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Systematic Literature Review

A Scoping Review of Investment Cases for Vaccines and Immunization Programs

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ABSTRACT

Background: Many investment cases have recently been published intending to show the value of new health investments, but without consistent methodological approaches.

Objectives: To conduct a scoping review of existing investment cases (using vaccines and immunization programs as an example), identify common characteristics that define these investment cases, and examine their role within the broader context of the vaccine development and introduction.

Methods: A systematic search was conducted from January 1980 to November 2017 to identify investment cases in the area of vaccines and immunization programs from gray literature and electronic bibliographic databases. Investment case outcomes, objectives, key variables, target audiences, and funding sources were extracted and analyzed according to their reporting frequency.

Results: We found 24 investment cases, and most of them aim to provide information for decisions (12 cases) or advocate for a specific agenda (9 cases). Outcomes presented fell into 4 broad categories—burden of disease, cost of investment, impact of investment, and other considerations for implementation. Number of deaths averted (70%), incremental cost-effectiveness ratios (67%), and reduction in health and socioeconomic inequalities (54%) were the most frequently reported outcome measures for impact of investment. Health system capacity (79%) and vaccine financing landscape (75%) were the most common considerations for implementation. A sizable proportion (41.4%) of investment cases did not reveal their funding sources.

Conclusions: This review describes information that is critical to decision making about resource mobilization and allocation concerning vaccines. Global efforts to harmonize investment cases more broadly will increase transparency and comparability.

Keywords: cost, immunization, investment, systematic reviews, vaccine, value.

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Introduction

Governments and funders face high demand for health investment to achieve progress toward national health objectives and Sustainable Development Goals. In recent years, there has been an increasing number of reports described as "investment cases" that aim to articulate the need for specific investments in health.

Some investment cases argue for greater resource mobilization for the health sector in achieving the global development goals.[1] For example, the World Health Organization (WHO) recently published its first investment case to demonstrate the health and economic impact of increased funding for its strategic plan for 2019 to 2023.[2] Other investment cases target specific health interventions, advocating for increased funding at the global or country levels for areas such as community health worker programs,[3] breastfeeding,[4] and noncommunicable disease prevention.[5] The Global Financing Facility, an innovative financing mechanism for women, child, and adolescent health and nutrition, requires countries to develop their own investment case as a planning tool for identifying sector priorities and strategizing longer term financing.[6]

Conflicts of interest: The authors do not have any conflicts of interest directly relevant to the content of this article.

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Similarly, investment cases have also been actively used for decision making in vaccine development and introduction. The Global Vaccine Action Plan states that countries dealing with different priorities should consider that "expenditures must be linked to outputs and impacts showing a clear investment case for immunization."[7] Because of limited resources, immunization program funders need to set their priorities on the basis of available information about vaccines.[8] In addition, summary measures such as return on investment have informed decision makers about the return for every dollar invested in immunization in comparison with that of other social sector investments.[9,10]

Despite their increasing popularity, the definition and scope of an investment case in health are still poorly defined and have not been systematically studied in many key areas, such as vaccines and related immunization programs. For the growing number of investment cases to usefully inform resource allocation decisions, there needs to be a clearer definition of what investment cases are and how they benefit stakeholders with diverse information needs.

To address this issue, we conducted a scoping review of investment cases in the area of vaccines and immunization programs, an area where investment cases have been particularly popular. We identified common characteristics that define investment cases for vaccines and immunization programs and examined their role within the broader context of the vaccine development and introduction.

Methods

A systematic search of the literature was conducted from January 1980 to November 2017 to identify existing investment cases for vaccine and immunization programs that are available online in the public domain. Because many investment cases are not published in the academic literature, the systematic search targeted 2 sources of information: (1) websites of major organizations in the field of vaccines and immunization programs and (2) electronic bibliographic databases.

