NIPH
Norwegian Institute of Public Health

Global Strategy Lab

Strengthening International Collaboration for Capitalizing on Cost-Effective and Life-Saving Commodities' i4C

Prioritizing investments in vaccine development against epidemic infectious diseases

Novel decision science methods, with practical applications

Research seminar
Tuesday 8 October, 2019
Norwegian Institute of Public Health

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Five Strategies for Mobilizing of Global Collective Action	
Normative Strategies	Shaping norms, or the shared expectations for the behaviour of actors, around a global health issue
Financial Incentive Strategies	Providing actors with financial incentives to collaborate on addressing significant health issues
Informational Strategies	Improving the available information about the magnitude of a particular global health problem and the feasibility of addressing it
Political Pressure Strategies	Imposing reputational costs on actors to affect their credibility influence, prestige, and bargaining power for international forums
Administrative Procedural Strategies	Creating rules and processes that force actors to engage, nudge towards cooperative solutions, and provide a status quo bias to change

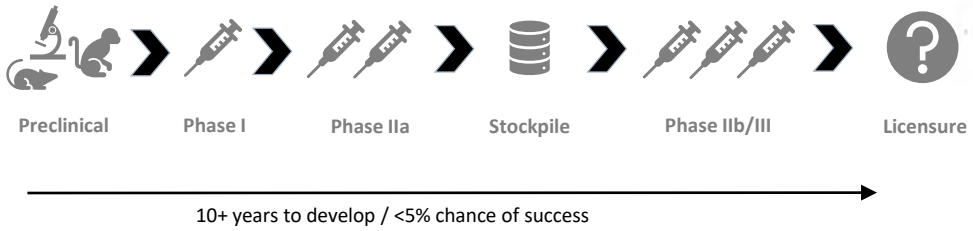
Overview

Challenges research project was established to address

Methods and results

Conclusions & lessons for future research and practice

The challenge



- Vaccine development an essential part in efforts to address emerging health challenges.
- Evidence on what it would cost and how to prioritize resources to successfully develop Epidemic Infectious Disease (EID) vaccines has been scarce.
    1. Paucity of explicit, publicly available Probability of Success (PoS) and cost data.
    2. Absence of global Research and Development (R&D) portfolio strategy and coordination.
    3. Little agreement across global actors on which EID investments should be prioritised and how.

The institutional response

2015 → Jan 2016 → May/June 2016 → Sep 2016 → Jan 2017

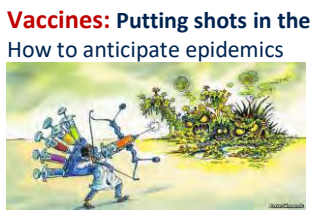
Leaders explore new ways to drive product innovation for EIDs

- Thought leaders from governments, industry, and civil society meet at the 2016 World Economic Forum in Davos, and agree to explore new ways to drive product innovation for high-priority epidemic threats.
- Three task teams convene to define solutions for EID vaccines.

Institutions take action

- The World Bank establishes the Pandemic Emergency Finance Facility (PEF) to quickly release funds to affected countries for epidemic responses.
- The WHO publishes a R&D Blueprint for EID preparedness & response, identifying 11 pathogens with potential to cause severe outbreaks in the near term.

Experts recommend a sustainable financing & coordination mechanism



- Task teams conclude recommendations and lead to formation of CEPI.

CEPI is formally launched

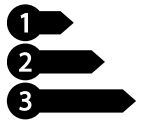
- CEPI formally launched at the 2017 World Economic Forum in Davos.

…and this project's perspective..

How to improve available information about the magnitude of the EID vaccine R&D prioritization problem and the feasibility of addressing it

