The implication of this was the selection of proposals that had modest value in terms of their combined performance across criteria *C1–C5* but which added desired platform diversity into CEPI's investment portfolio.

Second, the SAC placed less emphasis on cost-to-value, as in some cases proposed budgets were considered unrealistic. One implication of this was that some proposals that had small budgets but whose overall value was otherwise low were not prioritized.

Third, the SAC's deliberation pointed towards structural implications for the MCDA. A novel combined multiplicative-additive model structure was adopted. Few MCDA applications in healthcare have multiplicative components (Marsh et al., 2016) despite concerns that health technology assessment does not meet the analytical requirements of additive models (Marsh, Sculpher, Caro, & Tervonen, 2018). The multiplicative component of the model implicitly gave equal weight to criteria *C1*–*C5*, whereas the SAC deliberation seemed to emphasize some of these criteria more than others (e.g., *C2* and *C4*).

Fourth, the SAC's recommendations could imply alternative weights to those used in the model; specifically that an even greater weight was given to *O1* than what was elicited through the survey. Weights in the model were elicited using an iterative comparison of improvements in pairs of criteria. This method was chosen due to the small sample size providing insufficient power for a discrete choice experiment; and a desire to elicit ordinal data in a survey format (Tervonen et al., 2017). The result was that, on average, more weight was given to *O1*. Though there was also significant variation in SAC member weights. Given this variation, one possibility that would reconcile the SAC recommendations with the result of the MCDA is that SAC members who gave a higher weight to *O1* were more influential in the deliberation.

In conclusion, the analysis reported in this study demonstrates that it is possible to use a MCDA to support the prioritization of vaccine R&D investments in a complex decision context characterized by outcomes uncertainty, variance in expected performance of vaccines, and heterogeneity of stakeholder preferences. With the intention to aid, rather than replace deliberative stakeholder processes or prescribe decisions, the findings illustrate how MCDA can help differentiate investments, and support decision making.

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CONFLICT OF INTEREST

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix

Article title: Prioritizing investments in new vaccines against epidemic infectious diseases: a multi-criteria decision analysis

Journal name: Journal of Multi-Criteria Decision Analysis

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This document provides supplementary detail on: (1) the methodology used to define performance distributions for assessing proposals (Section 1); and (2) the performance levels used in the elicitation questions (Section 2).

Section 1. Defining performance distributions for assessing proposals

Reviewers' performance estimates were collected online using the CfP review platform at the Research Council of Norway. This posed the practical limitation that reviewer online submissions were required to use a 1-7 points scale whereas reviewers were required to define the most likely, worst-case and best-case performance of proposals on a scale of 0-100%. The approach described below was therefore used to address the practical limitations of the Research Council of Norway's submission system, in a way that would not impact the analytical objectives of this exercise.

Reviewers were asked to define the range of likely performance (%) of proposals on each criterion. Then assuming the worst-case was a score of 1 and the best-case was a score of 7, to give the most likely performance on the 1-7 scale.

A performance distribution was defined for each reviewer by following a number of steps:

- **Step 1.** Take the performance range and the most likely score (e.g. 60-100% with score 5)
- **Step 2.** Allocate this performance across a distribution of equal 5% blocks (see columns 'Block distribution' and 'Performance Range' in Table 1.1)
- **Step 3.** Assume a 100% probability that the performance falls within the performance range (see column 'Total Probability' in Table 1.1).

Step 4. Identify the 'most likely' performance block (the mode) as described in the following equation:

$$B_{mode} = B_L + \frac{(B_H - B_L)}{S_{max}} * S_{mode}$$

Where:

B_{mode} = Most likely performance [rounded to the nearest 5% block]

B_L = Lowest performance block

B_H = Highest performance block

S_{max} = Maximum score that can possibly be allocated, which is 7 according to criteria definitions

S_{mode} = Most likely score

E.g. for a performance 60-100% (score 5):

B_{mode} = 60% + $\frac{100\% - 60\%}{7} * 5$ = 88.6% [rounded up to 90%, the nearest 5% block]

Step 5. Allocate a probability of being within the mode block as described in the following equation:

$$p_{mode} = \begin{cases} 100\%, & if\ N = 1 \\ 50\%, & if\ N > 1 \end{cases}$$

Where:

$N =$ Total number of performance blocks $= 1 + \frac{(B_H - B_L)}{5\%}$ p_{mode} = probability of performance being within the mode block

E.g. for a performance of 60-100%:

$N = 1 + \frac{(100\% - 60\%)}{5\%}$ = 9

Therefore p_{mode} = 50%, given that N = 9 is greater than 1

Step 6. Allocate the remaining probability to the remaining blocks as described in the following equation:

$$p(B)n_i = \left[\frac{100\% - \sum\left(Xp(B)n_{i-1} + Xp(B)n_{i-2} + \cdots + Xp(B)n_{i-j} + p_{mode}\right)}{N - (Xn_i - Z)}\right] * 2$$

Where:

N = Total number of performance blocks

n_i = nth block deviation from B_{mode}

$$X = \begin{cases} 2, & if\ on\ the\ nth\ block\ deviation\ from\ B_{mode}\ there\ is\ a\ mirroring\ block\ on\ both\ sides\ of\ the\ distribution \\ 1, & if\ otherwise \end{cases}$$

$$Z = \begin{cases} 1, & if\ on\ the\ nth\ block\ deviation\ from\ B_{mode}\ there\ is\ a\ mirroring\ block\ on\ both\ sides\ of\ the\ distribution \\ 0, & if\ otherwise \end{cases}$$

$(B)n_i$ = Block in nth block deviation from B_{mode}

B_{mode} = mode block

p_{mode} = probability of performance being within the mode block

$p(B)n_i$ = probability of performance being within block(s) of nth block deviation from B_{mode}

E.g. for a performance of 60-100%, with B_{mode} = 90%, p_{mode} = 50%, N = 9 the remaining 50% probability is allocated as shown in table 1.1:

Table 1.1: Example performance distribution (performance range 60-100%, most likely performance score 5)

Block distribution	Performance Range	Total Probability	Assigned Probability by performance block
0%		*0% (for performance range 0-<60%)*	0%
5%			0%
10%			0%
15%			0%
20%			0%
25%			0%
30%			0%
35%			0%
40%			0%
45%			0%
50%			0%
55%			0%
60%	*60%*	*100% (for performance range 60-100%)*	$p(B)n_6 = \frac{100\%-(50\%+2*13\%+2*8\%+3\%+2\%+2\%)}{9-6} * 2 = 1.1\%$
65%	*65%*		$p(B)n_5 = \frac{100\%-(50\%+2*13\%+2*8\%+3\%+2\%)}{9-5} * 2 = 1.7\%$
70%	*70%*		$p(B)n_4 = \frac{100\%-(50\%+2*13\%+2*8\%+3\%)}{9-4} * 2 = 2.2\%$
75%	*75%*		$p(B)n_3 = \frac{100\%-(50\%+2*13\%+2*8\%)}{9-3} * 2 = 2.8\%$
80%	*80%*		$p(B)n_2 = \frac{100\%-(50\%+2*13\%)}{9-(2*2-1)} * 2 = 8.3\%$
85%	*85%*		$p(B)n_1 = \frac{100\%-50\%}{9-(2*1-1)} * 2 = 12.5\%$
90%	*90%*		$p_{mode} = 50\%$
95%	*95%*		$p(B)n_1 = \frac{100\%-50\%}{9-(2*1-1)} * 2 = 12.5\%$
100%	*100%*		$p(B)n_2 = \frac{100\%-(50\%+2*13\%)}{9-(2*2-1)} * 2 = 8.3\%$

To generate a criterion performance that combined individual reviewer assessments, a performance distribution was constructed by:

(1) assuming equal weighting of reviewer assessments
(2) assuming a 100% probability that the combined performance falls within the reported range of likely performance across all reviewers assessing the proposal on the given criterion
(3) randomly selecting one reviewer, and randomly selecting a performance estimate from their performance distribution, within a Monte Carlo framework

Section 2. Decision trees to inform preference elicitation

This section presents the decision trees that were developed using a swing weighting algorithm to inform the elicitation of preferences related to: (1) partial values of *O1* and *O2*; (2) weights of relative importance between *O1* and *O2*; (3) time preference.

Partial values of O1 and O2

For each of *O1* and *O2*, SAC members answered up to six pairwise choice questions that iteratively approached this value mid-point. For instance, for *O1* the first question was:

"Consider the following two proposals, each with different starting likelihoods of generating a vaccine that will be relevant for use in response to one of the CfP target pathogens. Imagine you are given the opportunity to improve the performance of one of these proposals. Which of the following options would you prefer?

- *Option A: Improve Proposal A so that the likelihood that it generates a vaccine that will be relevant for use in response to one of the CfP target pathogens increases from 10% to x%*
- *Option B: Improve Proposal B so that the likelihood that it generates a vaccine that will be relevant for use in response to one of the CfP target pathogens increases from x% to 60%*
- *Indifferent between options A and B"*

In the first question, *x* was set as the mid-point in the performance range (35%). If a respondent was indifferent, the partial value function was considered linear, and no further questions were asked. If a respondent chose option A or option B, the value of *x* was updated according the logic defined in Figure 2.1, which presents the value of x for each survey iteration and the associated performance range used to calculate a depending on choice between options A, B, or indifference.

The pairwise choice questions identified *a* to be within a range. It was assumed that *a* was the mid-point in this range.

The partial value function for $O1$ and $O2$ was then defined by equations 4 and 5:

$$PV_{O1j} = \begin{cases} \left[0.5 \,.\left(\frac{O1_i}{a_{O1j}}\right)\right].100, \; if \;\; O1_i < a_{O1j} \\ \left[0.5 + 0.5 \,.\left(\frac{O1_i - a_{O1j}}{1 - a_{O1j}}\right)\right].100, \; if \;\; O1_i \geq a_{O1j} \end{cases} \quad (4)$$

$$PV_{O2j} = \begin{cases} \left[0.5 \,.\left(\frac{O2_i}{a_{O2j}}\right)\right].100, \; if \;\; O2_i < a_{O2j} \\ \left[0.5 + 0.5 \,.\left(\frac{O2_i - a_{O2j}}{1 - a_{O2j}}\right)\right].100, \; if \;\; O2_i \geq a_{O2j} \end{cases} \quad (5)$$

Where:

a_{O1j} *= The value mid-point for* $O1$ *for survey respondent j*

a_{O2j} *= The value mid-point for* $O2$ *for survey respondent j*

Weights of relative importance between O1 and O2

In order to elicit weights between *O1* and *O2*, the following question was asked:

"Considering the following two proposals, which of these would you prefer?

- *Proposal A:*
  - *Likelihood of generating a vaccine that will be relevant for use in response to one of the CfP1 target pathogens = y%*
  - *Likelihood that the technology will be suitable for use in vaccine development against newly emerging/unexpected pathogens = 10%*
- *Proposal B:*
  - *Likelihood of generating a vaccine that will be relevant for use in response to one of the CfP1 target pathogens = 10%*

Likelihood that the technology will be suitable for use in vaccine development against newly emerging/unexpected pathogens = 60%"

Figure 2.2 presents the value of y for each survey iteration and the performance range used at the end of six questions to calculate b depending on choice between options A or B.

