

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



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



Summary

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

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

Findings The cost of developing a single epidemic infectious disease vaccine from preclinical trials through to end of phase 2a is US\$31–68 million (US\$14–159 million range), assuming no risk of failure. We found that previous licensure experience and indirect costs are upward drivers of research and development costs. Accounting for probability of success, the average cost of successfully advancing at least one epidemic infectious disease vaccine through to the end of phase 2a can vary from US\$84–112 million (\$23 million–\$295 million range) starting from phase 2 to \$319–469 million (\$137 million–\$1.1 billion range) starting from preclinical. This cost includes the cumulative cost of failed vaccine candidates through the research and development process. Assuming these candidates and funding were made available, progressing at least one vaccine through to the end of phase 2a for each of the 11 epidemic infectious diseases would cost a minimum of \$2.8–3.7 billion (\$1.2 billion–\$8.4 billion range).

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

Funding This work was partly supported by the Research Council of Norway through the Global Health and Vaccination Programme GLOBVAC.

Copyright © 2018 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND 4.0 license.

Introduction

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

In response to the 2014 Ebola epidemic in west Africa, WHO prioritised 11 pathogens that are most likely to cause severe outbreaks in the near future:⁴ Crimean

Congo haemorrhagic fever, chikungunya, Ebola, Lassa, Marburg, Middle East respiratory syndrome coronavirus, Nipah, Rift Valley fever, severe acute respiratory syndrome, severe fever with thrombocytopenia syndrome, and Zika. WHO has now updated this list,⁵ however all 11 diseases remain of considerable epidemic preparedness importance.

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

Lancet Glob Health 2018;
6: e1386–96

Published Online
October 17, 2018
[http://dx.doi.org/10.1016/S2214-109X\(18\)30346-2](http://dx.doi.org/10.1016/S2214-109X(18)30346-2)

See [Comment](#) page e1266

Norwegian Institute of Public Health, Oslo, Norway (D Gouglas MSc); CEPI—Coalition for Epidemic Preparedness Innovations, Oslo, Norway (D Gouglas MSc, T Thanh Le MSc, K Henderson PhD, T Danielsen MSc, N C Hammersland MSc); Independent consultant, North Balgowlah, NSW, Australia (K Henderson PhD); Norwegian University of Science and Technology, Faculty of Economics, Department of Industrial Economics and Technology Management, Gjøvik, Norway (Prof A Kaloudis PhD); Independent consultant, Chester, MD, USA (J M Robinson MS); Bill & Melinda Gates Medical Research Institute, Cambridge, MA, USA (P M Heaton MD); and Research Council of Norway, Lysaker, Norway (Prof J-A Røttingen MD)

Correspondence to: Dimitrios Gouglas Research Fellow, Norwegian Institute of Public Health, Bygg D, 0473 Oslo, Norway
dimitrios.gouglas@fhi.no

Research in context

Evidence before this study

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

Added value of this study

Our study presents a comprehensive dataset of vaccine research and development candidates against 11 epidemic infectious diseases, which combines a systematic search of a substantially sized literature and the confirmation of current development status of these candidates by vaccine developers active in the field. Moreover, our study attempts to overcome

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

Implications of all the available evidence

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

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

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

CEPI has committed to fundraise and invest at least US\$1 billion until 2021.¹⁰ Our previous analysis, which was presented as part of the CEPI preliminary business plan 2017–21,¹¹ examined the total number of vaccine candidates CEPI would need to invest in today, to advance two to three candidates for two to three epidemic infectious diseases through to phase 2a and stockpile

for phase 2b–3 and emergency use in 5 years, under a \$1 billion budget constraint.

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

Methods

Study design

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

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

Data collection

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

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

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

N/A=not applicable.

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

outbreaks, including stockpile estimates for phase 3 trials and for emergency use (the latter not reported in the paper); specify main drivers of R&D costs and technical success to date and identify potential drivers of future costs and technical risks for bringing vaccine candidates through late phases of clinical development. Organisations were those whom we identified as owners, partners, or supporters of epidemic infectious disease vaccine research and development (appendix).

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

Drivers of vaccine development costs

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

See Online for appendix

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

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

Table 2: Stochastic optimisation model parameters across solution stages

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

Expected vaccine research and development costs

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

or most likely, values that collectively define the boundaries and shape of the distribution triangles (appendix).

To move from single vaccine candidate costs to portfolio costs accounting for probability of success, we ran the simulation 10000 times, each time randomly drawing from the following: cost distributions—for each group and research and development phase, each iteration randomly selected one cost estimate from the respective distribution; probability of success distributions—for each research and development phase, each iteration randomly drew a probability of success estimate from the respective distribution.