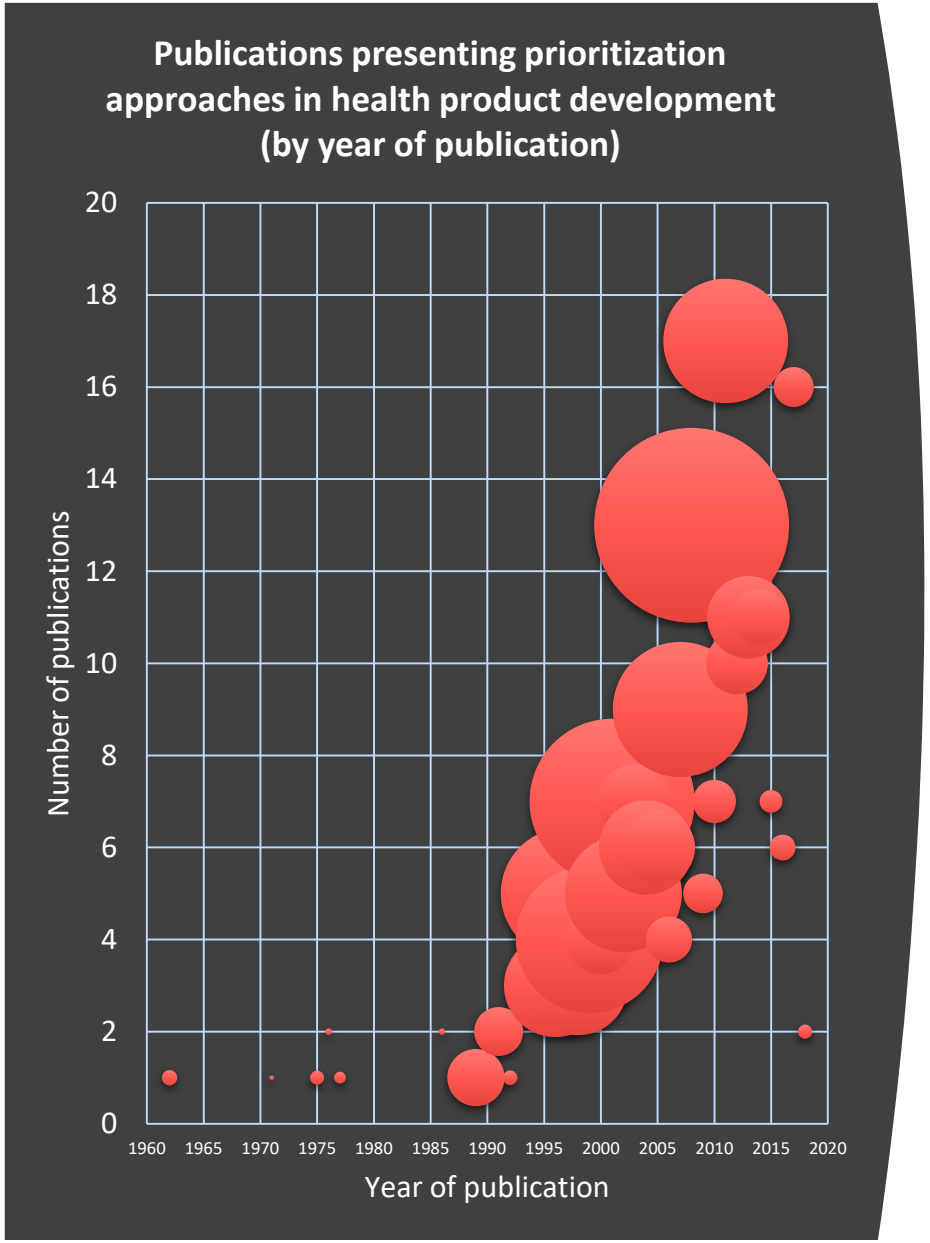
Project rationale

- Need by stakeholders of choosing what R&D strategies and alternatives to pursue



- Effective use of prioritization models can provide insights into the relative value of new health product development

- In absence of appropriate prioritization approaches in place, risk of misallocation of resources



Health product development prioritization is not the same as priority setting for health research

Wide variety of problems highlighted at the individual company level that are often of repeated nature e.g.:

- Strategic / Long range planning
- Project / Portfolio selection
- Project / Portfolio scheduling
- Pipeline / Portfolio management

Approaches draw largely from decision sciences

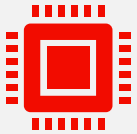
They revolve around notions of value, risk, cost, balance, constraints

Use of sophisticated analytical techniques but often lacking formal preference considerations, or practical applications and use in non-commercial settings

Project objectives

What would it cost to develop vaccines against EIDs and how significant a resource-allocation problem would this entail?

How can decision analysis support a rational approach to EID vaccine R&D strategy formulation that accounts for and ranks the preferences of multiple stakeholders in an international coalition setting?



How can decision analysis support the prioritization of EID vaccine R&D investments given the uncertainties in technology performance and heterogeneity in decision maker preferences?

3.1. Methods & results (1/2)

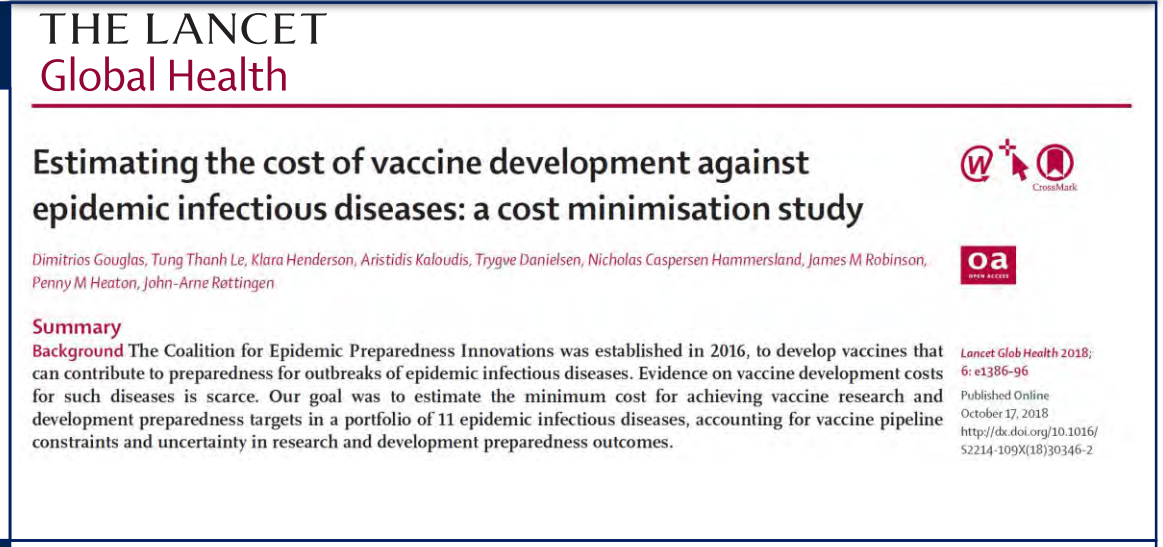
1. What would it cost to develop vaccines against EIDs and how significant a resource-allocation problem would this entail?