Weights were then estimated for $O1$ and $O2$ for each SAC member (*j*) as described in equations 6 to 8:

$$W_{O1j} = \frac{k_j}{1+k_j} \quad (6)$$

$$W_{O2j} = \frac{1}{1+k_j} \quad (7)$$

Where

$$k_j = \frac{60-10}{b-10} \quad (8)$$

Time preference

In order to identify the value of c, such that SAC members were indifferent between a z% chance of successfully delivering a proposal within 5 years, and a 100% chance of doing so within 10 years, the following question was asked in several iterations:

"Considering the following two proposals, which of these would you prefer?

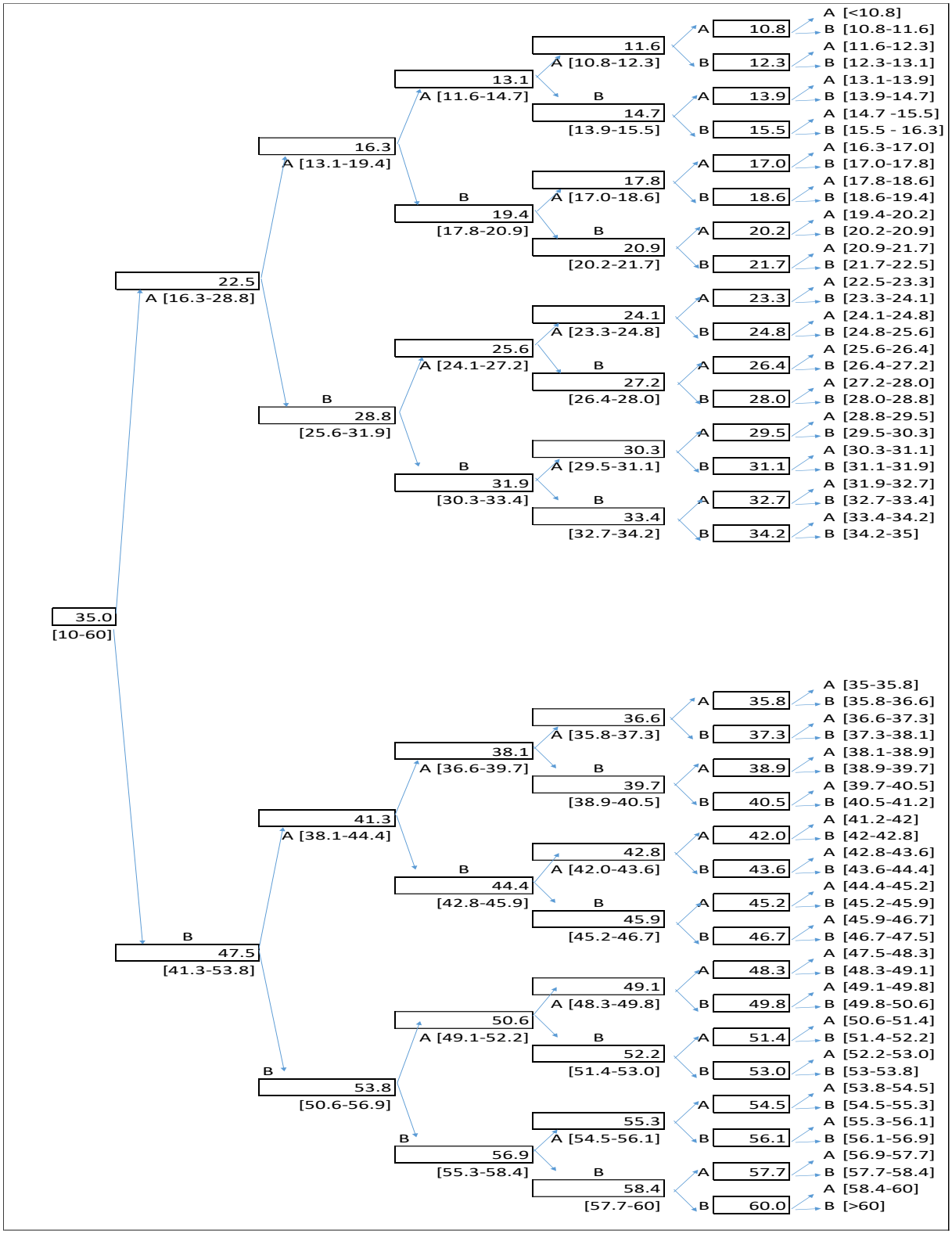
- *Proposal A:*
  - *Time-to-completion = 5 years*
  - *Likelihood of successful completion = z%*
- *Proposal B:*
  - *Time-to-completion = 10 years*
  - *Likelihood of successful completion = 100%*
- *Indifferent between Proposal A and Proposal B"*

Figure 2.3 presents the value of z for each survey iteration and the associated performance range used to calculate z depending on choice between options A, B, or indifference.

Given a value of c for survey respondent *j*, their discount rate was estimated using equation 9:

$$r_j = \left(\frac{1}{c_j}\right)^{\frac{1}{5}} - 1 \quad (9)$$

Figure 2.1: Levels used in choice questions to inform partial values of *O1, O2**



**If between iteration 1 and 6 a respondent chose indifference between options A and B, the performance range used to calculate a.is provided in [ ],*

Figure 2.2: Levels used in choice questions to inform *O1* and *O2* weights

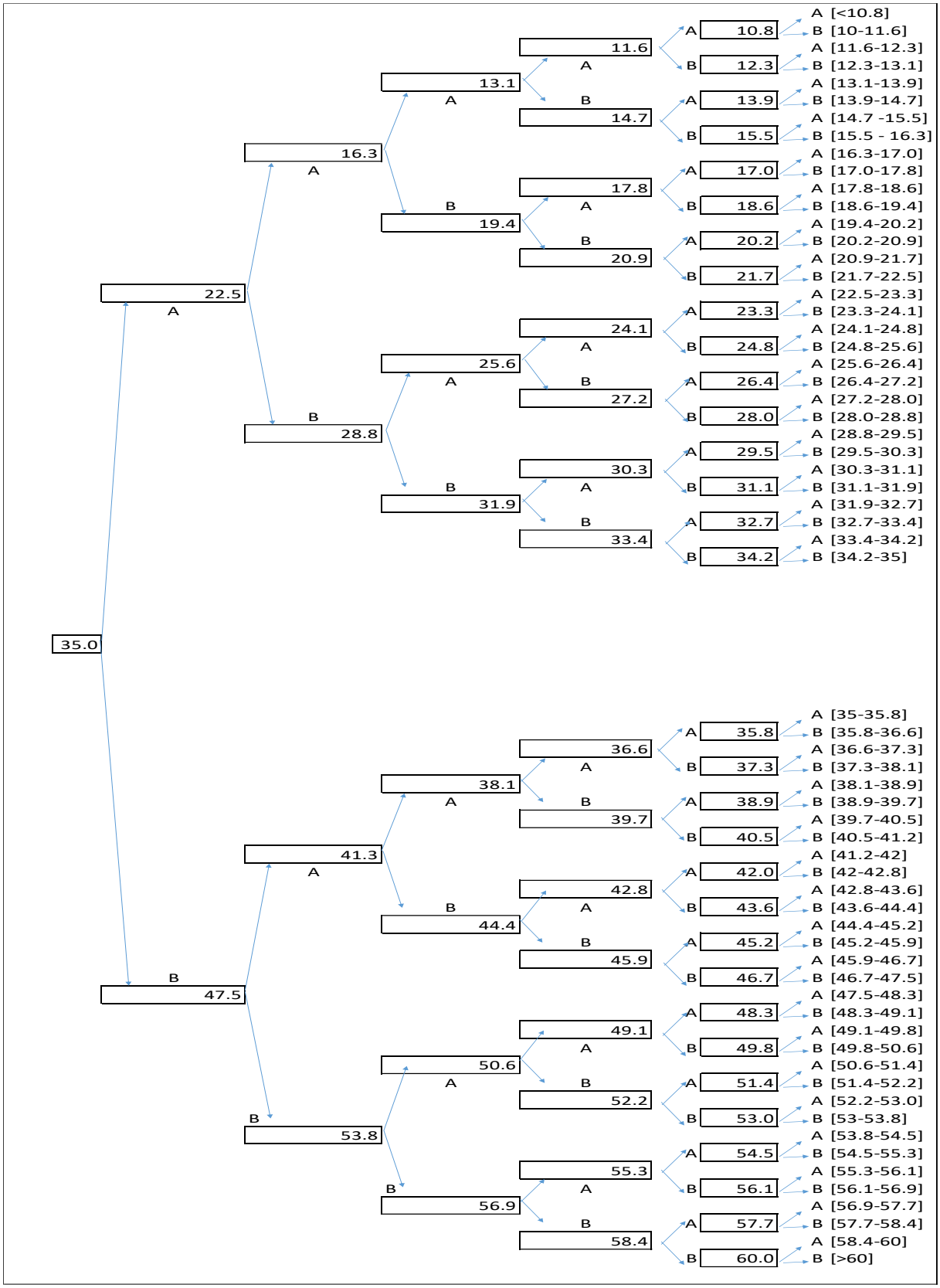
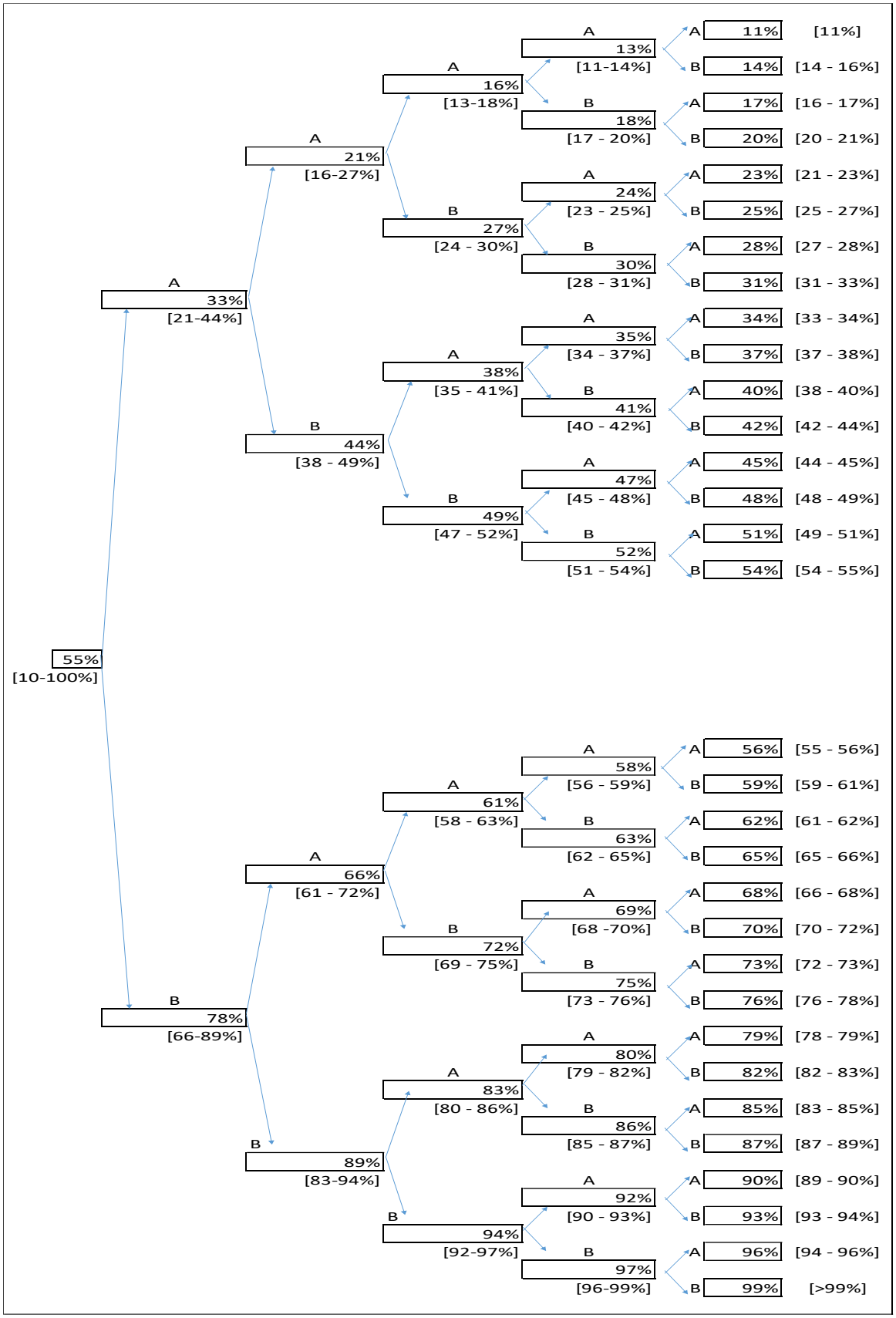