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

Stochastic optimisation of research and development portfolios and costs

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

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

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

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

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

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

In this model, we treated cost and probability of success by research and development phase parameters as random variables with the same distributions as in the simulation. The stochastic modelling approach ensured the robustness of our optimisation findings—ie, allowed

us to run probabilistic sensitivity analyses on all the outputs of the model, capturing both the sources of variability as well as the probabilities attached to different modelling outputs expected (see appendix for more details).

Role of the funding source

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

Results

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

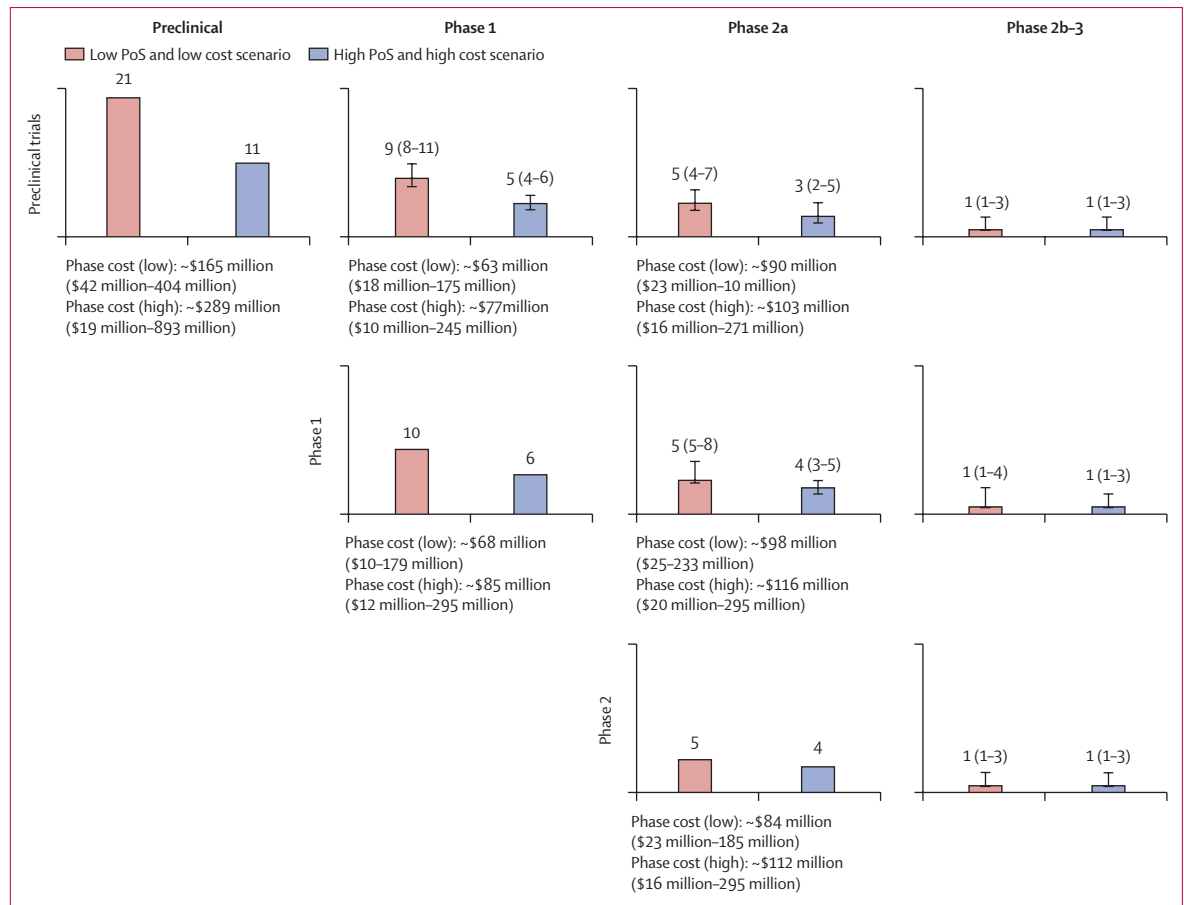


Figure: Estimated cost of progressing at least one epidemic infectious disease vaccine from preclinical through to end of phase 2a
PoS=probabilities of success. Figures in US\$.