The challenge

- Evidence on vaccine development costs is scarce and either descriptive, based on expert opinions with limited data inputs to validate claims, focused on single pathogens or only on clinical research and development (R&D) phases.
- Goal was to estimate the minimum cost for advancing vaccines successfully through clinical safety and immunogenicity studies (preclinical through to end of clinical Phase IIa) in a portfolio of 11 EIDs, accounting for pipeline constraints and uncertainty in R&D outcomes.

The approach

- R&D pipeline, cost and attrition mapping via lit. search and surveys (>6,000 refs, 224 candidates; 64 survey respondents)
- Significance testing of potential drivers of development costs via regression models and hierarchical cluster analyses
- Estimation of attrition-adjusted development costs per EID via Monte Carlo simulation
- Minimum cost calculations for progressing ≥1 vaccine through end phase 2a per EID via stochastic optimisation



THE LANCET
Global Health

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

Dimitrios Gouglas, Tung Thanh Le, Klara Henderson, Aristidis Kaloudis, Trygve Danielsen, Nicholas Caspersen Hammersland, James M Robinson, Penny M Heaton, John-Arne Røttingen

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.

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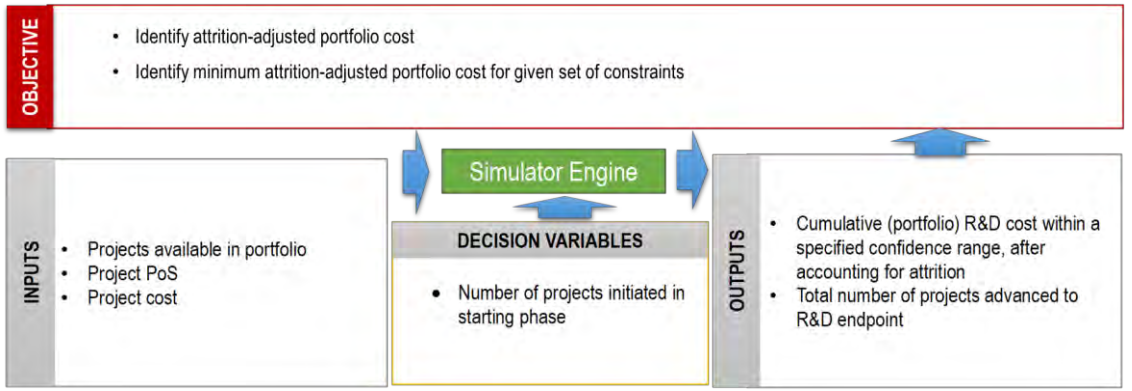
Figure: A simplified illustration of the optimization model employed



3.1. Methods & results (2/2)

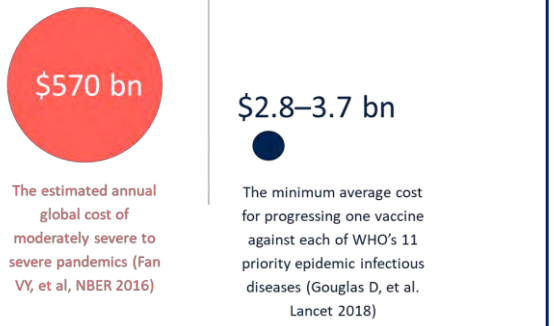
1. What would it cost to develop vaccines against EIDs and how significant a resource-allocation problem would this entail?

Key findings

- $31–68m is the average project cost prec-phII.
- $84–469m successful project cost, accounting for attrition and starting phase.
- $2.8 – 3.7bn for at least 1 successful candidate against all EIDs.
- Cost drivers: PoS, licensure track-record and indirect costs (upward); previously licensed vaccines for disease (downward).
- Too few candidates for Nipah, CCHF, SARS, and SFTS to guarantee phII outcomes.