The review included hand searches for gray literature available on 42 websites of major public health organizations, development partnerships, manufacturers, associations, product development partnerships, and networks (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.002). The websites were identified via expert consultations as well as customized Google searches. Published articles, abstracts, and meeting reports were identified through 7 electronic bibliographic databases: PubMed (MEDLINE), EMBASE, Web of Science, WHO Index Medicus, Econlit with Full Text (EBSCOhost), Business Abstracts with Full Text (EBSCOhost), and ABI/INFORM Collection (ProQuest).

Any work in the public domain that was described as "investment case," "case for investment," "value proposition," or "business case" for vaccines, vaccine-related technologies, or immunization was included in the review (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.002). Search terms were broken down into 2 concepts, which include terms related to (1) vaccine or immunization and (2) investment case. Relevance of the search results using such alternative terms was determined through full-text article assessment using full eligibility criteria (see Appendix 2 in Supplemental Materials). More details on search terms specific to databases are available in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.002.

Although the principles of systematic search have been applied to this review, gray literature search inherently faces the challenges of selection bias due to the absence of proper indexing, limited functionality of Boolean searching, and lack of reproducibility of the search process, among others. Given these limitations, all stages of literature review including execution, screening, and information management adopted proper strategies to mitigate the risk of introducing unintentional bias.[11] In executing the search, key terms and the search process for each website were documented in a spreadsheet in accordance with record-keeping principles. Preliminary screening took place simultaneously with search using the eligibility criteria, and only the relevant items were saved for further examination. For investment cases for which the content was only partially available, the authors were contacted and asked to provide the full versions. Additional investment cases were identified during the process.

Once duplicate citations were removed, all remaining materials were screened on the basis of titles and abstracts. In the next stage, full-text articles and gray literature were assessed according to the full eligibility criteria (see Appendix 3 in Supplemental Materials). The review aimed to identify investment cases of ex-ante nature for any technologies or activities related to vaccines and immunization. The basic information about the investment cases, such as year of publication, authors, type of vaccine, target audience, and stated objective, was extracted as reported by the authors.

For the categories of outcomes, given the lack of standardized definitions for investment cases, the initial data extraction form did not contain a predefined set of criteria, and new types of outcomes were added as they were identified from each investment case. The initial form was revised after finding relevant new criteria, and all cases were reviewed again according to the revised set of outcomes. Each outcome was recorded in a particular category on the basis of whether it was described in the investment case qualitatively or quantitatively, irrespective of the depth of analysis. For example, Gavi's PneumoADIP investment case includes an in-depth cost-effectiveness analysis (CEA) including explanation of the analytic method, model structure, and key assumptions, whereas a small section is dedicated to equity impact of pneumococcal conjugates with reference to 1 study on their impact of diminishing racial inequities.[12] In this case, each corresponding outcome, "incremental cost-effectiveness ratio" and "equity (health)," represented 1 point for the frequency column. For analysis, the frequency of appearance of an outcome was ranked in descending order and also measured against the total number of investment cases reviewed to demonstrate the proportion of investment cases that contain the specific outcome of interest. The objectives and aims of each result were extracted verbatim, and keywords from the phrases were further categorized into groups that served a similar purpose. Information related to financing of vaccines and immunization programs was extracted from the investment cases that described internal and external sources of funding for the proposed investment.