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

Reported vaccine development costs from preclinical testing through to end of phase 2a range from \$8 million to \$350 million (table 3). Based on the regression analysis, previous licensure experience and indirect costs associated with operating models of vaccine developers are statistically significant explanatory factors driving an increase in research and development costs. Previous licensure of vaccines for a given disease can potentially drive a reduction in research and development costs. However, a licensed prophylactic vaccine for humans does not exist for any of the 11 epidemic infectious diseases. A hierarchical clustering analysis suggests that increased research and development costs in

clinical research and development phases may also potentially be associated with increased industrial sector affiliation. Substantial variation in reported costs cannot be explained despite considering several factors, including, in addition to the above, research and development timelines and previous licensure track-record of platform technologies (appendix).

The simulation suggests that the advancement of a single epidemic infectious disease vaccine candidate from preclinical through end of phase 2a can cost \$31–68 million (\$14–159 million range), assuming no risk of failure (table 3). However, the total cost of progressing one epidemic infectious disease vaccine successfully through to end of phase 2a is dependent on the probability of success and on the shape of the vaccine research and development pipeline. As the figure demonstrates, accounting for probability of success and assuming no clinical vaccine candidates exist for a given epidemic infectious disease, 11 to 21 preclinical candidates would be required if at least one of these were to progress through to end of phase 2a, at a cost of \$319–469 million (\$137 million–\$1.1 billion range). Similarly, six to ten phase 1 candidates would

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

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

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

be needed for at least one candidate to advance through to end of phase 2a, at a cost of \$167–201 million (\$61 million–\$485 million range). Assuming vaccine candidates and funding were made available, progressing at least one vaccine through to end of phase 2a for each of the 11 epidemic infectious diseases would cost a minimum of \$2.8–3.7 billion (\$1.2 billion–\$8.4 billion range). Finally, at least one candidate would progress through to end of phase 2a, out of initial investments of \$84–112 million (\$23 million–\$295 million range) in four to five phase 2 candidates.

At the time of writing, there are 194 preclinical trials, 24 phase 1, and six phase 2 vaccine candidates under development for 11 epidemic infectious diseases. As table 4 demonstrates, 13 candidates (six to 34 range) would progress through to end of phase 2a at a cost of \$3.6 billion (\$1.6–6.6 billion range), in a low probability of success and low cost scenario (table 4). Under a high probability of success and high cost scenario, the cost for 43 phase 2b–3 ready candidates (26–70 range) would amount to \$9.8 billion (\$2.4–21.6 billion range). Seven epidemic infectious diseases—Zika, Ebola, chikungunya, Rift Valley fever, Marburg, and Lassa—have sufficient vaccine pipelines for investments (if made available) to guarantee successful phase 2a outcomes regardless of probability of success (in reality, phase 2b–3 ready candidates already exist for Ebola). Under a low probability of success scenario, the successful progression of a vaccine through to end of phase 2a cannot be guaranteed for Nipah, given the available candidates for this epidemic infectious disease. Vaccine pipelines for Crimean Congo haemorrhagic fever, severe acute respiratory syndrome, and severe fever with thrombocytopenia syndrome comprise too few candidates for any phase 2a outcomes to be predicted

through investments in these, even under a more optimistic probability of success.

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

A probabilistic sensitivity analysis is embedded in the findings through stochastic modelling (appendix). This analysis demonstrates that whereas zero phase 2a outcomes are unlikely given the numbers of vaccine candidates supported by research and development phase under the low and high probability of success scenarios, outcomes previously mentioned and beyond one phase 2b–3 ready candidate per epidemic infectious disease are dependent on the probability of success. In a scenario in which low costs were associated with high probability of success distributions, the same numbers of vaccine candidates would need to be supported as per the high probability of success and high cost scenario to achieve minimum phase 2a outcomes per epidemic infectious disease, but the overall portfolio cost would reduce to US\$1.6 billion (\$715 million–2.9 billion range). In contrast, in a scenario where high costs were associated with low probability of success distributions,

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

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

the same numbers of vaccine candidates would need to be funded as per the low probability of success and low cost scenario to successfully advance at least one vaccine through to end of phase 2a successfully. In this case, however, the associated portfolio cost would increase to \$6.8 billion (\$1.5-15.1 billion range; appendix).

