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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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- 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).

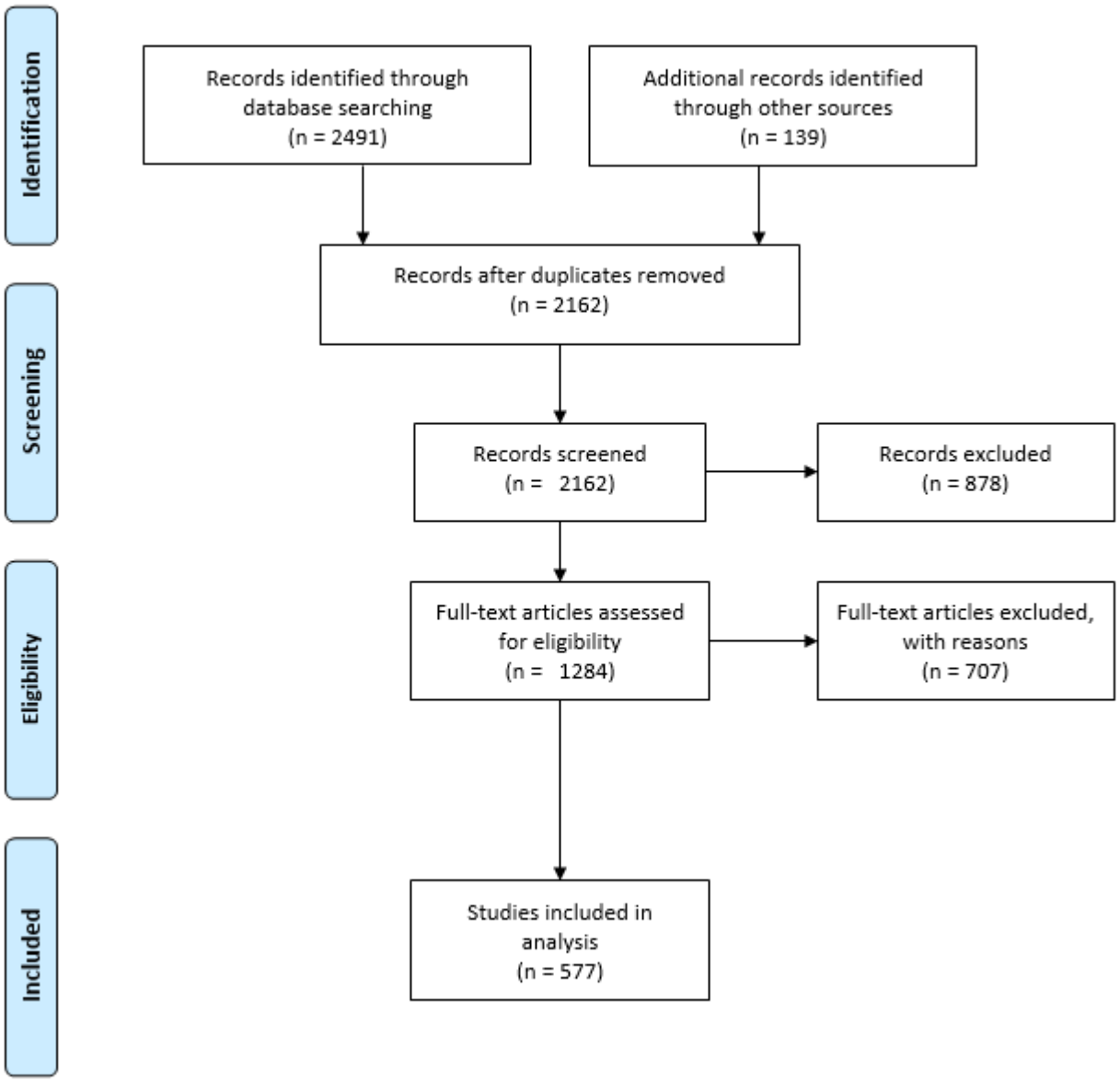
From January 2017 to September 2017 the original pipeline database was updated. Specifically, we applied different search strategies on the following sources:

- **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)