Figure 2.3: Levels used in choice questions to inform time preferences*



**If between iteration 1 and 6 a respondent chose indifference between options A and B, the performance range used to calculate c.is provided in [ ],*

PAPER IV

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RESEARCH ARTICLE

Prioritizing investments in rapid response vaccine technologies for emerging infections: A portfolio decision analysis

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Abstract

This study reports on the application of a Portfolio Decision Analysis (PDA) to support investment decisions of a non-profit funder of vaccine technology platform development for rapid response to emerging infections. A value framework was constructed via document reviews and stakeholder consultations. Probability of Success (PoS) data was obtained for 16 platform projects through expert assessments and stakeholder portfolio preferences via a Discrete Choice Experiment (DCE). The structure of preferences and the uncertainties in project PoS suggested a non-linear, stochastic value maximization problem. A simulation-optimization algorithm was employed, identifying optimal portfolios under different budget constraints. Stochastic dominance of the optimization solution was tested via mean-variance and mean-Gini statistics, and its robustness via rank probability analysis in a Monte Carlo simulation. Project PoS estimates were low and substantially overlapping. The DCE identified decreasing rates of return to investing in single platform types. Optimal portfolio solutions reflected this non-linearity of platform preferences along an efficiency frontier and diverged from a model simply ranking projects by PoS-to-Cost, despite significant revisions to project PoS estimates during the review process in relation to the conduct of the DCE. Large confidence intervals associated with optimization solutions suggested significant uncertainty in portfolio valuations. Mean-variance and Mean-Gini tests suggested optimal portfolios with higher expected values were also accompanied by higher risks of not achieving those values despite stochastic dominance of the optimal portfolio solution under the decision maker's budget constraint. This portfolio was also the highest ranked portfolio in the simulation; though having only a 54% probability of being preferred to the second-ranked portfolio. The analysis illustrates how optimization modelling can help health R&D decision makers identify optimal portfolios in the face of significant decision uncertainty involving portfolio trade-offs. However, in light of such extreme uncertainty, further due diligence and ongoing updating of performance is needed on highly risky projects as well as data on decision makers' portfolio risk attitude before PDA can conclude about optimal and robust solutions.

of KM played no role in the study. KM reports personal fees from CEPI, during the conduct of the study. The funder provided support in the form of personal fees and research materials for KM, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

Competing interests: KM reports personal fees from CEPI, during the conduct of the study. KM is employed by a commercial company. DG reports grants from the Research Council of Norway, during the conduct of this study (ref. 234608). DG reports paid employment by CEPI, during the conduct of the study. Names of projects evaluated in this study are anonymized due to confidentiality restrictions by CEPI. These do not alter our adherence to PLOS ONE policies on sharing data and materials.

1. Introduction

The Coalition of Epidemic Preparedness Innovations (CEPI) was set up in 2016 to support the development of vaccines for Epidemic Infectious Disease (EID) threats, contributing to the world's preparedness for unexpected EID outbreaks [1–3]. A key strategic objective of CEPI has been to establish platform technology capabilities that can accelerate development, manufacturing and clinical evaluation of vaccines in response to outbreaks of newly emerging infections [1,4]; its importance exemplified by the world's vaccine development response to the COVID-19 pandemic. In 2017, CEPI launched a Call for Proposals (CfP) to select a portfolio of platform technologies that would enable achievement of this strategic objective through an initial total investment of approximately US$ 140 million [5]. It was anticipated that supporting a diverse range of vaccine platforms could improve response to epidemic outbreaks by facilitating the rapid development of a novel vaccine should a previously unknown pathogen emerge [6]. Six platform projects that had participated in this CfP are now developing COVID-19 vaccines, several of which are in advanced clinical trials.

Platform technologies can generally be viewed as standardized, reproducible processes to develop and manufacture vaccines, which have previously been established through the development of other vaccines. Rapid response platforms can, in principle, improve the efficiency and overall timeframe of vaccine development; allowing for the start of clinical phase 1 testing just months after the viral sequence of a given pathogen is identified [6–9].

The decision to invest in the development of rapid response platforms to aid the response to the emergence of previously unknown pathogens faces challenges. First, whether an investment will generate benefit is subject to significant uncertainty. The successful development of a platform is highly uncertain, facing obstacles associated with organizational know-how and capabilities, technical and regulatory hurdles, and sustained utilization [10]. These challenges compound the well documented challenges of vaccine development–long timelines, scientific risks and operational complexities [11–15]. Assuming a platform is successfully developed, the benefit that the platform will deliver is subject to other sources of uncertainty [16], including: not knowing if the platform will enable the development of a vaccine that will protect against an unexpectedly emerging pathogen; and not knowing what the value of that protection will be–i.e., how many people would be put at risk by the pathogen and what risk the pathogen would pose to them.

Given these challenges, a single standardized financial or health-economic value metric is unlikely going to be able to measure the value of investments. In such a context, a multi-criteria value framework could be more appropriate, incorporating stakeholder preferences to inform how criteria should be traded off [17–19]. Such a framework would require the elicitation of preferences of relevant stakeholders involved.

Any such analysis is also likely to have to accommodate portfolio level effects. A single platform approach may be insufficient for rapid vaccine development in response to outbreaks caused by a multitude of unknown pathogens. Instead, a mix of platforms may be required to increase the likelihood of protection [6,20,21].

This study reports on a Portfolio Decision Analysis (PDA) application [22] to address the above challenges, and support CEPI's investment decisions. To the best of the authors' knowledge, no previous PDA to support pharmaceutical R&D has attempted to simultaneously test all above challenges–uncertainty in project evaluation; portfolio-level effects; and formally incorporating stakeholder preferences.

PDA has been increasingly used in R&D project selection across multiple application domains [22–26] due to its support in reducing the number of portfolio alternatives considered to a manageable size [27,28]; enhancing transparency through the consideration of all

relevant criteria [22,24,25]; making relevant conflicts explicit [17,22,24]; accounting for the interconnectedness of projects [29] and providing insight about the overall value, cost and balance of a portfolio [29–32].

The increased use of PDA has also been seen in the field of pharmaceutical R&D decision making specifically [29–33]. This literature includes studies that address uncertainty and that incorporate stakeholder preferences. But to the best of the authors' knowledge, no study has addressed both challenges simultaneously.

A commonly acceptable measure of uncertainty for pharmaceutical R&D portfolio decision-making is lacking [34]. Uncertainty has been addressed through use of decision tree analyses [33,35–37] as well as stochastic optimization methodologies [e.g. 34,38–47]. In all these studies the notion of uncertainty is partly conflated with that of risk of project failure, or inversely, probability of success (PoS). However, several studies introduce measures of uncertainty that capture variance of R&D portfolio performance more broadly, such as: Value at Risk (VaR) or Conditional Value at Risk (CVaR) [34], fuzzy value [43], reward/loss ratios [38,44,46] or value probability thresholds [34,38,40,44–46,48,49], variance of portfolio value distribution [39,42,44,50,51], semivariance below or above portfolio value thresholds [42], or covariance of portfolio value, cumulative probability distribution of portfolio value and Gini criteria [41]. A final set of methods emerging from the health economic literature attempt to measure the impact of this variance on the probability that a portfolio is chosen [42,52,53]. The main logic of these approaches is to generate model outputs in multiple iterations within a Monte Carlo simulation, and to determine, across all iterations, the proportion of outputs that fall favourably in relation to a given decision maker satisfaction threshold; allowing this way for probabilistic rankings to be constructed.

A handful of studies have formally incorporated decision maker preferences into PDA for pharmaceutical R&D [16,54,55], and few other studies have illustrated how preferences could be applied in hypothetical pharmaceutical R&D portfolio selection problems [43,44,46,48]. [54] employed an Analytic Hierarchy Process to assess the intensity of importance of decision criteria and alternatives in pairwise comparisons, allowing them to generate weighted scores to rank alternatives and to inform strategic investment decisions in a pharmaceutical company setting. [17] elicited stakeholder preferences using a swing-weighting technique, and then incorporated these into a multi-criteria decision analysis (MCDA) to evaluate projects, and consequently to generate an efficiency frontier. Building on the [17] model, [55] illustrated how optimal solutions along such a value-to-cost frontier can be generated when considering budget constraints and project interdependencies. [43] used fuzzy set theory to model imprecise and preference information associated with R&D project performance, project interactions, and stakeholder satisfaction degrees in resource constraint distributions, enabling the estimation of an optimal portfolio that maximizes monetary benefits under fuzzy resource constraints. A handful of other studies assumed stakeholder preferences as priority indices determining the sequencing of projects entering illustrative pharmaceutical R&D pipeline optimization problems [44,46,48]. However, no formal preference elicitation process, or outcome, was reported in any of these studies.

This study attempts to explicitly address uncertainty and formally incorporate stakeholder preferences into the optimization process. It does so through discrete choice modelling and testing of multiple uncertainty analysis methods within a stochastic optimization framework, in a real-life application with a high impact portfolio decision to be made. A commercially available simulation-optimization algorithm is employed to identify optimal portfolio solutions, and different uncertainty analysis techniques are compared to assess whether the identified solutions are also stochastically nondominated and robust.

2. Materials & methods

2.1.Scope and objective

The analysis focused on 16 platform projects that were submitted for an extended review following on the launch of a Call for Proposals (CfP) [5]. Projects were reviewed by CEPI between March and May 2018. The 16 platform projects had a combined budget of US$ 390 million, with budgets ranging from US$ 6 million to US$ 65 million, and with a median cost of US$ 22 million (see S1 Data). The goal of the PDA framework was to identify an optimal portfolio of platform technology investments that would maximize portfolio value under a US$ 140m budget constraint.

All projects were at the preclinical development phase, with the aim that CEPI funding would advance them through their testing against up to three pilot pathogens to the end of clinical phase 1. Projects covered 5 different types of platform technologies: RNA, Viral Vector, DNA, Protein, and gene-encoded mAb. Due to confidentiality restrictions, project owner/development partner names have been anonymized throughout the remainder of this manuscript. Projects have been labelled as P1 to P16 and their grouping by platform type 1–5 is summarized in Table 1.