Discussion

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

Our analysis demonstrates that it is possible to use simulation-optimisation techniques to generate vaccine

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

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

The handful of articles published on vaccine research and development costs to date are either too descriptive or based on expert opinions with little data input to validate those claims,^{16,28,35} focusing on single pathogens¹⁵ or only on clinical research and development phases.^{15,28} Studies^{3,36}—one drawing on source data and assumptions from the other—have attempted to overcome several of the above limitations, focusing their analyses on either poverty diseases or epidemic infectious diseases, which are both characterised by poor commercial potential, as well as differentiating more systematically between costs associated with incremental versus breakthrough innovations.^{3,36}

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

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

Our study has several limitations. First, the average vaccine development project cost estimates, from which

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

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

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

Fourth, our analysis is limited in scope to 11 priority epidemic infectious diseases. There are many other infectious diseases of epidemic potential that deserve attention according to different priority lists⁴¹ and experts'

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

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

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

Seventh, the study estimates costs for only a small part of a much bigger picture in epidemic infectious disease vaccine research and development preparedness. The research and development scope of our analysis is restricted to preclinical, phase 1, and phase 2a. It excludes costs associated with phase 2b–3 trials, stockpiles of phase 2b–3 ready material, regulatory, and delivery activities (including for having in-country infrastructure to support emergency response activities)—all critical elements of vaccine research and development preparedness needs in response to public health emergencies.

Issues pertaining to clinical trial design, locations, and target populations of clinical studies, are some of the many factors that are likely to drive clinical development costs but which have not been explicitly considered in our study. These issues, together with factors pertaining to stockpile strategies and phase 2b–3 trial complexities under different disease outbreak scenarios, clinical trial designs, and regulatory requirements, deserve special attention and a separate analysis, which we hope a future study will provide.

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

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

Contributors

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

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

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank the CEPI CEO, Dr Richard Hatchett, and the CEPI Deputy CEO, Dr Frederik Kristensen, as well as all CEPI staff for their technical support, enthusiasm, and facilitation of a smooth implementation of the study.

We are grateful to all vaccine development organisations and their funders who have provided us with vaccine research and development pipeline and cost information relevant to this study. The views and opinions expressed in this Article are those of the authors and do not necessarily represent the official position or opinion of CEPI as an organisation.