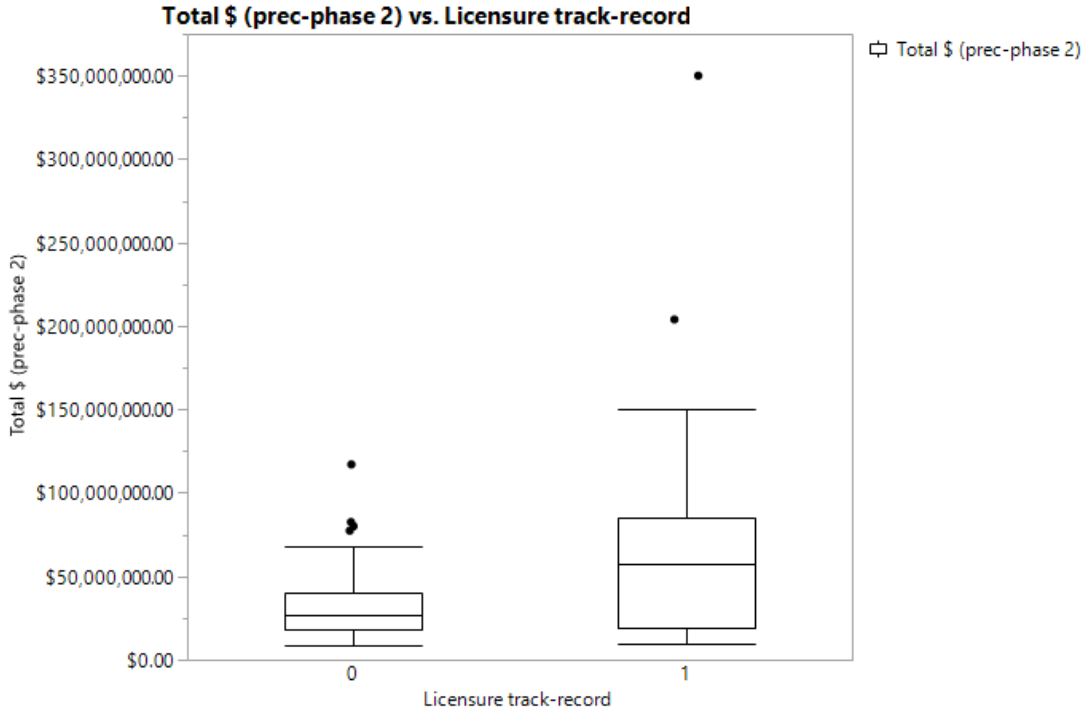
Descriptive Statistic	R&D timeline preclinical through phase II (# years)	Indirect cost share preclinical through phase II (%)
Mean	~7 years	~23%
Standard Deviation	+/-2 years	+/-18%
Median	6 years	20%
Maximum	4 years	79%
Minimum	15 years	0%

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%

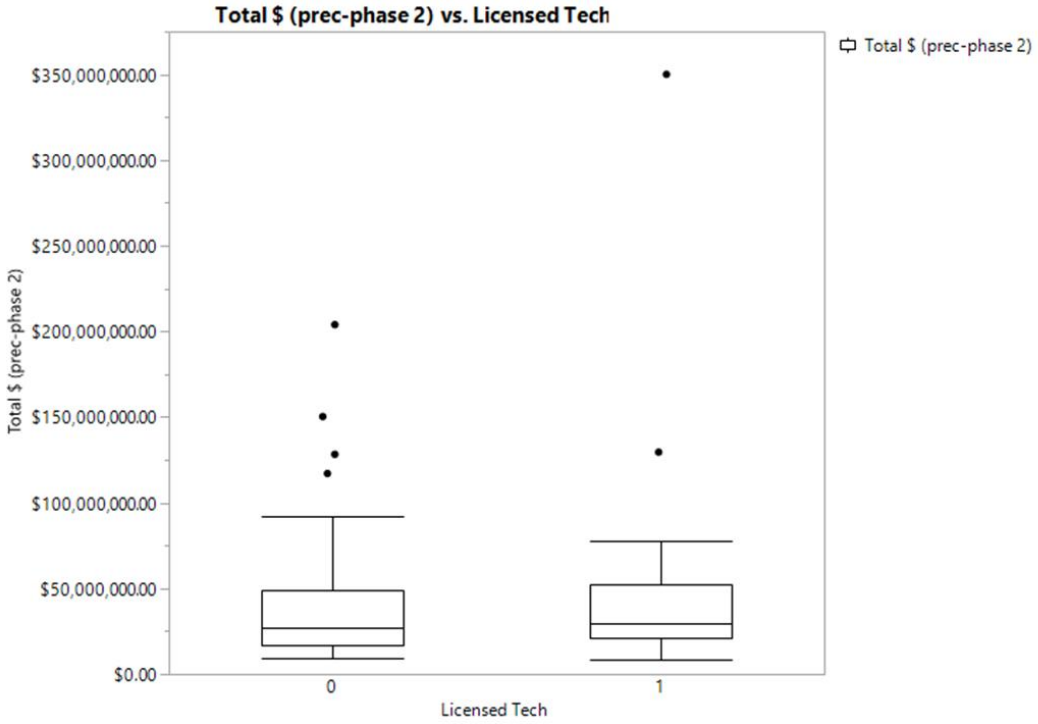
As Appendix box plots 3.1 to 3.4 below demonstrate, the distribution of reported costs from preclinical through phase II is skewed more upwards for vaccine developers with previous vaccine licensure track-record than those without (box plot 1), whereas they are relatively the same for technologies for 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