2.2.Study design

Six steps were undertaken to determine the optimal platform technology portfolio solution. First, project-level and portfolio-level evaluation factors were identified that were of interest to the decision makers, via stakeholder consultations and review of the literature. Second, these factors were structured into a platform technology portfolio valuation framework, accounting for parameter uncertainty. Third, expert assessments of platform project performance were collected and combined into performance estimates using a Monte Carlo simulation. Fourth, decision maker preferences were elicited on different types of technology platforms via a Discrete Choice Experiment (DCE). Fifth, project performance and decision maker preferences were combined in a simulation-optimization model to determine optimal portfolio solutions. Sixth, stochastic dominance and robustness of the optimization output were tested through a variety of uncertainty analysis techniques.

2.3.Step 1. Identifying evaluation factors

Stakeholder consultations (see S1 Appendix for details) identified the factors relevant to the evaluation of platform project portfolios. First, the probability of at least one project per platform type considered induces a sustainable, protection enabling accelerated vaccine R&D

Table 1. Platform projects evaluated under the call for proposals for platform technologies to enable rapid vaccine development for epidemic prone infections.

Platform Type	Platform Projects
RNA (Platform Type 1)	P2 (mRNA), P7 (saRNA), P11 (mRNA), P16 (mRNA)
Viral Vector (Platform Type 2)	P4 (Replication-defective Chimpanzee adenovirus), P10 (Plasmid-Launched-Live-Attenuated Virus YF), P12 (Simian Adenovirus), P13 (Recombinant attenuated vesicular stomatitis virus)
DNA (Platform Type 3)	P3 (DNA-Needle Free Injection System), P8 (DNA-Electropolation Device), P15 (Lentiviral gene transfer vector)
Protein (Platform Type 4)	P1 (Nanoparticle-Subunit), P9 (Tobacco Mosaic virus—Virus Like Particle), P14 (Molecular Clamp Sub-unit)
Gene-encoded mAb (Platform Type 5)	P5 (Adeno Associated Virus-mediated monoclonal antibody), P6 (RNA vectored monoclonal antibody)

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response to unexpected epidemic infection emergencies ($PoS_{\geq 1}$). The consultation identified seven factors influencing $PoS_{\geq 1}$ (see Table 2). Second, stakeholders suggested different value to $PoS_{\geq 1}$ generated by different platform types and a non-linearity in preferences for $PoS_{\geq 1}$.

2.4.Step 2. Defining R&D portfolio value

Based on the factors emerging from the previous step as relevant to the assessment of projects and of project portfolios, project PoS is defined per Eq (1) as the product of those factors contributing to the overall PoS of project *i* for a given technology platform type *k*. *N* indicates the total number of project PoS factors considered (which in this case is seven; for descriptions see Table 1). These factors were defined to be consequentially independent–i.e. the occurrence of one factor would not affect the probability of occurrence of others–even if some of these could potentially be correlated with each other in practice. This allowed for their multiplicative combination to generate overall project PoS estimates. The independence of the factors was ensured through the engagement of experts in the definition and structuring of the PoS factors. For instance, the risk of project failure because of staff competence (the inverse of factor C1) was deemed independent to the risk of project failure because of technical factors (C2-C5), as was the prospect that a project demonstrates clinical benefit (C3) but is not safe (C4), and vice versa.

$$\tilde{p}_{i_k} = \prod_N \tilde{C}_{N_{i_k}} \quad (1)$$

Where:

$\tilde{p}_{i_k}$ = platform project PoS

$\tilde{C}_{N_{i_k}}$ = factors contributing to the overall PoS of platform project i

For each platform type *k*, the probability of at least one project being successfully developed is defined per Eq (2). This is calculated as the difference between 1 and the product of no

Table 2. Factors influencing PoS of rapid response vaccine platform technology development projects.

Project PoS factor	Metric
C1. Applicant competency	Likelihood that the applicant is sufficiently competent to deliver on the proposed activities of the project
C2. Project feasibility	Likelihood that the project plans and procedures in place are of sufficient quality to ensure that three target pathogens are effectively investigated through to preclinical proof of concept, whereof two target pathogens are further effectively investigated through clinical Phase I studies
C3. Clinical benefit	Likelihood that the platform will enable immune responses providing protection/ clinical benefit against novel emerging infectious diseases on the basis of evidence provided on any pathogen
C4. Safety potential	Likelihood that the platform will be able to generate vaccines, with an acceptable safety profile, against novel emerging infectious diseases on the basis of evidence provided against any pathogens on the same platform
C5. Manufacturing scalability & speed	Likelihood that the platform will enable fast development and production, from design through clinical release of vaccine, in volumes sufficient to respond to outbreaks of novel emerging infectious diseases on the basis of evidence provided against each of the target pathogens and/or any other evidence provided on other pathogens as part of this application
C6. Operational suitability	Likelihood that the platform will enable stable storage and uncomplicated delivery of vaccine product in an outbreak response under extreme conditions
C7. Operational sustainability	Likelihood that the candidate platform developed through this project will remain in use and available to respond to newly emerging or unexpected pathogen outbreaks

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project being successfully developed. *s* indicates here the total number of projects representing a technology platform type *k*. Here, the level of at least one successful project $POS_{\geq 1(k)}$ associated with a given platform type *k* suggests that: a) more than 1 platform projects are being considered, at least one of which will succeed with a given probability; b) the PoS of each of these projects, as defined by Eq 1, will affect the overall probability of $POS_{\geq 1(k)}$ for the platform type *k* they comprise.

$$\widetilde{POS}_{\geq 1(k)} = 1 - (\prod_{i_k}^{s}(1 - \tilde{p}_{i_k})) \quad (2)$$

Where:

$\widetilde{POS}_{\geq 1(k)}$ = probability of at least one project being successfully developed for platform type k

As per Eq (3), overall portfolio value is defined as the weighted sum of products of $POS_{\geq 1(k)}$ per platform type *k*. A weighting factor ($\tilde{w}_k$) was added to the value function to reflect stakeholder feedback that their goal was more than simply maximising $POS_{\geq 1(k)}$ and that the value of $POS_{\geq 1(k)}$ varied between pathogens. It was not possible to define the source of this value more precisely and thus captured this as another factor in the value framework. Thus, the variation in the value of $POS_{\geq 1(k)}$ by platform type was incorporated into the framework as a weighting factor and captured by eliciting stakeholder preferences (see methods step 4).

$$\tilde{V}_p = \sum_{k=1}^{t} \tilde{w}_k \cdot \tilde{POS}_{\geq 1(k)} \quad (3)$$

Where:

$\tilde{V}_p$ = Overall portfolio value

$\tilde{w}_k$ = preference coefficient for platform type k

t = total number of platform types k included in the portfolio

2.4.1.Step 3. Generating project PoS estimates (C1, C2, C3, C4, C5, C6, C7). Each project *i* was quantitatively assessed against PoS factors $C1_i$ to $C7_i$ by four to five reviewers, each of whom assessed three to four projects, ensuring their balanced assignment in terms of numbers as well as representation of required review competencies per project (see S1 Appendix for details). Overall, a total pool of 27 reviewers was used for assessment of projects. For each of $C1_i$ - $C7_i$, reviewers were asked to define the most likely, worst-case and best-case outcomes for each project. Reviewers provided initial assessments online (step 3.1 –initial reviewer assessments) and final assessments following a face-to-face meeting (step 3.2—final reviewer assessments). Results of project assessments against $C1_i$ - $C7_i$ were combined to estimate projects' overall PoS as per Eq (2), through a random sampling process (10,000 iterations). In each iteration a reviewer was randomly selected and a PoS factor estimate was randomly drawn from that reviewer's distribution, assuming the reviewers' estimates defined a triangular distribution, and factors were combined as described in Eq (1). Across iterations of the simulation it was then possible to estimate the mean and variance in projects' PoS.

2.5.Step 4. Eliciting platform preferences (w_k). A DCE [56] was employed to help elicit stakeholder preferences for platform types, denoted as w_k. A DCE elicits from survey participants' their choices between pairs of decision options [57]. The options are described using a pre-defined set of attributes, such that the analysis of choices can be used to generate a utility function which describes how variation in attributes contributes to the preference for an option [57].

DCE participants involved 48 individuals, comprising a diverse group of expert stakeholders: 27 external expert reviewers; 8 CEPI expert staff; and 13 members of the Scientific Advisory Committee (SAC). The SAC is CEPI's formal governance body responsible for making

recommendations for funding to the CEPI Board. It is an independent, expert and invested group, under no obligation to agree with expert reviewer assessments or with formal investment decisions made by the CEPI Board. At the time of this CfP, the SAC comprised: 8 representatives of governments, regulators and multilateral organizations; 7 representatives of non-profit R&D organizations; 6 academics; 4 industry representatives; and 4 independent subject-matter experts [58].

The 48 DCE participants were given a series of choice sets, in which they were asked to choose between portfolio alternatives defined by different levels of achievement ($POS_{\geq 1(k)}$). For each platform type (the attributes), this likelihood was defined as one of three levels of achievement (Table 3). Given lack of published evidence on rapid platform project PoS, and given the time constraints on the analysis, the levels included in the choice model were informed by the initial reviewer assessments (step 3.1).

Each choice set comprised three portfolios (see example in Fig 1). An experimental design of 2 blocks of 16 choice sets (32 choice sets in total) was generated using JMP® Pro 13.2.1 software. In order to minimize bias in responses, the order of the attributes within each choice set and of the choice sets within each survey was randomized between DCE participants, and the experimental design was assessed for orthogonality and balance. Internal validity of responses was assessed through dominance and consistency tests (see S1 Appendix for details).

Participants' choices were analysed using a conditional logistic regression of the following form and applied using JMP®, Version 13. SAS Institute Inc., Cary, NC, 1989–2007:

$$U_j = \sum_{k=1}^{t} [\beta_{b(k)} X_{b(k)} + \beta_{c(k)} X_{c(k)}] \quad (4)$$

Where:

U_j = *Utility produced by portfolio choice j*

$X_{b(k)}$ = *the middle level* (*b*) *of* $PoS_{\geq 1}$ *performance for platform type k*

$X_{c(k)}$ = *the upper level* (*c*) *of* $PoS_{\geq 1}$ *performance for platfrom type k*

$\beta_{b(k)}$ = *Part worth associated with moving from the lower level of* $PoS_{\geq 1}$ *performance (a) to the medium level of performance (b) on platform type k*

$\beta_{c(k)}$ = *Part worth associated with moving from the medium level of* $PoS_{\geq 1}$ *performance (b) to the upper level of performance (c) on platform type k*

Results of the model were used to estimate preference functions w_k for the different platform types as per Eq (5), where values w_k are estimated depending on whether $POS_{\geq 1(k)}$ falls within a *b—a* versus a *c—b* range of achievement in the choice model (see Table 2); *a* being the lower level of $POS_{\geq 1(k)}$ achievement (which is equal to zero), *b* the middle level of $POS_{\geq 1(k)}$ achievement and *c* the upper level of $POS_{\geq 1(k)}$ achievement, for each platform type *k*

Table 3. Attributes and levels of achievement employed in the DCE.

Platform types (*k*)	Lower level (*a*)	Middle level (*b*)	Upper level (*c*)
RNA (Platform Technology Type 1)	($POS_{\geq 1}$ = 0%)	($POS_{\geq 1}$ = 30%)	($POS_{\geq 1}$ = 60%)
Viral Vector (Platform Technology Type 2)	($POS_{\geq 1}$ = 0%)	($POS_{\geq 1}$ = 30%)	($POS_{\geq 1}$ = 60%)
DNA (Platform Technology Type 3)	($POS_{\geq 1}$ = 0%)	($POS_{\geq 1}$ = 28%)	($POS_{\geq 1}$ = 56%)
Protein (Platform Technology Type 4)	($POS_{\geq 1}$ = 0%)	($POS_{\geq 1}$ = 20%)	($POS_{\geq 1}$ = 40%)
Gene-encoded mAb (Platform Technology Type 5)	($POS_{\geq 1}$ = 0%)	($POS_{\geq 1}$ = 6%)	($POS_{\geq 1}$ = 12%)

$POS_{\geq 1(k)}$ represents the likelihood of successfully developing at least one project by platform type *k*.