Figure: Cost of progressing at least one EID vaccine from preclinical through to end of phase IIa

	Number of confirmed vaccine candidates		
	Preclinical	Phase 1	Phase 2
Ebola	37	4	1
Zika	28	8	1
Chikungunya	20	5	2
Lassa	28	..	..
MERS	21	4	..
Marburg	19	2	..
Rift Valley fever	15	..	2
Nipah	13	..	..
CCHF	6	1	..
SARS	6	..	..
SFTS	1	..	-
Total	194	24	6



	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)	
	Number of available candidates	Number of new candidates needed			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)
Zika	..	..	4–8	1	149 million (54–299 million)	158 million (45–357 million)
Rift Valley fever	5–13	..	..	2	224 million (100–409 million)	244 million (61–570 million)
MERS	3–12	..	4	..	244 million (108–439 million)	245 million (71–543 million)
Marburg	7–16	..	2	..	274 million (119–495 million)	358 million (86–792 million)
Lassa	11–21	..	..	..	319 million (137–590 million)	469 million (99–1100 million)
CCHF	6	3–12	1	..	289 million (125–531 million)	414 million (94–911 million)
Nipah	11–13	0–8	..	..	319 million (137–590 million)	469 million (99–1100 million)
SARS	6	5–15	..	..	319 million (137–590 million)	469 million (99–1100 million)
SFTS	1	10–20	..	..	319 million (137–590 million)	469 million (99–1100 million)
Total	50–91	18–55	13–20	5	2800 million (1200–5000 million)	3700 million (900–8400 million)

Tables: Pipeline today and min. cost for moving at least one vaccine through end of phase 2a, per EID

3.2. Methods & results (1/2)

2. How can decision analysis support a rational approach to EID vaccine R&D strategy formulation that accounts for the preferences of multiple stakeholders in an international coalition setting?

The challenge

- Leaders convened in 2016 to formulate CEPI's strategic goals; needing to agree on well-defined objectives & principles.
- Efforts to generate consensus at risk of devolving into a bargaining process with non-representative/ambiguous results, given >100 stakeholders with diverse perspectives.
- Transparency and rigour to the task of strategic objective setting would allow CEPI to determine the strategic decision context within which future investment decisions could be made.

The approach

- An Exploratory Decision Analysis process was employed, combining Value-Focused Thinking and a Discrete Choice Experiment (DCE) to identify, structure and explore the relative importance of CEPI's strategic objectives:
    1. 31 stakeholder consultations and lit. review.
    2. Means-ends argument chain mapping.
    3. Group discussions and objectives hierarchy structuring.
    4. Preference elicitation via a DCE (55 respondents).

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

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Table: Means-Ends objectives as attributes and levels of importance in the DCE

Criterion (ends)	Indicator (means)
Maximize level of preparedness	• Advance vaccines developed to latest stage possible • Achieve translational R&D milestones • Achieve regulatory innovations
Maximize response speed	• Get facilities ready to manufacture • Get clinical infrastructure ready to test • Develop rapid response platform technologies
Improve market predictability	• Achieve positive externalities • Minimize disruptions • Secure long-term predictability of financing
Improve equity	• Promote vaccine access • Promote LMIC capacity benefits • Increase sharing of responsibilities

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

3.2. Methods & results (2/2)

2. How can decision analysis support a rational approach to EID vaccine R&D strategy formulation that accounts for the preferences of multiple stakeholders in an international coalition setting?

Key findings

- EIDs unpredictable & coordination lacking; Vaccines improve preparedness but face problems; Actors may tackle problems via different functions provided through institutional partnerships.
- Equitable access, cost and risk sharing should be the boundaries with which an institutional response should be operationalized.
- Strategic objectives should target R&D preparedness and market predictability whilst building technical rapid response capabilities and distributing financing responsibility across regions.

Figure: Provisional strategic objectives hierarchy for CEPI

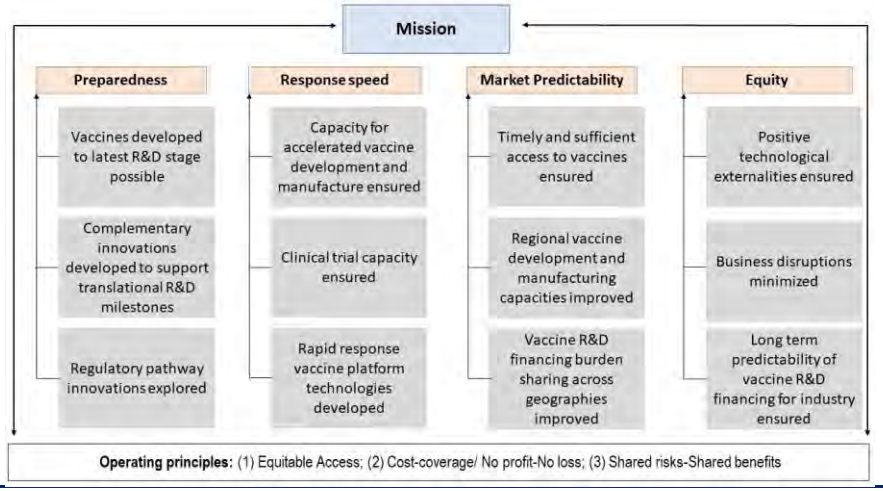
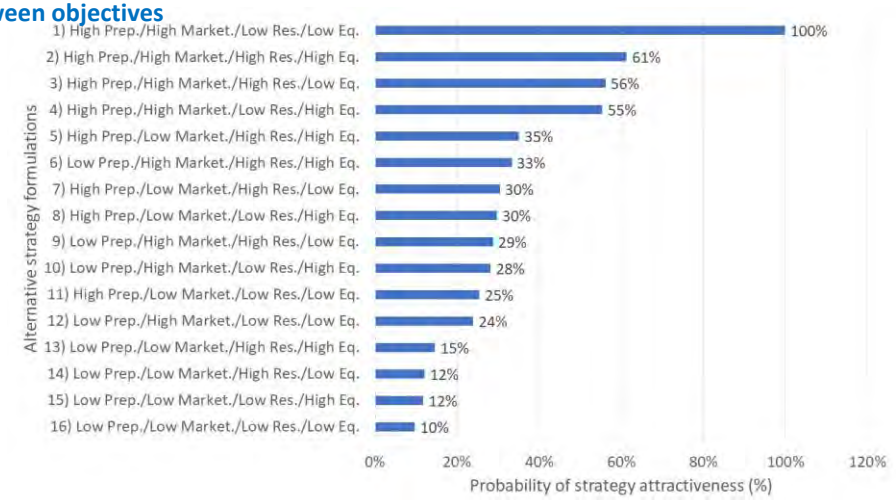