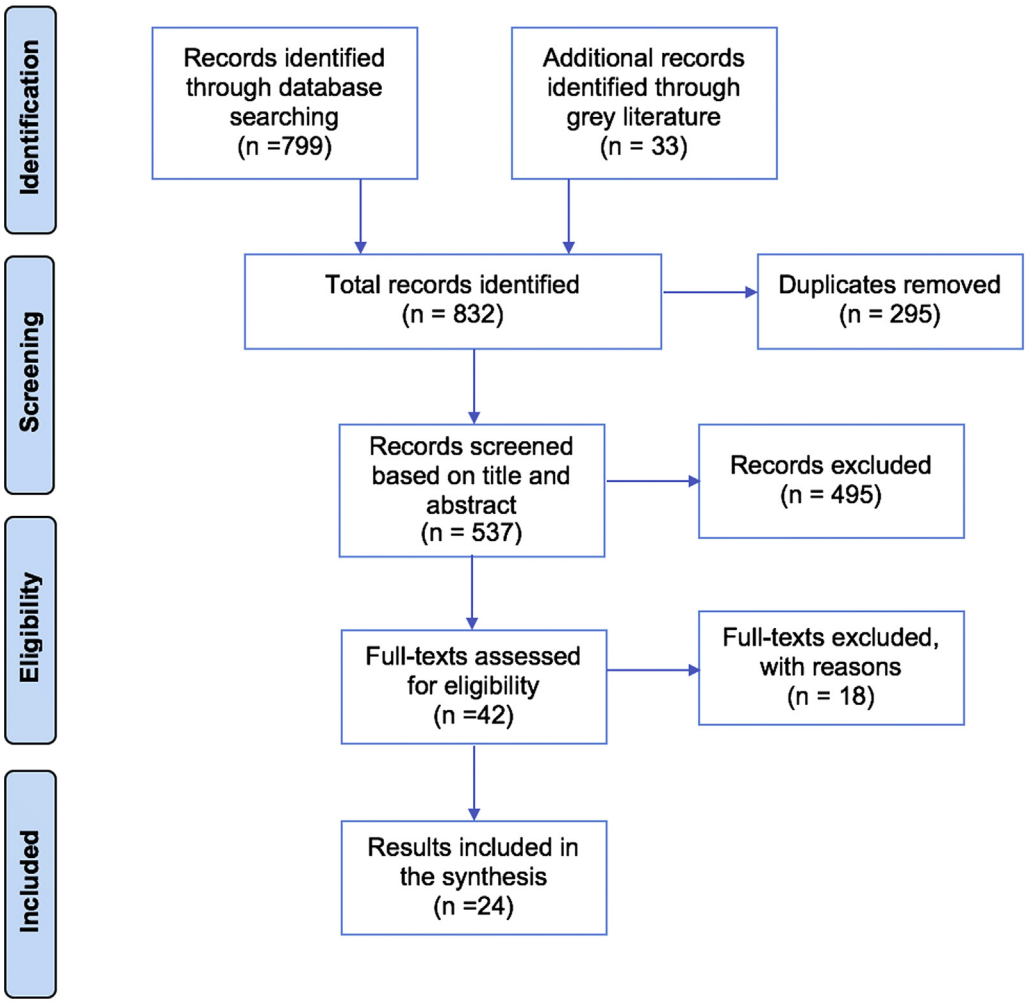
One reviewer (S.S.) conducted the search, screened the titles and abstracts, and extracted data. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines for the review.

Results

Investment Cases Reviewed

The searches yielded 832 results, of which 537 were screened on the basis of their titles and abstracts (see Fig. 1 for a flow diagram). After excluding 495 results on the basis of their titles and abstracts, the full texts of the remaining 42 self-described

Figure 1. Literature search flow diagram based on PRISMA and modified by the author.



PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

investment cases were assessed for eligibility. Twenty-four results met the full eligibility criteria and were included in the review.

Of the 24 investment cases found, 17 (70%) corresponded to gray literature, and the remaining 7 (29%) comprised 5 full journal articles, 1 meeting report, and 1 abstract (Table 1). As seen in Figure 2, most of the investment cases were published during the past 2 decades, but 1 result dates back to 1982. Fifteen investment cases (62.5%) were published between 2010 and 2017, showing an increasing trend over time. The length of the investment cases, defined by the number of pages of each written case, ranges from 1 page to 200 pages. Most of the investment cases (87.5%) focused on the global level as their target region, but 3 investment cases (12.5%) targeted individual countries.