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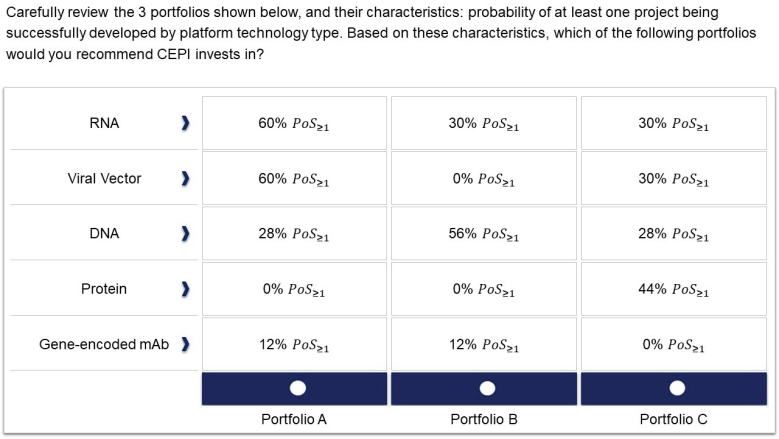

Fig 1. Example choice set in the DCE.

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considered in the choice model.

$$\tilde{w}_k = \begin{cases} \tilde{\beta}_{b(k)} \cdot \dfrac{1}{b-a}, \text{if } \tilde{POS}_{\geq 1(k)} \leq b \\ \dfrac{\tilde{\beta}_{b(k)}}{\tilde{POS}_{\geq 1(k)}} + \dfrac{\tilde{\beta}_{c(k)}}{\tilde{POS}_{\geq 1(k)}} \cdot \dfrac{\tilde{POS}_{\geq 1(k)} - b}{c-b}, \text{if } \tilde{POS}_{\geq 1(k)} > b \end{cases} \quad (5)$$

Where:

$\tilde{\beta}_{b(k)}$ = *stochastic parameter of* $\beta_{b(k)}$, *following a Normal distribution*

$\tilde{\beta}_{c(k)}$ = *stochastic parameter of* $\beta_{c(k)}$, *following a Normal distribution*

Given the anticipated heterogeneity in stakeholder preferences, w_k was modelled as a stochastic preference parameter in the overall value function described in Eq (3), drawing randomly (10,000 iterations) from the respective platform type's utility coefficient distribution fit to the DCE data. Utility coefficients generated from conditional logistic regression models are normally distributed, justifying the distributional choices in Eq 5.

2.6.Step 5. Constructing optimal portfolios

To construct optimal portfolios a mathematical programming problem was solved using a simulation-optimization algorithm provided by the Analytic Solver® platform of FrontlineSolvers®. The R&D portfolio selection problem was to select a set of platform projects from a pool of candidate projects that maximizes portfolio value under a given budget constraint. Since performance uncertainty and preference heterogeneity were expected to be encountered in making R&D project portfolio decisions, a stochastic mixed integer programming model was designed to support optimal R&D portfolio decisions in an uncertain R&D environment, per Eq (6).

$$\arg\max_x f(x) := \{x | f(x) = \tilde{V}_p = \textstyle\sum_{k=1}^{t} \tilde{w}_k [1 - (\prod_{i_k}^{s} (1 - \tilde{p}_{i_k} X_{i_k}))]\} \quad (6)$$

$$s.t. \quad \sum 1 \leq i_k \leq s \, B_{i_k} X_{i_k} \leq B \quad (6.1)$$

$$1 \leq k \leq t$$

$$X_{i_k}\{0,1\}\forall i_k \tag{6.2}$$

Indices and sets		***Parameters***	
$i \in I$	Projects	$\tilde{p}_{i_k}$	PoS distribution of project i representing technology platform type k
$k \in K$	Technology platform types	$\tilde{w}_k$	Preference coefficient for a given $\tilde{POS}_{\geq 1}$ in a technology platform type k.
V_p	Value of the portfolio	B_{i_k}	Budgetary cost of project i representing technology platform type k
B	Budget available		
s	The total number of projects representing a technology platform type		
t	The total number of technology platform types		
		Variables	
		X_{i_k}	$\begin{cases} 1, \text{ if project } i \text{ representing platform type } k \text{ is selected} \\ 0, \textit{ otherwise} \end{cases}$

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Given the above non-smooth optimization problem formulation has many potentially feasible solutions, the Analytic Solver® platform's evolutionary algorithm was used to identify optimal portfolios. The algorithm starts by randomly drawing from a population of candidate solutions. It learns and adapts its search for better optima in relation to a current solution, as the composition of the population of candidate solutions changes. This adaptation is supported by random changes to the original population of candidate solutions, yielding new and improved candidate solutions. Throughout this process, an evolutionary algorithm selects the fittest and eliminates the least fit candidate solutions.

Given that the optimization objective function depends on multiple, stochastically independent uncertainties, the evolutionary algorithm applied to the objective of maximizing expected V_p is unlikely to identify the highest V_p. Instead, V_p was maximized given chance constraints, defined as the percentile of the values computed for this objective function, across trials of the Monte Carlo simulation. Specifically, the addition of a chance constraint $VaR_a\ V_p \geq 95\%$ to the optimization model allowed the identification of portfolio solutions with the highest V_p under different budget constraints, which other model runs did not when maximizing by expected V_p or by V_p against $50\% \leq VaR_a\ V_p \geq 90\%$. Varying project allocations under different budget constraints from US$ 6 million (lowest budget of the evaluated projects) to US$ 390 million (total budget if all projects were to be considered), the model was also able to identify optimal portfolio solutions along an efficiency frontier.

2.7.Step 6. Uncertainty analysis

To further test the impact of uncertainty on the optimization, all possible portfolio alternatives were first identified under the US$ 140 million constraint, through multiple optimization runs (approximately 40,000 runs), each time marginally varying the budget constraint (by approximately US$ 0.0003 million). For each portfolio alternative under the given budget constraint, their mean, variance, semivariance, absolute deviation, and the mean-Gini statistic were then estimated, allowing for stochastic dominance testing (see S1 Appendix for details).

A probabilistic sensitivity analysis was also conducted to test robustness of the optimal portfolio solution, by estimating the rank probability of portfolio alternatives. This was done in pairwise comparisons between the optimal portfolio and all alternative portfolios identified at

the US$ 140 million budget constraint. For each pairwise comparison, the pair of portfolios were ranked in each of 10,000 simulation iterations, and the probability that the optimal portfolio would outrank each of these portfolio alternatives by V_p was estimated across all iterations.

3. Results

3.1.Project PoS

Fig 2A–2C present the PoS distributions of the 16 projects, based on initial *versus* final reviewer assessments. They demonstrate that PoS estimates substantially overlap between

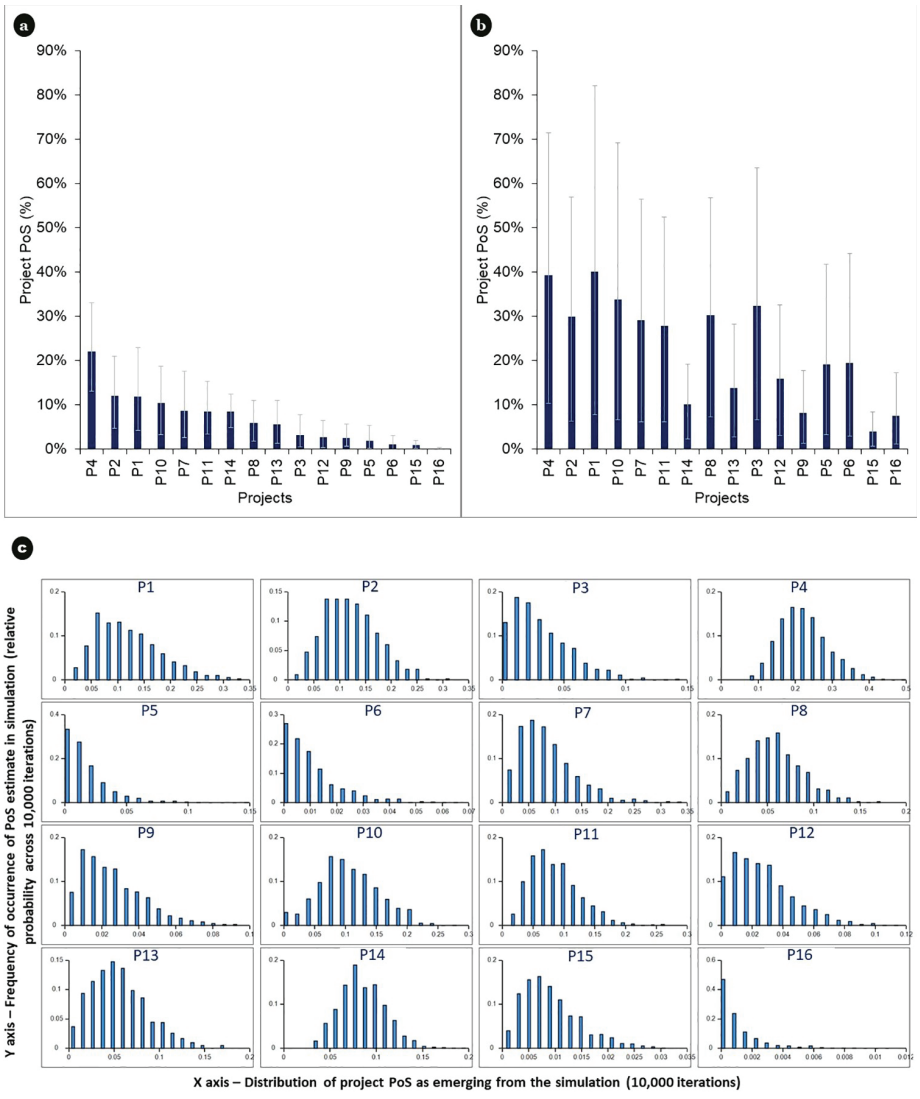

Fig 2. a, b. Project PoS (Mean, 95% CI). Displaying the mean and variance in PoS of projects generated by the simulation (10,000 iterations) under methods steps 3.1 and 3.2 (initial versus final reviewer assessments). c. Project PoS distributions (final reviewer assessments). Displaying the final project PoS distributions for the 16 projects assessed. Each bar chart represents another project, with the vertical axis indicating the frequency of occurrence of PoS estimates out of 10,000 simulation iterations, and the horizontal axis indicating different levels of PoS estimates emerging across the 10,000 simulation iterations.

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projects, though final PoS estimates are significantly lower than per initial assessments, changing the rank ordering of projects by PoS, within and between platform types.