Figure: Reasoning Diagram Illustrating Means–Ends Chain of Arguments Constructed to Identify Strategic Objectives for CEPI

Figure: Predicted probabilities a CEPI strategy will be preferred given different levels of importance between objectives



3.3. Methods & results (1/2)

3. How can decision analysis support the prioritization of EID vaccine R&D investments given the uncertainties in technology performance and heterogeneity in decision maker preferences?

The challenge (project ranking)

- In 2016, CEPI launched a Call for Proposals (CfP) for vaccine development against Lassa, MERS and Nipah (Strategic obj. 1).
- CEPI is faced with complex decisions that involve confronting trade-offs between multiple objectives, diverse stakeholder perspectives, and uncertainty in vaccine performance.
- Goal was to undertake a quantitative valuation and ranking of 18 proposals against criteria of interest to CEPI. It was assumed that up to 14 proposals could be funded, given available resources.

The approach

- Multi-Criteria Decision Analysis employed and compared with Scientific Advisory Committee (SAC) recommendations:
  1. Criteria identification via consultations & lit. review.
  2. Performance measurement by 44 experts giving ranges from worst-to-best case performance (%).
  3. Weight elicitation via a swing-weighting technique.
  4. Value-for-Money measurement and probabilistic ranking in a Monte Carlo simulation.

Table: Criteria CfP vaccine development Lassa-MERS-Nipah

Criterion	Metric
C1. Applicant experience & track-record	Likelihood that the applicant is sufficiently competent to deliver on the proposed activities of the project (%)
C2. Technical feasibility	Likelihood that the development of the candidate vaccine through phase II is technically feasible (%)
C3. Manufacturing scalability & speed	Likelihood that the vaccine candidate is manufacturable and scalable in timeframes and volumes to respond to outbreaks (%)
C4. Use potential for target pathogens	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 (%)
C5. Use potential for new pathogens	Likelihood that the platform technology supporting the candidate vaccine(s) will be suitable for use in vaccine development against newly emerging/unexpected pathogens (%)

Outcomes:

- ***O1 = C1 x C2 x C3 x C4***
- ***O2 = C1 x C2 x C3 x C5***

Where:

O1 = Likelihood of generating a vaccine for a target pathogen (%)

O2 = Likelihood that the platform technology will be suitable for vaccine development against new pathogens (%)

Table: Preference elicitation findings

	O1 weight	O2 weight	O1 mid-point	O2 mid-point	Time disc.
Mean	0.72	0.28	0.40	0.43	0.22
St. Dev.	0.13	0.13	0.12	0.09	0.11
Lowest	0.50	0.10	0.17	0.22	0.04
Highest	0.90	0.50	0.60	0.60	0.46

- Partial value functions were defined by identifying the point on a 10-60% performance range that reflected the value mid-point. The mean mid-point suggested a non-linear value function with increasing marginal returns.
- Weights for $O1$ and $O2$ were elicited via pairwise comparisons to identify the indifference point between improving $O1$ from 10% to 60% and improving $O2$ from 10% to 60%.
- Time preference was estimated through pairwise comparisons to identify the indifference point between a z% chance of successfully delivering a project within 5 years, and a 100% chance of doing so in 10 years.

3.3. Methods & results (2/2)

3. How can decision analysis support the prioritization of EID vaccine R&D investments given the uncertainties in technology performance and heterogeneity in decision maker preferences?

Key findings

- Uncertainty in performance reflected in substantial overlap of confidence intervals around most proposals' performance.
- Greater weight attached to target pathogen (O1) than new pathogen platform potential (O2); increasing rate of preference as potential rises; sense of urgency (discount rate >20%).
- Rankings not affected by budget differentials; Clear proposal rankings despite performance and preference variations, with CEPI decisions marginally deviating from MCDA findings.