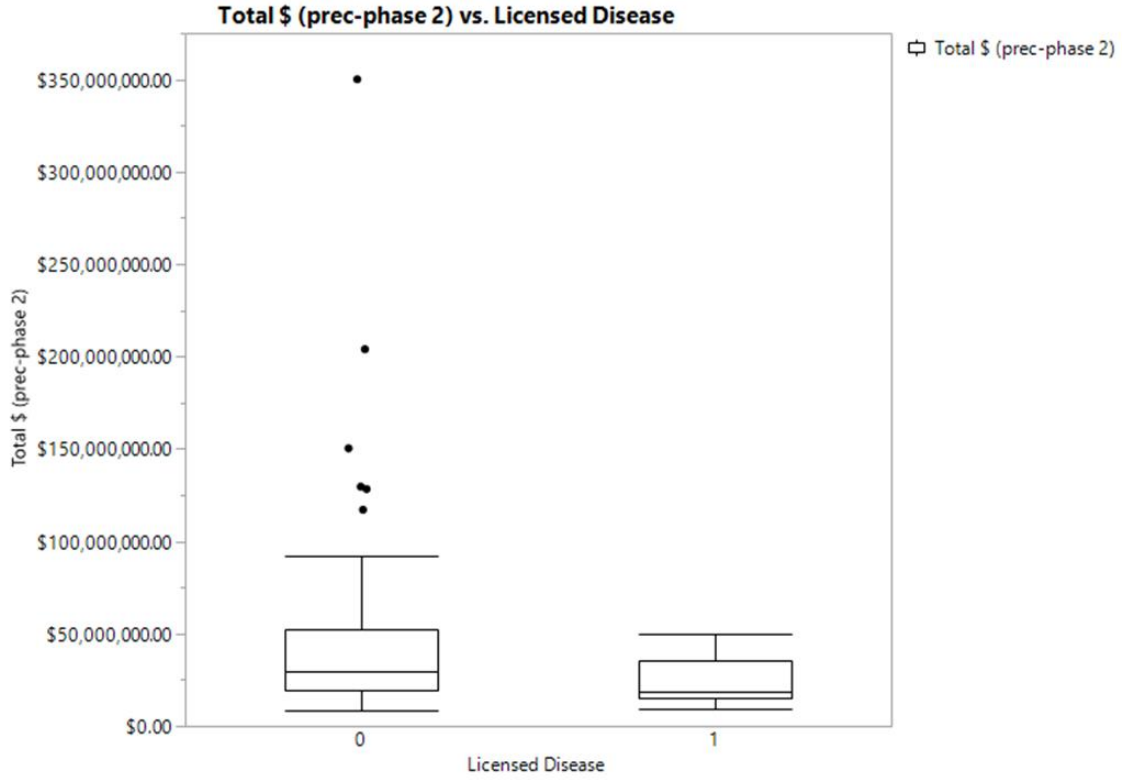
**Number of observations for licensure track-record (=1) = 33*
***Number of observations for no licensure track-record (=0) = 105*

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



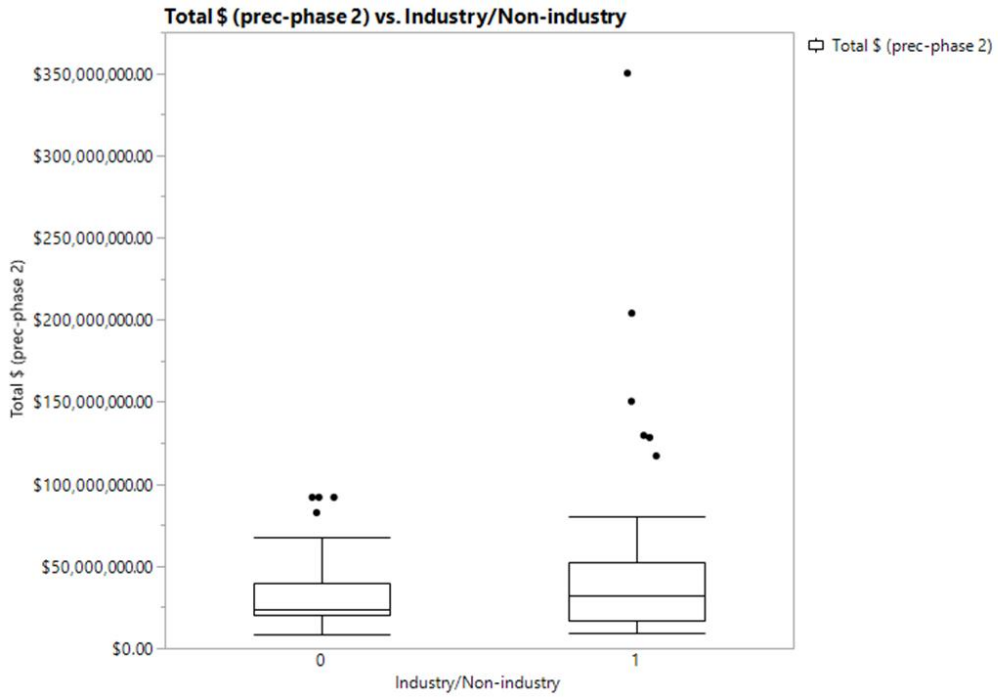
**Number of observations for licensure track-record (=1) = 56*
***Number of observations for no licensure track-record (=0) = 82*
****Platform technologies with licensure track-record include: attenuated virus- based technologies; inactivated pathogen- based technologies; Sub-Unit Protein- based technologies*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