We also categorized the investment cases into 3 broad areas that they were meant to inform—procurement and delivery (38%), research and development (21%), and comprehensive disease control strategies (54%). These categories are not mutually exclusive because a single investment case could inform multiple areas. In terms of vaccines, 14 investment cases considered licensed vaccines and 5 were intended for pipeline vaccines. In 2006, Johns Hopkins University's Gavi PneumoADIP focused on the procurement and delivery of both licensed (PCV7) and next-generation pipeline vaccines (PCV10 and PCV13) against *Streptococcus pneumoniae*.[12] More than half of the investment cases (54%) targeted comprehensive disease control packages rather than a single vaccine.

The value of the investment being evaluated ranged from $9.8 million (International Vaccine Institute's cholera vaccine in Bangladesh) to $3.4 billion (Gavi's Vaccine Investment Strategy 2013 malaria vaccine in all Gavi-supported countries) for procurement and delivery, and from $193 million (BCG replacement prime vaccine) to $1.2 billion (tuberculosis vaccine prime-boost strategy) for research and development (see Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.002). These figures were available only for 12 investment cases that contained detailed investment plans.

Stated Objectives of Investment Cases

Six investment cases were found to include more than 1 objective, and the total counts for each category are not mutually exclusive (Table 1). The most frequently stated objective was to provide information for decision making. Twelve investment cases aimed to provide the evidence base for decisions regarding technical or financial support for vaccine introduction by donors

and country stakeholders, or investment decisions on vaccine development made by donors or private investors. Nine investment cases aimed to advocate for a specific goal such as global eradication or an agenda such as the establishment of Gavi financing or increased private sector investment. Two investment cases aimed to outline a comprehensive strategic plan for introduction of vaccines. Two had the objective of informing standardization of investment cases on the basis of findings from systematic literature reviews or expert consultations. Eight investment cases did not state their objectives (see Appendix 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.002).

Categories of Outcomes Reported

Sixty-seven outcomes and their frequency, defined as the number of cases that contain the specific outcomes, were identified during the review (Fig. 3). They fell into 4 broad categories: (1) burden of disease, (2) cost of investment, (3) impact of investment, and (4) other considerations for the implementation of the proposed investment. Appendix 6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.002 shows the outcomes and order of frequency for each of the 3 areas—procurement and delivery, research and development, and disease control.

Eighty-three percent of the investment cases contained information about the burden of disease. This outcome is presented at the beginning of each investment case to specify the magnitude of the problem. Deaths (83% of all investment cases) and cases (75% of all investment cases) are the most frequently used measures for this category. Economic burden was also presented in investment cases, and it comprised direct cost (54%) and indirect cost (12%) of treatment, although the total cost of illness, the total amount reported without itemization that includes both direct and indirect costs, was most frequently used (63%).

With vaccine price (71%) and quantity demanded (54%) as fundamental building blocks, the cost of investment differs according to stakeholder. Eleven investment cases (46%) present the perspective of payers with total procurement, and 10 investment cases (42%) also include delivery costs in the cost of investment. Delivery costs identified from investment cases included costs associated with cold chain, training and supervision, vehicles and transport, social mobilization and awareness raising, surveillance, monitoring and evaluation, waste management, and overhead cost. Four investment cases (17%) presented the producer's perspective. The cost of investment for producers comprised the cost of discovery, clinical trials (phases I-III), process development, manufacturing, regulatory processes, marketing, and post-marketing activities.

The impact of the investment category encompassed the potential health and economic benefits, which primarily served as the rationale for investment. The most common outcome measures reported were deaths averted (71%) for health impact and incremental cost-effectiveness ratios (67%) for economic impact. We found that 13 health investments (54%) incorporated health impact models that were modified from published studies and adapted for the purpose of the investment cases. Also, 15 investment cases (63%) included economic models for CEA or benefit-cost analysis (BCA). Investment cases varied in the way they reported model structures, and assumptions varied across the investment cases. For example, many investment cases omit information about vaccine efficacy, herd effects, vaccine duration, and vaccine coverage for health impact models. In economic models, the method of valuation for economic or indirect costs and the discount rate were often omitted. In addition to these traditional outcomes, a few investment cases also reported broader economic benefits. These were often described qualitatively because of the limited available empirical data. Reduction of health and socioeconomic inequalities across population groups is most frequently mentioned as a broader economic benefit of vaccination (54%).