Figure: Top 1-14 rank likelihood by Value and Cost-to-Value

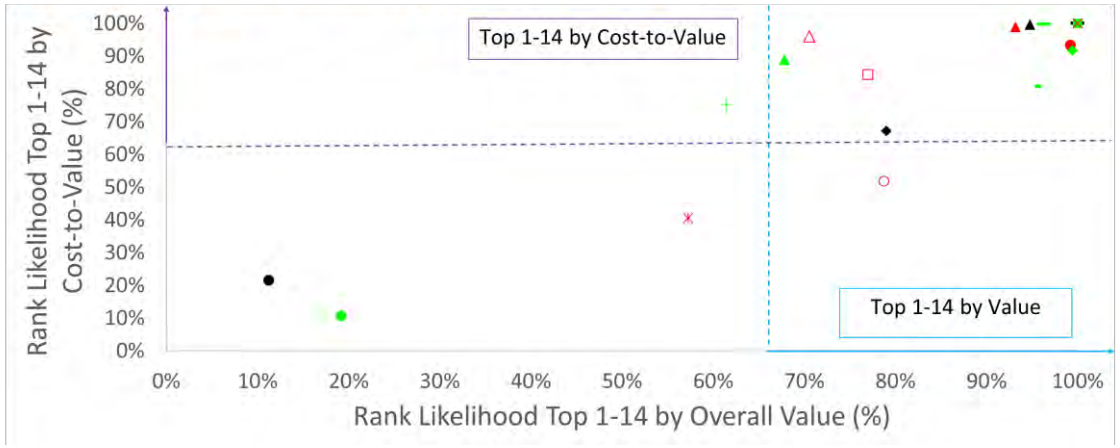


Figure: Proposal performance on outcomes O1 and O2 (mean, 95% CI)

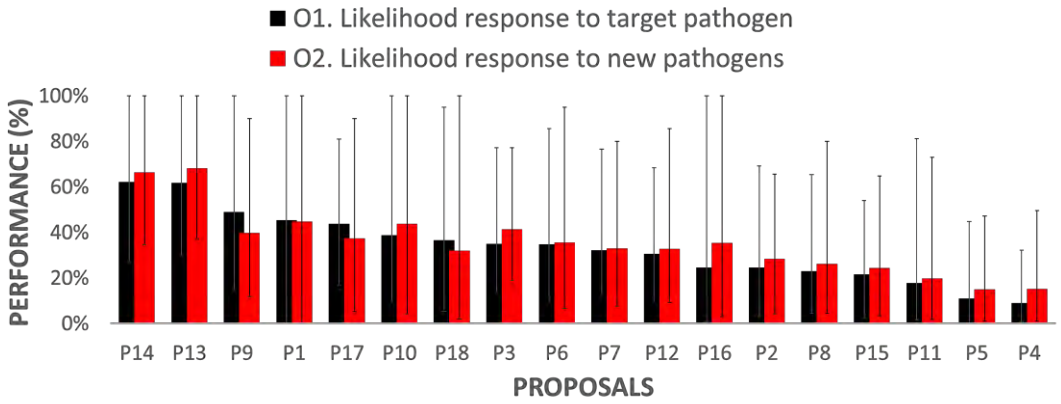
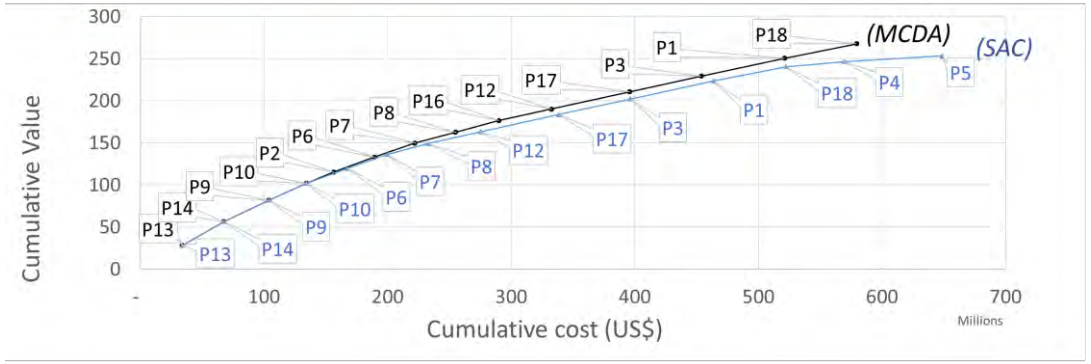


Figure: Proposals ranked by cost-to-mean value in MCDA vs SAC recommendations



- Possible reasons for deviations of MCDA to decisions as per SAC discussions: lower emphasis on cost-to-value; lower emphasis on feasibility and manufacturing scalabiliy and higher emphasis on new pathogen platform potential; platform technology diversity considerations.

3.4. Methods & results (1/2)

3. How can decision analysis support the prioritization of EID vaccine R&D investments given the uncertainties in technology performance and heterogeneity in decision maker preferences?