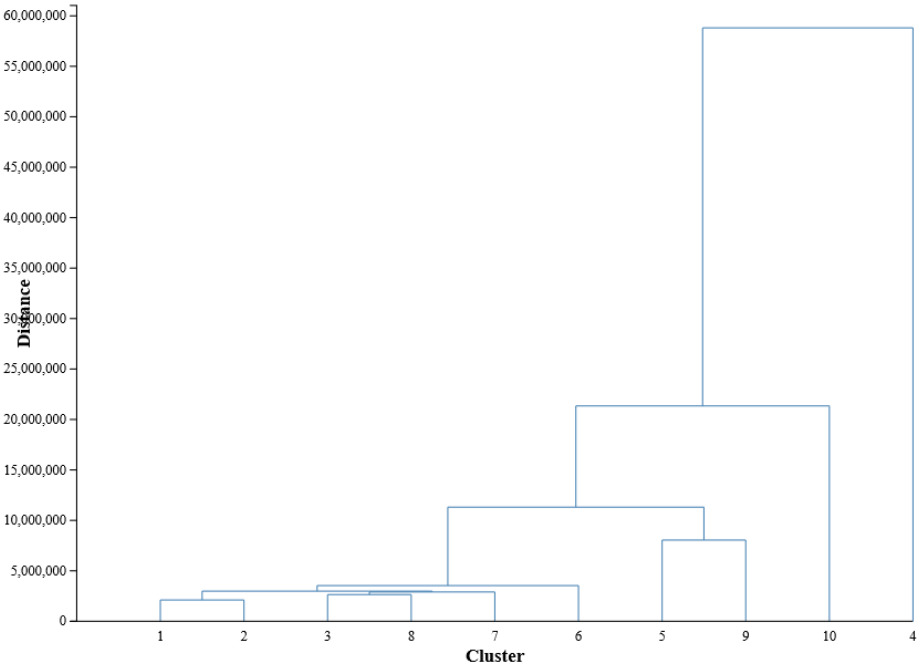
Hierarchical clustering analysis

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).

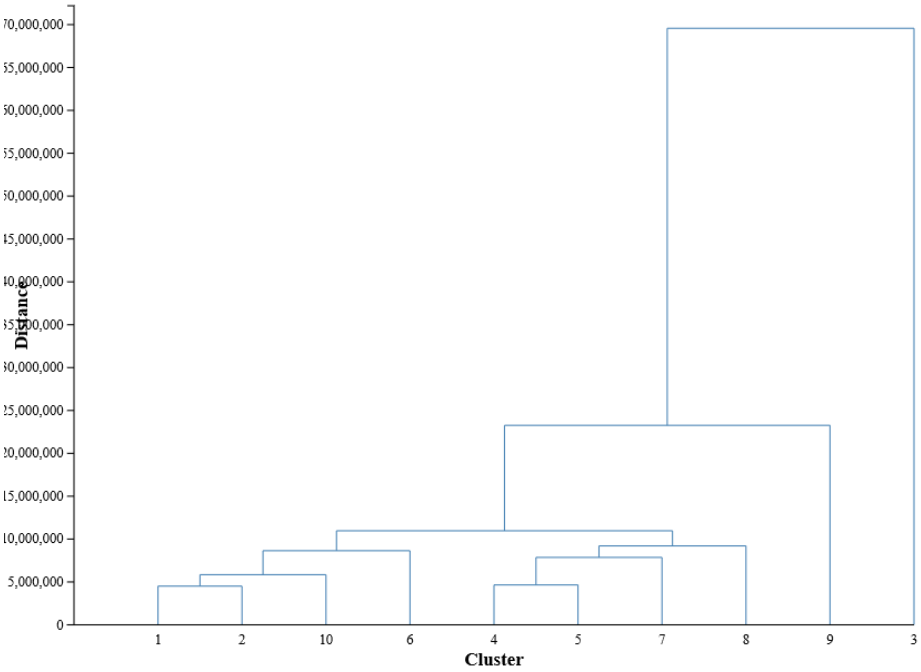
We therefore ran a hierarchical clustering analysis to identify potential clusters of cost estimates in our sample and associated cost drivers not captured in the tested variables above which could improve the explanatory power of the model. We did this by computing the distance between clusters using 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.