The other considerations for implementation category provided information on contextual factors that contribute to the implementation of the investment plan or potential risks affecting the level of the impact on the population. The factors with the highest frequency of appearance are health system capacity (79%) and the vaccine financing landscape (75%). Health system factors such as the current immunization program capacity, human resources, cold chain, transportation, and the need for integration of services could serve as constraints to implementation, affecting the potential impact of new vaccines. The vaccine financing landscape puts the proposed investment in a broader context that encompasses various stakeholders who provide or receive funding for vaccine development and introduction.

Stakeholders

Figure 4 shows that 15 investment cases (63%) targeted all relevant stakeholders as their target audience. Six were submitted exclusively to the Gavi board, and these investment cases tend to include detailed plans with cost estimates, health and economic impact models, and other considerations for implementation.[12-16,19] One was submitted to the Bill & Melinda Gates Foundation by the Global Polio Eradication Initiative and McKinsey & Company.[29] Another was the BIO Ventures for Global Health and the Boston Consulting Group intended to build the case for private sector investment on tuberculosis vaccines,[23] and PATH's malaria investment case targeted both public and private sector stakeholders.[20]

More than half of the investment cases in the review (59%) were funded by private nonprofit foundations (Bill & Melinda Gates Foundation, Novartis Foundation, and German Science Foundation), 10.3% by bilateral donors (the Swedish International Development Agency and the US Centers for Disease Control and Prevention), 6.9% each by Gavi and another multilateral donor (WHO), and 3.4% by a for-profit company (Sanofi Pasteur). The remaining (41%) of the investment cases were missing information about funding source. Gavi served as both funder and audience for its vaccine investment strategy. Since 2008, the Gavi secretariat has developed a vaccine investment strategy every 5 years to make final recommendations for new vaccine investments to the Gavi board.[36]

Funders of the investment cases are not necessarily the same people who fund the actual health investment (Table 2). Indeed, 75% of the investment cases described external and internal funding sources needed to meet the demand. In some cases, there were detailed projections of costs of investment, financing by type of funder, and future funding gaps. Comprehensive multiyear plans and cost-effectiveness estimates are mentioned as core information needed to ensure financial sustainability at the country level.

Investment cases for vaccine research and development identified private pharmaceutical firms, national governments, bilateral/multilateral donors, and foundations as key funding sources in the different stages of the vaccine development spectrum. To attract private sector investment, these investment cases provided information on estimated development costs as well as potential market size based on demand and price forecasts. Donor

Table 1. Overview of investment cases.