The challenge (portfolio selection)

- In 2017 CEPI launched a CfP to select a portfolio of platform technologies that would accelerate development of vaccines in response to outbreaks of unknown infections (Strategic obj. 2).
- CEPI faced with complex decisions that involve uncertainty in platform performance and portfolio diversity trade-offs.
- Goal was to assess 16 proposals against criteria of interest to CEPI & identify an optimal portfolio that maximizes value under a $140m constraint, accounting for performance uncertainties and portfolio diversity preferences.

The approach

- Portfolio Decision Analysis employed & compared with SAC recommendations:
  1. Criteria identification via consultations & lit. review.
  2. Performance measurement by 27 experts giving ranges from worst-to-best case performance (%).
  3. Weight elicitation via a DCE.
  4. Optimal portfolio identified via simulation-optimization.
  5. Robustness of findings tested in a Probabilistic Sensitivity Analysis within a Monte Carlo framework.

Table: Criteria CfP Platform technologies to enable rapid vaccine development for epidemic prone infections

Criterion	Metric
C1. Applicant competency	Overall likelihood that the applicant is sufficiently competent to deliver on the proposed activities of the project (0-100%)
C2. Feasibility	Overall 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 (0-100%)
C3. Proof of protection/ Clinical benefit	Overall 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 (0-100%)
C4. Safety potential	Overall 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 (0-100%)
C5. Manufacturing scalability & speed	Overall 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 (0-100%)
C6. Operational suitability	Overall likelihood that the platform will enable stable storage and uncomplicated delivery of vaccine product in an outbreak response under extreme conditions (%)
C7. Operational sustainability	Overall likelihood that the candidate platform developed through this project will remain in use and available to respond to newly emerging or unexpected pathogen outbreaks (0-100%)

OUTCOME MEASURE → **PORTFOLIO VALUE**

$\tilde{p}_{i_k} = \prod_n \tilde{C}_{n_{i_k}}$

Where: criteria C1 to C7 are defined as in table 1.

$\tilde{p}_{i_k}$ = probability of successful development of project *i*, for a given platform technology type *k*.

$\tilde{V}_p = \sum_k^s \tilde{w}_k \cdot {}' \geq \widetilde{1\,PoS'}_k$ *Where:*

V_p = Value of portfolio *p*

w_k = Portfolio diversity weight, i.e. weight given to platform type *k* in a portfolio

$${}' \geq \widetilde{1\,PoS'}_k = 1 - \left(\prod_{i_k}^{s} (1 - \tilde{p}_{i_k}) \right)$$

Figure: Example choice set in the DCE

Carefully review the 3 portfolios shown below, and their characteristics: number of projects and the probability of at least one project being successfully developed by platform technology type. Based on these characteristics, which of the following portfolios would you recommend CEPI invested in?

Platform Type 1	4 projects (60% ≥1 PoS)	2 projects (30% ≥1 PoS)	2 projects (30% ≥1 PoS)
Platform Type 2	4 projects (60% ≥1 PoS)	0 projects (0% ≥1 PoS)	2 projects (30% ≥1 PoS)
Platform Type 3	2 projects (28% ≥1 PoS)	4 projects (56% ≥1 PoS)	2 projects (28% ≥1 PoS)
Platform Type 4	0 projects (0% ≥1 PoS)	0 projects (0% ≥1 PoS)	4 projects (44% ≥1 PoS)
Platform Type 5	2 projects (12% ≥1 PoS)	2 projects (12% ≥1 PoS)	2 projects (0% ≥1 PoS)
	●	●	●

3.4. Methods & results (2/2)

3. How can decision analysis support the prioritization of EID vaccine R&D investments given the uncertainties in technology performance and heterogeneity in decision maker preferences?

Key findings

- Uncertainty in project PoS reflected in substantial overlap and spread of project PoS distributions.
- Decreasing preference to investing in a single platform type as cumulative PoS increases - desire to invest in a diverse portfolio.
- PDA's selection of the optimal portfolio corresponded with the SAC's recommendation to CEPI.
- 54% probability of optimal portfolio outranking 2nd best portfolio, suggesting further due diligence on high risk projects before investments are initiated.