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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.

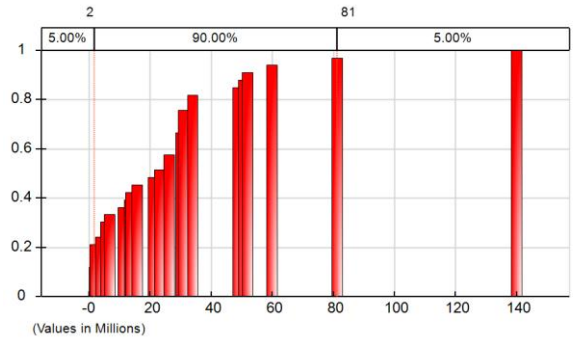
The figures below present the cumulative distribution functions for the lower and upper bounds of vaccine R&D costs by R&D phase. These figures demonstrate that vaccine project costs used for the simulation scenarios fall between:

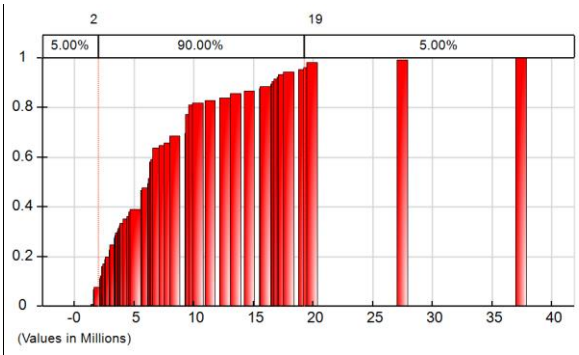
- US$ 1.7m – US$ 140m (upper bound) and US$ 1.8m – US$ 37.4m (lower bound) for preclinical
- US$ 1.9m – US$ 70m (upper bound) and US$ 1m – US$ 30.2m (lower bound) for phase I
- US$ 3.8m – US$ 140m (upper bound) and US$ 4.4m – US$ 54.5m (lower bound) for phase II

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

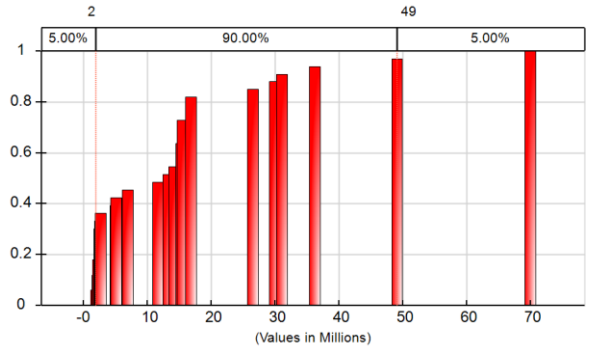
Figures 4.4. to 4.6.: Lower bound cumulative cost distributions by R&D phase, based on product developers with no vaccine licensure track-record