3.2.Portfolio preferences (w_k)

Table 4 shows the choice model estimated from the DCE. It demonstrates how the utility that stakeholders place on a chosen portfolio varies with the probability of at least one project successfully developed per platform type $POS_{\geq 1(k)}$. Stakeholders attach different value to $POS_{\geq 1}$ generated by different platforms. For instance, there is a non-overlap between confidence intervals in 0–30% $POS_{\geq 1(k)}$ gains of RNA *versus* Protein and in 0–28% gains of Viral Vectors *versus* DNA. Moreover, there are consistently decreasing returns to investing in increasing $POS_{\geq 1(k)}$ of a single platform type. For instance, stakeholders prefer a gain of 0% to 30% in $POS_{\geq 1(k)}$ of RNA to the same gain in $POS_{\geq 1(k)}$ of other platforms. However, once it goes above 30%, the incremental return on $POS_{\geq 1(k)}$ for RNA becomes less, justifying diversifying the portfolio into other platform types.

Fig 3A shows the cumulative value of projects, grouped by platform type and ordered by $POS_{\geq 1}$ as identified through the initial reviewer assessments. Fig 3B shows the same output, but drawing from final reviewer assessments. As PoS estimates in this step were reduced, even cumulative PoS often were not as high as the mid-points in the preference function and thus failed to reflect the non-linearities in stakeholder preferences. This was an artefact of study timelines necessitating the design of the DCE based on initial reviewer assessments.

3.3.Optimal portfolios

Fig 4A demonstrates the optimal portfolio solution under the US$ 140 million budget constraint, which was also the SAC recommendation to CEPI–composed of the two best performing projects under each of the platform technology types 1 (RNA), 2 (Viral Vector), and 4 (Protein). The portfolio that was finally approved for funding by the CEPI Board excluded 1 Viral Vector and 1 Protein project from this recommended portfolio. This followed further due diligence of the recommended projects by internal CEPI expert teams. This portfolio was also positioned on the optimal value-to-budget frontier. Fig 4A also demonstrates which projects would have been selected if ranked by their PoS-to-Cost–including a third Viral Vector project (P12) that the Board did not approve but excluding one RNA project (P2) that was approved for funding.

Table 4. Choice model derived from responses to the DCE survey.

Term	Utility Coefficient (β)	Std Error	Lower 95%	Upper 95%	p value
RNA (Platform Type 1)_ $POS_{\geq 1}$ [0%-30%]	1.313	0.081	1.156	1.474	<0.001
RNA (Platform Type 1)_ $POS_{\geq 1}$ [30%-60%]	0.360	0.070	0.223	0.498	<0.001
Viral Vector (Platform Type 2)_ $POS_{\geq 1}$ [0%-30%]	1.167	0.082	1.009	1.329	<0.001
Viral Vector (Platform Type 2)_ $POS_{\geq 1}$ [30%-60%]	0.463	0.070	0.326	0.600	<0.001
DNA (Platform Type 3)_ $POS_{\geq 1}$ [0%-28%]	0.833	0.076	0.685	0.984	<0.001
DNA (Platform Type 3)_ $POS_{\geq 1}$ [28%-56%]	0.118	0.073	-0.026	0.261	0.11
Protein (Platform Type 4)_ $POS_{\geq 1}$ [0%-20%]	0.710	0.077	0.560	0.861	<0.001
Protein (Platform Type 4)_ $POS_{\geq 1}$ [20%-40%]	0.266	0.075	0.121	0.413	<0.001
Gene-encoded mAb (Platform Type 5)_ $POS_{\geq 1}$ [0%-6%]	0.133	0.073	-0.011	0.277	0.07
Gene-encoded mAb (Platform Type 5)_ $POS_{\geq 1}$ [6%-12%]	-0.043	0.076	-0.193	0.106	0.57

AICc = 2706.86; BIC = 2760.6; -2*LogLikelihood = 2686.73.

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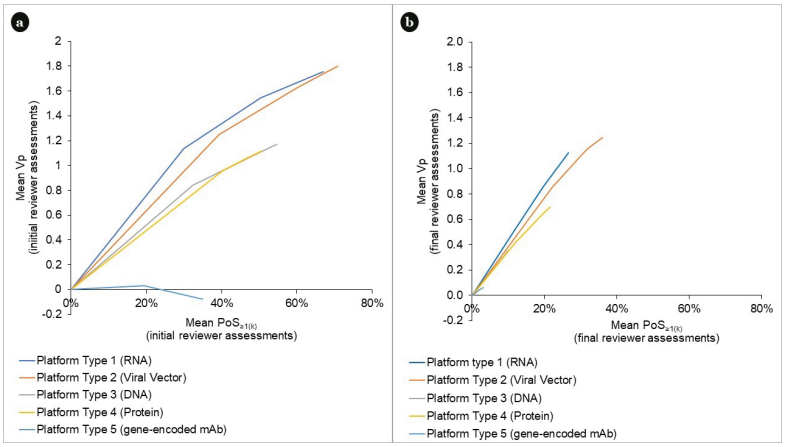

Fig 3. a. Portfolio value associated with probability of ≥1 project successfully developed per platform type (initial reviewer assessments). Mean $POS_{\geq 1(k)}$ and V_p estimates are calculated by running the optimization process under step 5 separately for each platform type *k*, as follows: maximizing V_p several times, each time incrementally increasing the number of projects (decision variables in the model) entering the portfolio, and repeating this process until all projects are added. b. Portfolio value associated with probability of ≥1 project successfully developed per platform type (final reviewer assessments). Mean $POS_{\geq 1(k)}$ and V_p estimates are calculated by running the optimization process under step 5 separately for each platform type *k*, as follows: maximizing V_p several times, each time incrementally increasing the number of projects (decision variables in the model) entering the portfolio, and repeating this process until all projects are added.

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Fig 4B shows the optimal frontier updated to draw from the initial reviewer assessments of project PoS. In this case, the impact of the non-linear preference function becomes more evident, as reviewer assessments are distributed across the ranges of performance reflected in the levels in the DCE.

3.4.Uncertainty analysis

The confidence intervals presented in Fig 4A demonstrate the large amount of uncertainty in final portfolio valuations. Fig 5 compares the optimal (and SAC recommended) portfolio and CEPI Board approved portfolios with alternatives under the decision maker's budget constraint through various means of variance–mean-variance, mean-semivariance, mean-standard deviation, and mean-absolute deviation. This suggests that the optimal portfolio is stochastically dominant to the CEPI Board approved portfolio. In addition, no portfolio alternative with lower, equal or higher variance than the SAC recommended portfolio has an equal expected value.

The notion of stochastic dominance tested in Fig 5 requires assumptions about the shape of decision makers' utility function and the shape of the probability distribution of the optimization outcomes, which appear to not be in line with the CEPI Board concerns about the level of acceptable risk present in the optimal portfolio. Assessment of stochastic dominance using the Mean-Gini relaxes these assumptions, just requiring that decision makers are risk averse [42,59].

Fig 6 illustrates the optimal value-to-budget frontier under a US$140 million constraint using the Mean-Gini statistic. Given that the optimal portfolio solution has both the highest mean V_p (Figs 4, and 5) and the highest mean-Gini statistic (Fig 6), this analysis confirms stochastic dominance of the optimization solution, given the assumptions on decision maker attitudes to risk underlying these models. Similarly to Fig 4A, the mean-Gini to budget analysis marginally differentiates from findings of a simple ranking of projects by PoS-to-Cost.

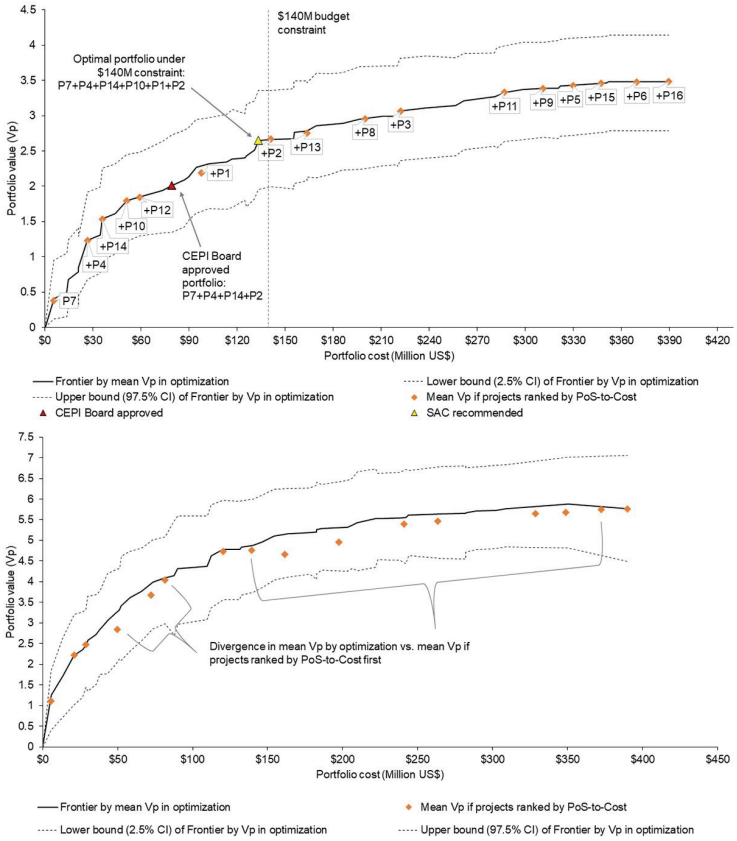

Fig 4. a. Optimal Frontier by maximizing portfolio value drawing from final reviewer assessments of project PoS. Fig 4A shows the efficiency frontier constructed by the optimization process under step 5, drawing from final reviewer assessments of project PoS. This is compared against the frontier that would have been generated if projects were simply ranked by expected PoS-to-Cost, then incrementally added to the portfolio without accounting for whether the resulting portfolios would maximize V_P under different budget constraints. b. Optimal Frontier by maximizing portfolio value drawing from initial reviewer assessments of project PoS. Fig 4B shows the efficiency frontier constructed by the optimization process under step 5, drawing from initial reviewer assessments of project PoS. This is compared against the frontier that would have been generated if projects were simply ranked by expected PoS-to-Cost, then incrementally added to the portfolio without accounting for whether the resulting portfolios would maximize V_P under different budget constraints.

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Fig 7A illustrates that out of all pairwise comparisons between the optimal solution and each of the 8,866 unique alternatives with a budget under US$ 140 million, the optimal portfolio had a >54–100% chance of outranking portfolio alternatives. Fig 7B illustrates to what extent the chance of the optimal portfolio outranking other portfolios changes according to changes in their project composition.

The optimal portfolio under the budget constraint has a 54% probability of outranking the second-best portfolio by value. The latter comprises one less project under platform technology type 4 (Protein), one additional project under platform technology type 2 (Viral Vector), and one new project under platform technology type 3 (DNA).

Projects P4, P7, P14 and P2 are included in over 80% of the 88 portfolios that are outranked by the optimal portfolio by a 54–75% chance in the simulation. Projects P10 and P1, which were not approved for funding by the CEPI Board, are included in only 56% and 42% of these portfolios. The probability that other portfolios outrank the optimal portfolio decreases as the extent that projects P4, P7, P14 and P2 are excluded from these portfolios increases.

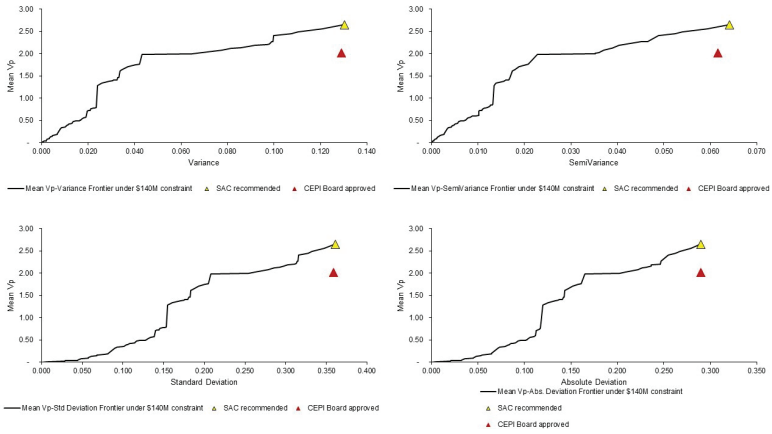

Fig 5. Optimal frontiers by mean-variance, mean-semivariance, mean-standard deviation, and mean-absolute deviation, under a US$140 million constraint.