Figure: Portfolio value accounting for platform diversity preferences

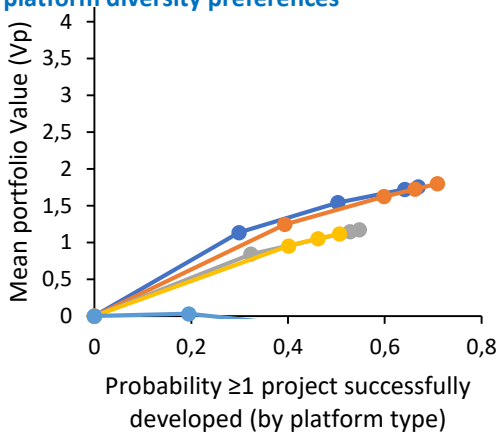


Figure: Optimal portfolio under CEPI budget constraint

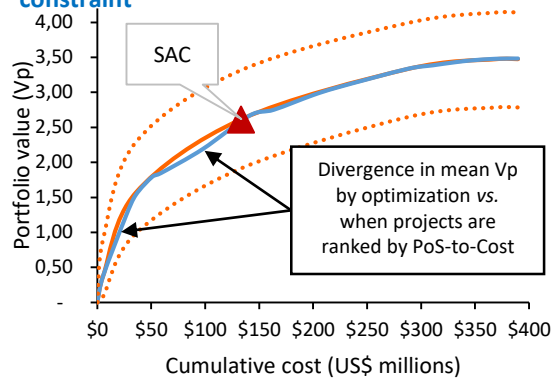
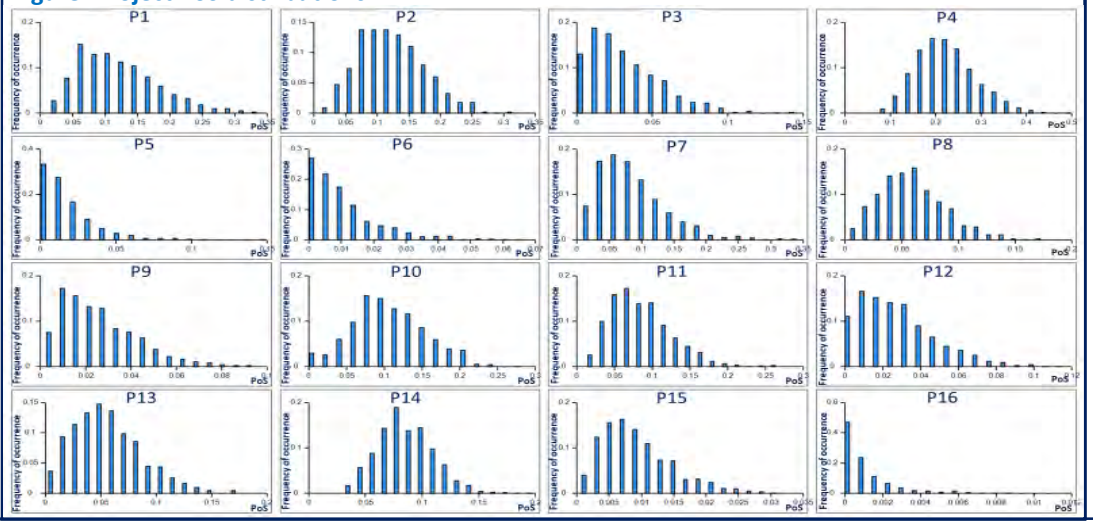
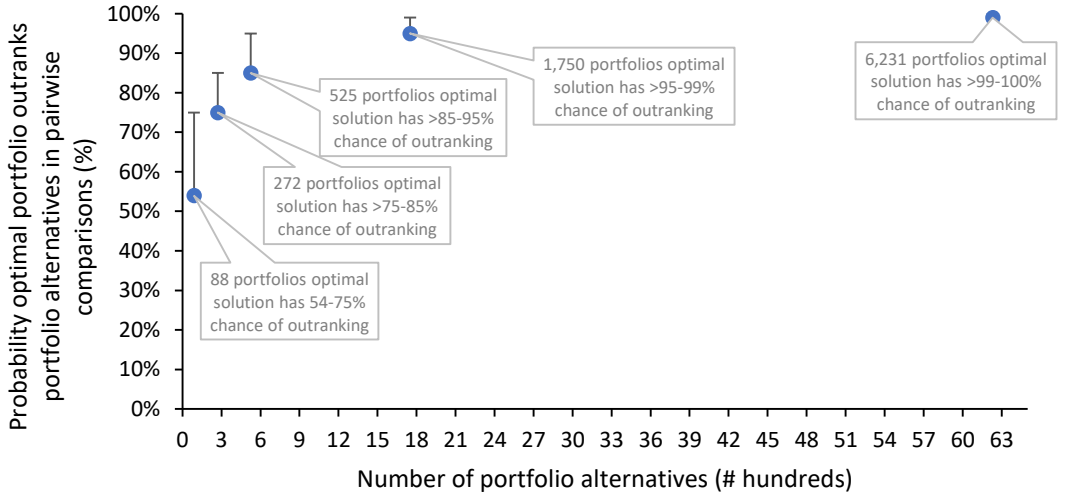


Figure: Project PoS distributions





Conclusions

FINDINGS

- Substantial investment gap, with several EID pipelines empty of new candidates to achieve minimum vaccine R&D preparedness targets.
- A global strategic objective framework established to address gap, with help of rigorous problem structuring methods.
- EID R&D investments prioritized against strategic objectives, aided by decision analytic models to account for large R&D uncertainties and differences in stakeholder perspectives.

LESSONS

- Pipeline and cost optimization modelling can benefit assessments of investment needs in global health R&D.
- Prioritizing investments in complex settings can benefit from clear formulation of strategic objectives, setting the context in which consequent decisions are made.
- Decision analytic tools offer a rational and transparent approach to R&D prioritization if tailored according to identified needs, while balancing rigor with a practical, supportive function.
- As new strategies and governance structures for global health continue to emerge, it will be important to apply such techniques to elicit clear investment priorities through participatory and transparent means.