References

- Kieny MP, Röttingen JA, Farrar J, on behalf of the WHO R&D Blueprint team and the R&D Blueprint Scientific Advisory Group. The need for global R&D coordination for infectious diseases with epidemic potential. *Lancet* 2016; **388**: 460–61.
- Norwegian Institute of Public Health. Outcome document financing of R&D preparedness and response to epidemic emergencies. Oct 29–30, 2015. Oslo, Norway. <http://www.who.int/medicines/ebola-treatment/Outcome.pdf?ua=1> (accessed Sept 30, 2018).
- World Health Organization. An R&D blueprint for action to prevent epidemics: Funding & coordination models for preparedness and response. May 2016. http://www.who.int/csr/research-and-development/workstream_5_document_on_financing.pdf (accessed March 28, 2017).
- World Health Organization. An R&D blueprint for action to prevent epidemics: Plan of Action. May 2016. http://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf?ua=1 (accessed Sept 30, 2017).
- World Health Organization. List of Blueprint priority diseases. <http://www.who.int/blueprint/priority-diseases/en/> (accessed Feb 21, 2018).
- Pronker ES, Weenen TC, Commandeur H, Claassen EH, Osterhaus AD. Risk in vaccine research and development quantified. *PLoS One* 2013; **8**: e57755.
- Chapman N, Abela-Oversteegen L, Doubell A, Chowdhary V, Gurjav U, Ong M. Policy cures research: Neglected disease research and development: a pivotal moment for global health. 2016. <http://www.policycuresresearch.org/downloads/Y9%20GFINDER%20full%20report%20web.pdf> (accessed July 25, 2018).
- Plotkin SA, Mahmoud AAF, Farrar J. Establishing a global vaccine-development fund. *N Engl J Med* 2015; **373**: 297–300.
- Röttingen JA, Gouglas D, Feinberg M, et al. New vaccines against epidemic infectious diseases. *N Engl J Med* 2017; **376**: 610–13.
- Brende B, Farrar J, Gashumba D, et al. CEPI—a new global R&D organisation for epidemic preparedness and response. *Lancet* 2017; **389**: 233–35.
- Coalition for Epidemic Preparedness Innovations. Coalition for Epidemic Preparedness Innovations preliminary business plan 2017–2021. November 2016. <http://cepi.net/sites/default/files/CEPI%20Preliminary%20Business%20Plan%20061216.pdf> (accessed Feb 9, 2017).
- Davis MM, Butchart AT, Coleman MS, et al. The expanding vaccine development pipeline, 1995–2008. *Vaccine* 2010; **28**: 1353–56.
- Struck M. Vaccine R&D success rates and development times. *Nat Biotechnol* 1996; **14**: 591–92.
- BIO—Biotechnology Innovation Organization. Clinical development success rates 2006–2015. 2015. <https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf> (accessed July 25, 2018).
- Chit A, Parker J, Halperin SA, Papadimitropoulos M, Krahn M, Grootendorst P. Toward more specific and transparent research and development costs: the case of seasonal influenza vaccines. *Vaccine* 2014; **32**: 3336–40.
- Wilson P. Giving developing countries the best shot: an overview of vaccine access and R&D. Campaign for access to essential medicines, Medecins Sans Frontieres. April 2010. https://d1tn3vj7xz9fdh.cloudfront.net/s3fs-public/file_attachments/giving-developing-countries-best-shot-vaccines-2010-05_4.pdf (accessed Feb 6, 2018).
- DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003; **22**: 151–85.
- Wong CH, Siah KW, Lo AW. Estimation of clinical success rates and related parameters. *Biostatistics* 2018; published online Jan 31. DOI:10.1093/biostatistics/kxx069:1–14.
- Scherer FM. Research and development costs and productivity in biopharmaceuticals A2. In: Culyer AJ, ed. *Encyclopedia of health economics*. San Diego: Elsevier, 2014: 249–55.
- Gregersen JP. Scientific, technical, and economic aspects of vaccine research and development, 2nd edn. In: Kayser O, Warzecha H, eds. *Pharmaceutical biotechnology*. Weinheim: Wiley-VCH Verlag, 2012: 371–88.
- DiMasi JA, Grabowski HG, Vernon J. R&D costs and returns by therapeutic category. *Drug Inf J* 2004; **38**: 211–23.
- DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. Cost of innovation in the pharmaceutical industry. *J Health Econ* 1991; **10**: 107–42.
- DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. Research and development costs for new drugs by therapeutic category. A study of the US pharmaceutical industry. *Pharmacoeconomics* 1995; **7**: 152–69.
- Adams CP, Brantner VV. Estimating the cost of new drug development: is it really \$802 million? *Health Aff* 2006; **25**: 420–28.
- DiMasi JA, Grabowski HG. The cost of biopharmaceutical R&D: is biotech different? *Manage Decision Econ* 2007; **28**: 469–79.
- DiMasi JA, Grabowski HG. Economics of new oncology drug development. *J Clin Oncol* 2007; **25**: 209–16.
- DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ* 2016; **47**: 20–33.
- Light DW, Andrus JK, Warburton RN. Estimated research and development costs of rotavirus vaccines. *Vaccine* 2009; **27**: 6627–33.
- Mestre-Ferrandiz J, Sussex J, Towse A. The R&D cost of a new medicine. 2012. London: Office of Health Economics. <https://www.ohe.org/publications/rd-cost-new-medicine#> (accessed July 25, 2018).
- Morgan S, Grootendorst P, Lexchin J, Cunningham C, Greyson D. The cost of drug development: a systematic review. *Health Policy* 2011; **100**: 4–17.
- Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov* 2010; **9**: 203–14.
- Rawlins MD. Cutting the cost of drug development? *Nat Rev Drug Discov* 2004; **3**: 360–64.
- Vernon JA, Golec JH, Dimasi JA. Drug development costs when financial risk is measured using the Fama–French three-factor model. *Health Econ* 2010; **19**: 1002–05.
- Waye A, Jacobs P, Schryvers AB. Vaccine development costs: a review. *Expert Rev Vaccines* 2013; **12**: 1495–501.
- Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing—an overview. *Vaccine* 2017; **35**: 4064–71.
- Special Programme for Research and Training in Tropical Diseases (TDR). Health product research & development fund: a proposal for financing and operation. World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases 2016. http://apps.who.int/iris/bitstream/10665/204522/1/9789241510295_eng.pdf?ua=1 (accessed March 29, 2017).
- Fairchild KW, Misra L, Shi Y. Using triangular distribution for business and finance simulations in Excel. *J Financial Educ* 2016; **42**: 313–36.
- Perez-Escobedo JL, Azzaro-Pantel C, Pibouleau L. Multiobjective strategies for New Product Development in the pharmaceutical industry. *Comput Chem Eng* 2012; **37**: 278–96.
- Pronker ES, Weenen TC, Commandeur HR, Osterhaus ADME, Claassen HJHM. The gold industry standard for risk and cost of drug and vaccine development revisited. *Vaccine* 2011; **29**: 5846–49.
- Henaio-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* 2017; **389**: 505–18.