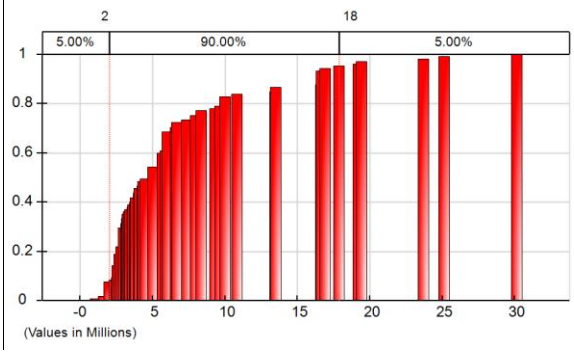
Preclinical phase



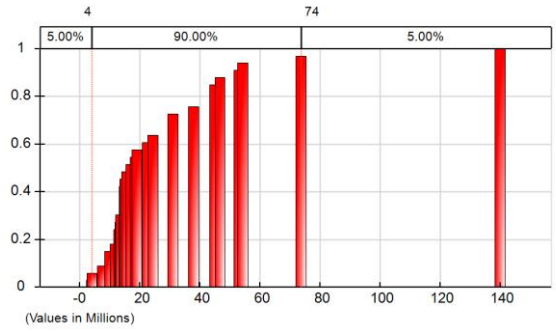


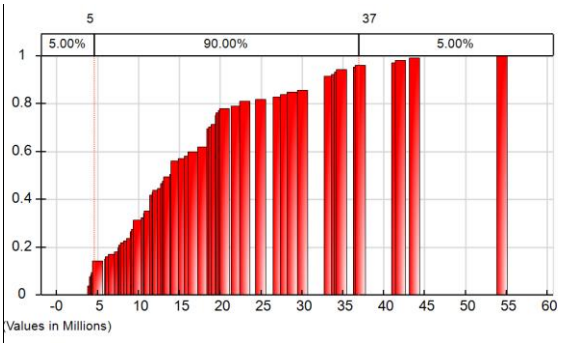
Phase I





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.

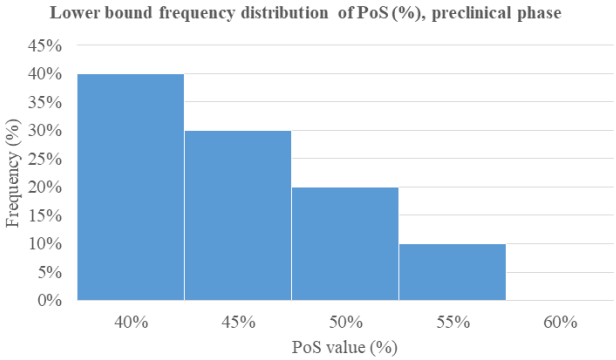
The figures for preclinical phase demonstrate that PoS:

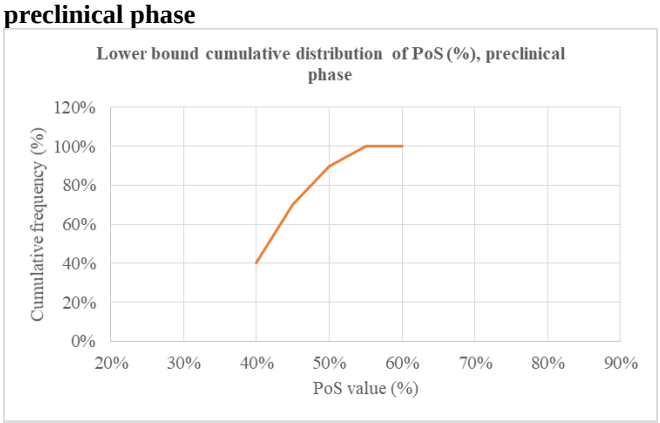
- Has in the *lower bound* scenario a modal value of 40%, and it ranges from 40% to 60%, with over two-thirds of the PoS % value falling between 40% and 45%
- Has in the *base case* scenario the same modal value, ranges and frequency distribution with the lower bound scenario
- Has in the *upper bound*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

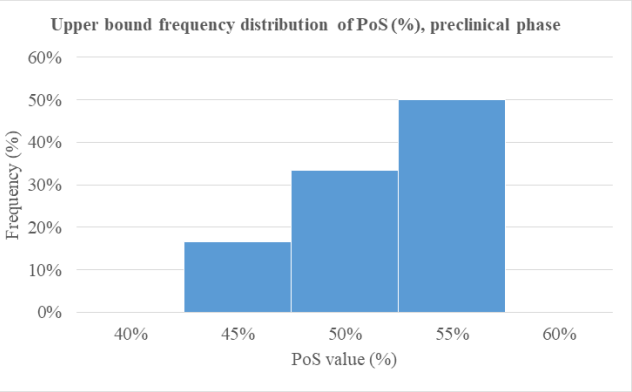
Figures 4.9 to 4.10: Cumulative distributions of PoS (%), preclinical phase

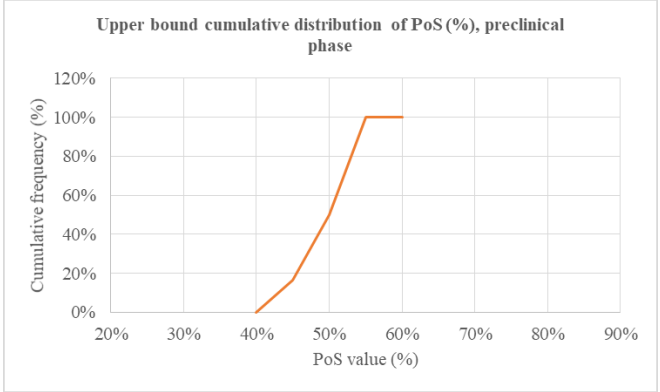
Lower bound





Upper bound





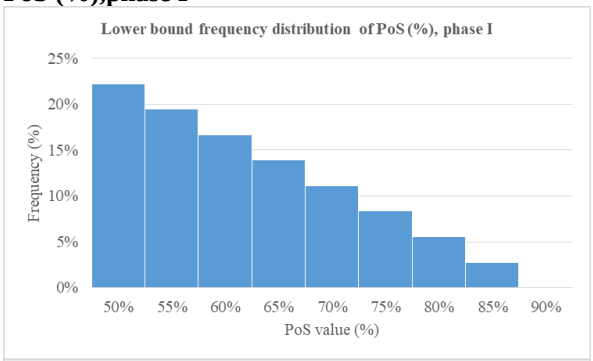
The figures for phase I demonstrate that PoS:

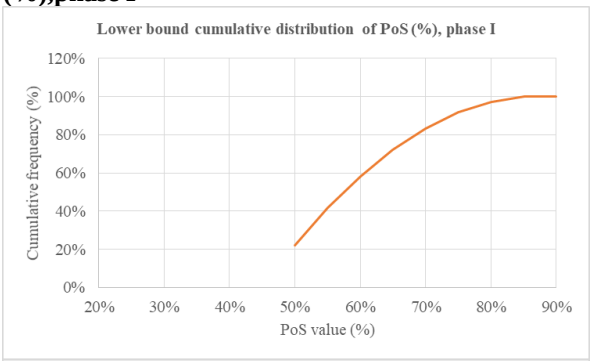
- Has in the *lower bound* scenario a modal value of 50%, and it ranges from 50% to 90%, with half of the PoS % value falling between 50% and 60%
- Has in the *base case* scenario a modal value of 80%, and it ranges from 50% to 90%, with over half of the PoS % value falling between 50% and 75%
- Has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

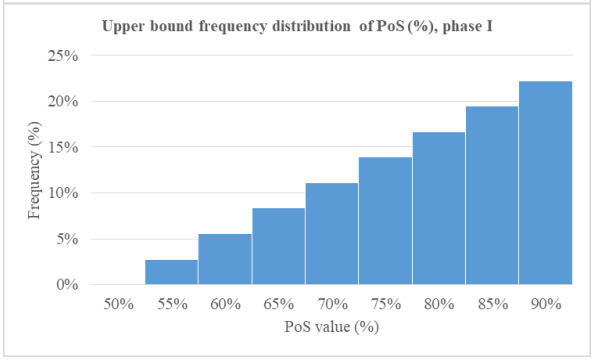
Figures 4.13 to 4.14: Cumulative distributions of PoS (%),phase I

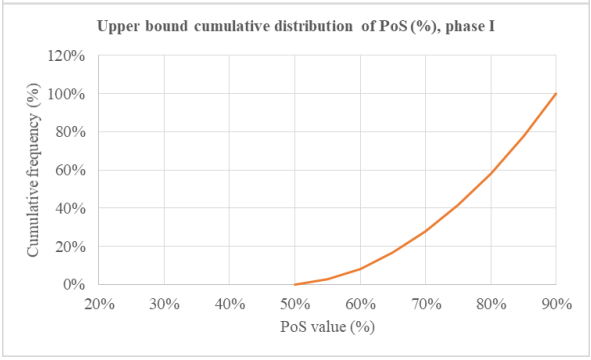
Lower bound





Upper bound





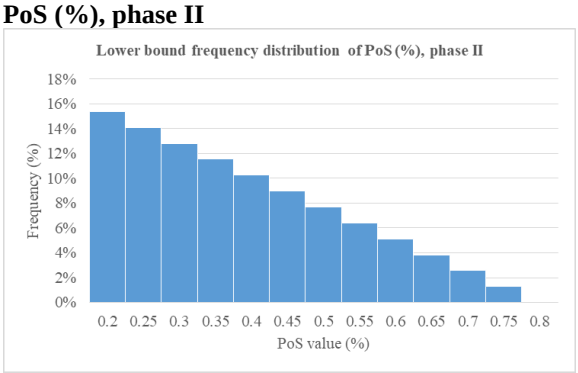
The figures for phase II demonstrate that PoS:

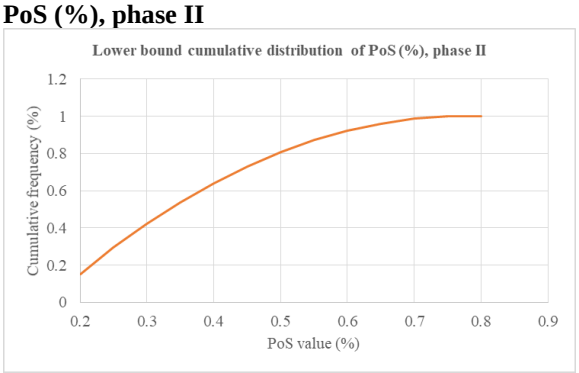
- Has in the *lower bound* scenario a modal value of 20%, and it ranges from 20% to 80%, with half of the PoS % value falling between 20% and 35%
- Has in the *base case* scenario a modal value of 30%, and it ranges from 20% to 80%, with half of the PoS % value falling between 25% and 40%
- Has in the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