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4. Discussion & conclusions

This study has reported on a PDA designed to support a global health R&D funding entity in making decisions to invest in platform technology projects to support response to unknown pathogen outbreaks. The funder faced significant uncertainty and portfolio selection trade-offs. This was particularly so in terms of the future use potential of platforms, but also in terms of the probability that platforms would be successfully developed and that they would be effective in the face of outbreaks.

There are three sets of findings that can be drawn from the study. First, the optimization output corresponded with the SAC's recommendation to CEPI to fund 2 RNA, 2 Viral Vector and 2 Protein platform projects. However, the two riskiest of the six projects were eventually not approved for funding by the CEPI Board. This raised questions about the robustness of the PDA solution relative to decision makers' attitude to portfolio risk.

The optimization demonstrated a positive correlation between the expected value of a portfolio and the variance around this estimate, suggesting a higher risk that the portfolio does not achieve the mean expected value. Despite this, various uncertainty analysis methods indicated

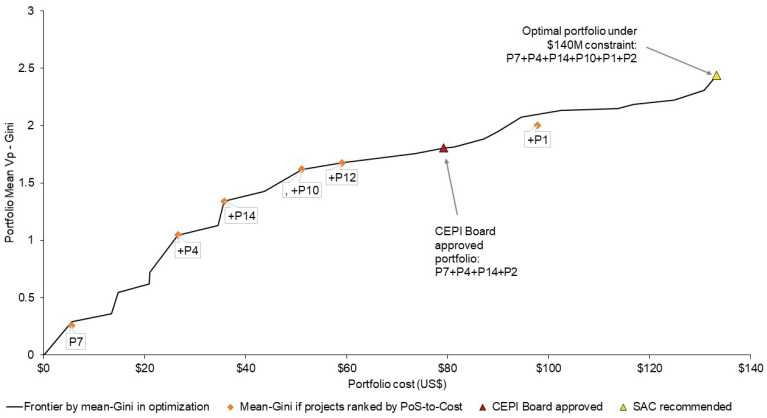

Fig 6. Optimal Frontier by Mean-Gini performance of the portfolio, under a US$140 million constraint.

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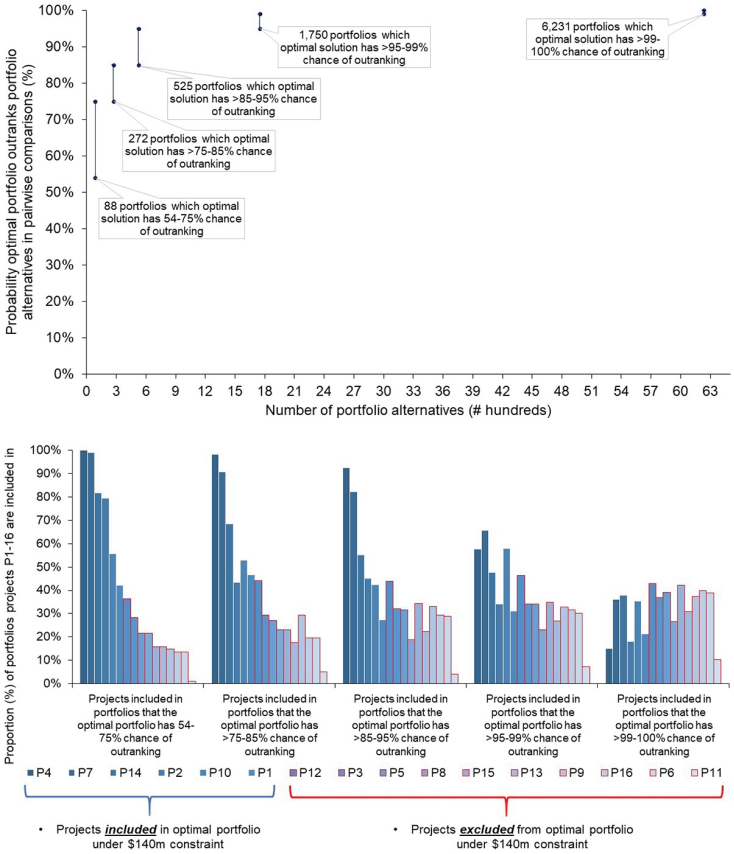

Fig 7. a. Probability ranges of optimal portfolio outranking alternative portfolios under a US$ 140 million constraint. b. Project composition of portfolio alternatives the optimal portfolio outranks under a US$ 140 million constraint.

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that the optimal portfolio is also stochastically nondominated, restricted in their conclusions however by assumptions on decision makers' attitudes to risk. The Monte Carlo Simulation suggested that this portfolio only had a 54% probability of ranking first compared with the second-best portfolio by value; and that this ranking probability was particularly sensitive to the downside risk of two out of the six projects comprising this portfolio. Whereas the sensitivity analysis was able to identify those downside risks, lack of information on decision makers' attitude to portfolio risk prevented the PDA from concluding as to portfolio robustness during the CfP process. This would include data on how decision makers trade-off increasing expected value and increasing variance in expected value, and data on the acceptable level of outranking probability. Several studies illustrate how this could be done by setting limits on the variation around an R&D portfolio's expected value (e.g. see [40,46,52]).

Practically, this finding also points to the importance of experience-based feedback to sequential updates of previous investment decisions as more information emerges about project strengths and risks. Mean-variance analyses ignore the impact of these learnings central to technology choice problems [60], which are dynamic in nature and require regular monitoring of progress of investments. The multi-armed bandit literature (e.g. [61,62] offers alternative perspectives on how portfolio choices can be made when decision-makers are faced with uncertainty. Here, the emphasis is on avoiding negative outcomes and particular attention is given on the dynamic process for decision making. The importance of such a sequential

strategy for managing uncertainty has been illustrated elsewhere in different ways [63,64]: with uncertainty in health product development gradually diminishing as candidates advance through development phases, more information about their actual potential is revealed, and periodic updates of portfolio decisions at key stage gates ensure returns are optimized. Regardless of whether one uses a multi-criteria decision analysis framework, statistical decision indices [65], real options [35] or other decision tree approaches [33], the common need in such a process is adaptation of models to new knowledge about portfolio performance and to evolving decision-maker priorities.

Second, the study illustrates some of the methodological challenges, and potential solutions, facing PDA in the context of early health R&D investment decisions. The analysis demonstrated that uncertainty was particularly evident in the likelihood that investments could generate platform projects that would be effective in face of an unexpected epidemic infection emergency. This is reflected in reviewers' assessments of project PoS. Given the uncertainties of whether any technology platform project can ever be applicable as well as rapidly respond to multiple such disease epidemics [8,66], it is unsurprising that project PoS estimates were low, despite the optimism of initial assessments informing the model; and with substantial variation.

The PDA considered the impact of this uncertainty and stakeholder preferences for different platform types on portfolio assessment; albeit preferences' impact on portfolio valuation was smaller than anticipated, given how levels in the choice model were set–drawing directly from the initial reviewer assessments, in absence of published benchmarks on rapid platform PoS. Because of this, capturing the diminishing returns to investing in the same platform types using the DCE generated only a marginally different optimality frontier than just focusing on project PoS-to-cost rankings.

Portfolio preferences have been captured in other studies by the introduction of a diversity criterion or constraint, for instance by: structuring R&D portfolios by disease area, platform technology type, or early *versus* late phase of development of projects considered (e.g. see [29,32,46,50,67–69]), imposing a limit on the allocation of resources between project types by strategic goal (e.g. see [43]), or restricting resource allocation between R&D activities because of resource dependencies (e.g. see [44,48]). In practice, platform potential emerges through the accumulation of evidence of performance against a variety of diseases. This point is exemplified by the experience with the accelerated development of several CEPI funded vaccines using RNA, Viral Vector, Protein and DNA platforms in response to the COVID-19 pandemic [70]. However, all projects considered in this study were at the same early stages of development. Moreover, there are extreme uncertainties around their use potential against multitudes of unknown pathogens if successfully developed in off-epidemic conditions. Valuing the portfolio by disease area or different phases of development would therefore be a challenging task. Other limit setting approaches would be less relevant as allocation limits are already a function of the $POS_{\geq 1(k)}$ and of constraints specified in the model.

This study modelled the optimization problem as a nonlinear stochastic problem and used an evolutionary algorithm to solve it. A key limitation of the evolutionary algorithm is premature convergence, i.e. the loss of diversity between sets of solutions too quickly in the solution search process, which can lead to outcomes that are not globally optimal. To avoid this, an optimization problem can be transformed to a linear or smooth problem, reducing its complexity and addressing the challenge of non-convergence. Ultimately, however, there is a degree of choice in how one models real-life problems and a trade-off that one needs to make between accurate reflection of real-life complexity and model simplification for computational efficiency and precision. In this study, the identification of all portfolio alternatives helped confirm the optimality of the solution generated by the model. This was possible because the

optimization problem was small but would be an intractable exercise in larger problems, where model transformations would allow for globally optimal solutions to be found in more efficient ways.

Finally, several practical limitations with the elicitation of stakeholder portfolio preferences were identified. First, the time constraints facing decision makers are not always amenable to rigorous preference elicitation. Second, in the context of sample size limitations, as is often the case when working with expert groups, there are limitations on the complexity of the value models that can be characterized by choice models, such as DCEs. However, this will be less of a concern when stakeholders' values of interest to decision makers is a larger group. In healthcare settings this typically relates to patients or the general population. In this study, it was the values of a broader set of experts beyond those (SAC members) making formal recommendations to the CEPI Board, which were of interest to decision-making. Consequently, the considerations of these values made it also practically possible for a DCE to be employed as the stakeholder group was large enough relevant to the number of attributes and levels considered in the model. In addition, logistical limitations meant that it was necessary to elicit preferences using a survey. This decision was vindicated by the results of the choice analysis, which was sufficiently precise to be able to differentiate the utilities associated with many of the levels in the choice sets. Other preference elicitation methods could also be employed, such as workshop-based swing weighting (e.g. [17]), however such methods are generally restricted by practical constraints of time, location and availability of stakeholders engaged.

The analysis demonstrates that while optimization modelling can help decision makers identify optimal portfolios in the face of significant decision uncertainty and portfolio trade-offs, in the presence of such problem characteristics further data on decision makers risk attitude is required before PDA can conclude about the optimal portfolio. Collecting such data will, however, face practical constraints. It will be necessary to identify such requirements early in the decision-making process, so that time and resources are available to elicit decision makers' preferences in the context of health R&D decision making.

Supporting information

S1 Appendix.
(DOCX)

S1 Data.
(XLSX)

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Funding acquisition: Dimitrios Gouglas.

Investigation: Dimitrios Gouglas.

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Project administration: Dimitrios Gouglas.

Validation: Dimitrios Gouglas.

Visualization: Dimitrios Gouglas.

Writing – original draft: Dimitrios Gouglas.

Writing – review & editing: Dimitrios Gouglas, Kevin Marsh.