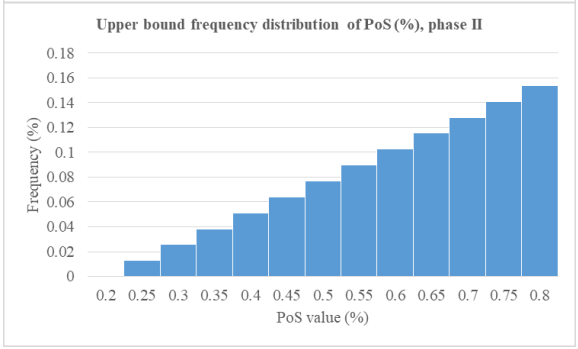
Figures 4.17 to 4.18: Cumulative distributions of PoS (%), phase II

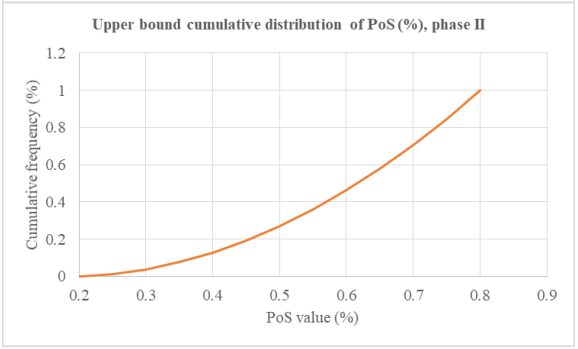
Lower bound





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

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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.

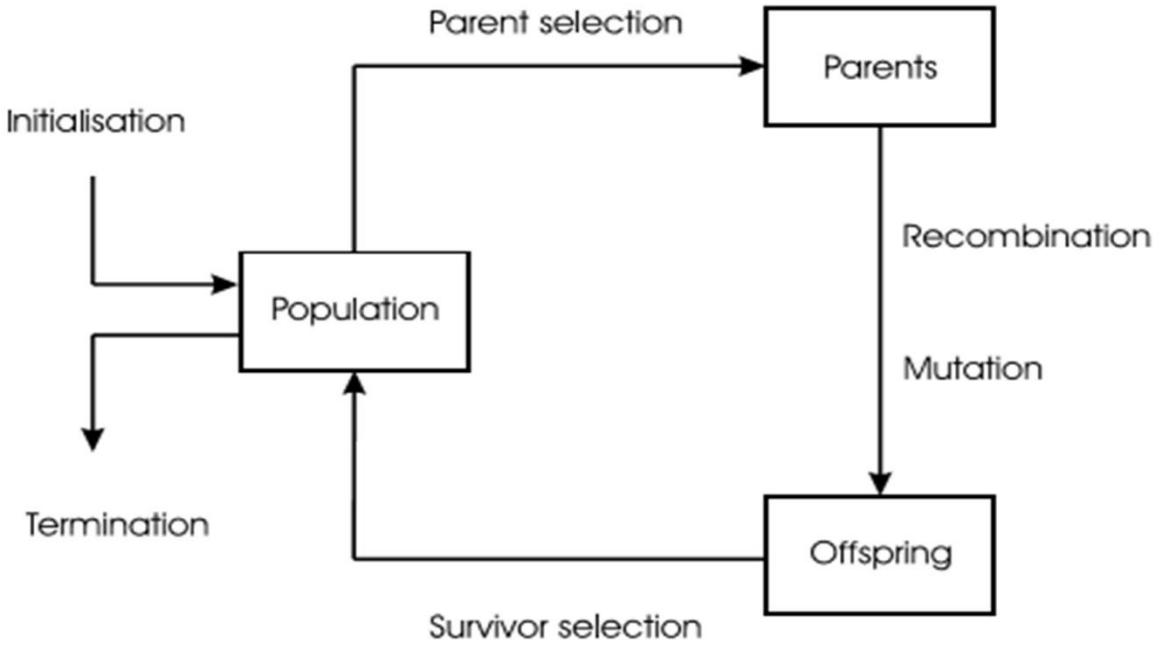
Given the nature of SNP/MIP problems it is unlikely that all possible solutions can be calculated or a globally optimal solution found. In SNP/MIP problems, traditional optimization techniques – such as linear or non-linear convex programming – break down, either due to the irregular structure of the 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 5^{th} and 95^{th} 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

Appendix 5 referecnes

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