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S1 Appendix

Article title: Prioritizing investments in rapid response vaccine technologies for emerging infections: a portfolio decision analysis

Journal name: PLOS One

This document provides supplementary detail on: (1) the methodology used to identify evaluation factors; (2) the methodology used to define performance distributions for assessing platform project proposals; (3) the methodology used to design and test the optimality of the discrete choice experiment employed for elicitation of portfolio preferences in the optimization model; and (4) definitions of stochastic dominance using different uncertainty analysis tests.

Supplementary information on Methods Step 1: Identifying evaluation factors

PoS factors

A list of potential factors that informed the PoS of a project was generated from semi-structured interviews with 11 members of the SAC, 10 CEPI staff (internal experts), and a review of: previous CEPI evaluation frameworks [1]; the CEPI Business Plan [2]; evaluation criteria used by other supporters of platform technology development – such as the WHO [3], BARDA [4], and the US Department of Defense [5,6]; and published literature [7-12]. All SAC members and select CEPI expert staff (33 individuals in total) were consulted on the initial list to determine which factors were most relevant to CfP decisions.

To narrow down the list of PoS factors, and combine these into the analytical framework, members of the SAC and CEPI staff were engaged first in an email survey and then in one-to-one interviews between October 2017 and December 2017 to determine: whether all PoS factors relevant to CfP decisions had been captured; the relationship between the factors, and whether any of these factors

should be removed or re-grouped if overlapping, or irrelevant. Based on this feedback, the research team developed a final list of seven factors contributing to project PoS, which was approved by CEPI's Scientific Advisory Committee (SAC) in February 2018 (Table 1). PoS factors were defined in such a way to ensure stochastic independence – i.e. the occurrence of one factor would not affect the probability of occurrence of others – allowing for their multiplicative combination to generate overall project PoS estimates (see equation (2) in the main manuscript).

Table 1: **Factors influencing PoS of rapid response vaccine platform technology development projects.**

Project PoS factor	Metric	Considerations that influence performance against the PoS factor
C1. Applicant competency	Likelihood that the applicant is sufficiently competent to deliver on the proposed activities of the project	• Technical competency/expertise of project staff • Experience in preclinical testing of vaccines • Experience of the applicant in executing Phase I/II clinical vaccine trials • Experience of the applicant in regulatory interactions with relevant authorities and licensing of vaccines • The applicant's vaccine manufacturing capabilities and skills
C2. Project feasibility	Likelihood that the project plans and procedures in place are of sufficient quality to ensure that three target pathogens are effectively investigated through to preclinical proof of concept, whereof two target pathogens are further effectively investigated through clinical Phase I studies	• The platform concept/ scientific rationale and ability to reach the 16-week timeline from antigen identification to product release for clinical trials • The development plan through to preclinical proof-of-concept for all three target pathogen vaccines • The early clinical development plan through to the end of Phase I for two target pathogen vaccines • The regulatory approach for advancing the project from preclinical through to Phase I • The process development and manufacturing plans, either in-house or via contract manufacturing partners
C3. Clinical benefit	Likelihood that the platform will enable immune responses providing protection/ clinical benefit against novel emerging infectious diseases on the basis of evidence provided on any pathogen	• Current evidence on the platform's ability to induce robust immune responses in humans • Potential of the proposed immunological response testing approach to provide adequate characterisation of the proposed platform in Phase I trial • Potential of proposed platform to induce robust immune responses in humans against two target pathogens • Potential of proposed platform to induce robust immune responses in humans against novel emerging infectious diseases as demonstrated by evidence on any pathogens • Probability of meeting a 6-week timeframe from administration of first dose to achievement of immunologic protection/clinical benefit
C4. Safety potential	Likelihood that the platform will be able to generate vaccines, with an acceptable safety profile, against novel emerging infectious diseases on the basis of evidence provided against any pathogens on the same platform	• Quality of the current safety evidence on the proposed platform (including preclinical toxicology data, e.g. neurovirulence, and biodistribution studies, studies where relevant) • Potential of proposed platform to demonstrate an acceptable safety profile for the vaccines against the target pathogens, based on assumptions and evidence to date • Potential of proposed platform to demonstrate an acceptable safety profile for vaccines against novel emerging infectious diseases as demonstrated by the rationale and evidence of any pathogen on the same platform, based on safety record in humans (no of individuals exposed) including preliminary data in children and other potential risk groups

Project PoS factor	Metric	Considerations that influence performance against the PoS factor
C5. Manufacturing scalability & speed	Likelihood that the platform will enable fast development and production, from design through clinical release of vaccine, in volumes sufficient to respond to outbreaks of novel emerging infectious diseases on the basis of evidence provided against each of the target pathogens and/or any other evidence provided on other pathogens as part of this application	• The process and release testing analytical methods and (including potency assays) to monitor process performance and expedite product release • Quality of the evidence and rationale on the platform's manufacturing performance and yield (if previous experience with the proposed platform exists) • Potential of the proposed platform to support rapid manufacturing, formulation, fill and finish of a 10,000/ 100,000/500,000/1,000,000 dose equivalent of bulk and vaccine product for clinical testing and emergency use • The anticipated Cost of Goods in manufacturing of 10,000/ 100,000/500,000/1,000,000 dose equivalent of bulk and vaccine product for clinical testing in an emergency response
C6. Operational suitability	Likelihood that the platform will enable stable storage and uncomplicated delivery of vaccine product in an outbreak response under extreme conditions	• Proposed platform's potential to deliver vaccines in minimal dosing schedules, in emergency situations • Proposed platform's potential to support stability of vaccine product ensuring a shelf life ≥6 months at temperature suitable for long term storage and reactive use of the vaccine • Proposed platform's feasibility for use in emergency response situations including potential requirement for delivery device
C7. Operational sustainability	Likelihood that the candidate platform developed through this project will remain in use and available to respond to newly emerging or unexpected pathogen outbreaks	• Evidence and rationale on platform's routine ongoing use for other pathogen vaccines • Evidence and rationale on platform's availability and use, via viable in-house or contract manufacturing partner facility operations, after the end of the project

Supplementary information on Methods Step 3. Generating project PoS estimates (C1, C2, C3, C4, C5, C6, C7)

Projects were quantitatively assessed against PoS factors C1 to C7 by 27 reviewers. Each project was assessed by four to five reviewers. They were selected through an open competitive process based on demonstrable experience – including years of work experience – in non-clinical, clinical, chemistry, manufacturing and control aspect of vaccine development. CEPI assigned reviewers to evaluate specific projects based on subject matter expertise on EID vaccine development and avoiding conflicts of interest. Reviewers received a manual and presentation providing detailed descriptions of PoS factors, scorecard templates, instructions and examples for filling in these templates. Further assistance and clarifications were provided in response to specific questions over email and phone, throughout the review process.

For each of C1-C7, reviewers were asked to define the most likely, worst-case and best-case outcomes for each project. Reviewers were first asked to provide individual assessments (between February and March 2018) and to submit these online using a customized reviews submission platform at CEPI. Reviewers then met in a face-to-face meeting (April 2018), and were asked to update their individual assessments, if needed, following group discussions on technical merits of the projects considered.

The results of the reviewer assessments of projects against C1-C7 were combined to estimate projects' overall PoS through a random sampling process (10,000 iterations). In each iteration a reviewer was randomly selected and a PoS factor estimate was randomly drawn from that reviewer's distribution, assuming the reviewers' estimates defined a triangular distribution. Factors were combined as described in equation (1) provided in the main manuscript. The mean and variance in project PoS across the iterations was then estimated.

Inter-reviewer variability was assessed for worst-case, most-likely and best-base estimates for each of C1-C7 based on the average difference of individual reviewers' estimates from the average estimate across all reviewers. Based on [13] classification, reviewer variability was assessed as good if it deviated less than 20% from the average, and excellent if it deviated less than 10% from the average. 7 of the 27 reviewers were found to have provided an estimate that deviated more than 20% from the average. In total, these deviations accounted for only 4% of the total number of worst-case, most likely, and best-case estimates collated from all reviewers, for all criteria (see S2 Data file for reviewer response data). These deviations reflected genuine differences of expert opinion, even after projects were thoroughly discussed during a face-to-face reviewer meeting.

Supplementary information on Methods Step 4. Eliciting platform preferences (w_k)

At least three key statistical properties need to be met to ensure optimality of DCE designs [14]: D efficiency, orthogonality, and balance. First, the software generated 10,000 alternative designs in

order for the most optimal design to be selected based on the D efficiency statistic [15-17] – a statistical measure commonly used to select the most efficient, though only fractional, factorial design, useful in situations where all combinations of the levels of the attributes are not possible to include. Given five attributes, each with three levels, considered in this DCE, a full factorial design would need to consider 243 choice sets, which would be practically prohibitive and tedious for DCE participants.

Second, statistical independence between attributes – which is a desired property of orthogonality in fractional factorial DCE designs [14] – was tested by computing pairwise correlations between attributes and their levels considered in the selected design. The highest correlation was 0.3, and the average correlation was 0.02, suggesting high orthogonality of the selected design. Third, manual edits to the DCE design were made to remove any dominant choice sets; and in doing so to improve the balance of the design, that is to ensure that each attribute level would occur equally often in the DCE, minimizing the variance in the parameter estimates.

Three other choice sets were added to each of the two blocks of choice sets: a practice question; a dominance test; and a consistency test. The inclusion of these tests intended to help clarify to what extent DCE respondents appropriately attended to the choice tasks. 75% of DCE survey respondents provided a consistent response and 85% correctly addressed the dominance question. When the probability that the dominance question was preferred was modelled based on the choice model [18] it was estimated that only 69% of respondents would be expected to select the dominant option, suggesting that DCE respondents attended to the task.

Supplementary information on Methods Step 6. Uncertainty analysis

A solution would be deemed as stochastically dominant in two alternative ways. According to the mean-variance statistics, stochastic dominance would be achieved if: a) the solution’s expected value

being greater than or equal to other portfolio alternatives for a given level of risk (equation (1.1)); and b) its variance being smaller than or equal to other portfolio alternatives for a given expected value (equation (1.2)):

$$E\left(V_{p(a)}\right) \geq E\left(V_{p(b)}\right) \quad (1.1)$$

and

$$\sigma_a \leq \sigma_b \quad (1.2)$$

Where:

$E\left(V_{p(x)}\right)$ = *expected value of portfolio x*

σ_x =*variance of portfolio x*

According to the mean-Gini statistic, stochastic dominance of the solution would be achieved if: a) its expected value being greater than or equal to other portfolio alternatives (equation (2.1)); and b) the distance between the expected value and twice the covariance of expected value and cumulative probability distribution of portfolio value being greater than or equal to other portfolio alternatives (equation (2.2)) [19,20]. A version of the Gini statistic as used in this study is reported in equation (2.3), also previously employed in [19,20].

$$E\left(V_{p(a)}\right) \geq E\left(V_{p(b)}\right) \quad (2.1)$$

And

$$E\left(V_{p(a)}\right) - \Gamma_{V_{p(a)}} \geq E\left(V_{p(b)}\right) - \Gamma_{V_{p(b)}} \quad (2.2)$$

Where:

$$\Gamma_{V_p} = 2cov\left[V_p, F\left(V_p\right)\right] \quad (2.3)$$

Notations:

Γ_{V_p} = *Gini statistic*

$E(V_{p(x)}) - \Gamma_{V_{p(x)}}$ = *Mean-Gini statistic for portfolio x*

$F(V_p)$ = *Cumulative Distribution Function of* V_p

S1 APPENDIX REFERENCES

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