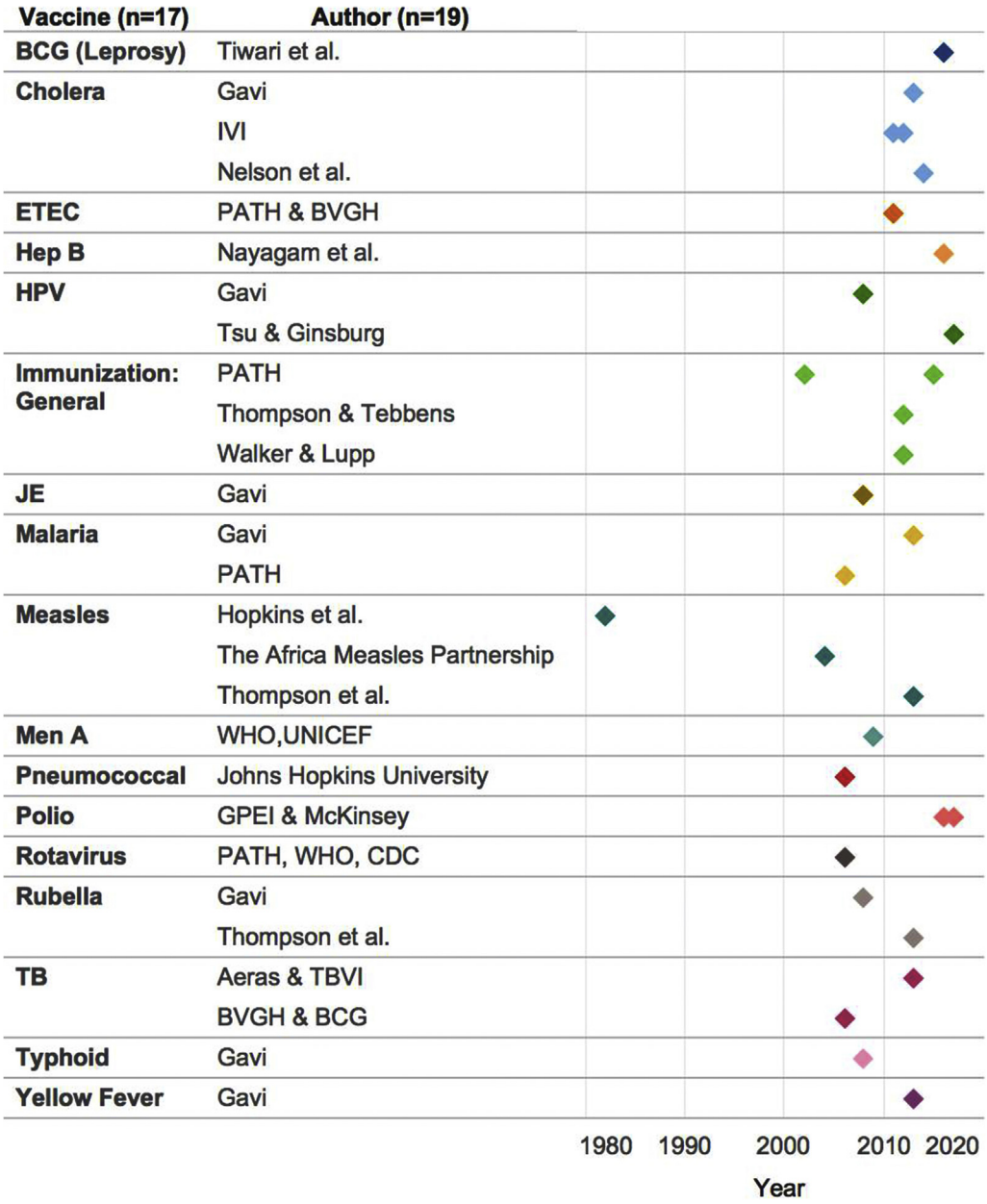
No.	Reference	Year	Vaccine	Audience	Region	Page
1	The Africa Measles Partnership[13]	2004	Measles	Donor (Gavi)	Global	80
2	PATH, World Health Organization, Centers for Disease Control and Prevention[14]	2006	Rotavirus	Donor (Gavi)	Global, Gavi-eligible countries	78
3	Johns Hopkins University[12]	2006	Pneumococcal	Donor (Gavi)	Global, Gavi-eligible countries	85
4	Gavi Vaccine Investment Strategy[15]	2008	HPV, JE, rubella, typhoid	Donor (Gavi)	Global, Gavi-eligible countries	–
5	World Health Organization and the United Nations Children's Fund[16]	2009	Meningitis A	Donor (Gavi)	Global, 25 Gavi-eligible countries	132
6	International Vaccine Institute[17]	2011	Cholera	All stakeholders	Cholera endemic countries	200
7	International Vaccine Institute[18]	2012	Cholera	All stakeholders	Bangladesh	134
8	Gavi Vaccine Investment Strategy[19]	2013	Yellow fever, cholera, malaria	Donor (Gavi)	Global, Gavi-eligible countries	–
9	PATH Malaria Vaccine Initiative[20]	2006	Malaria	Public and private sectors	Global	14
10	PATH and BIO Ventures for Global Health[21]	2011	ETEC	All stakeholders	Global	52
11	Aeras and the Tuberculosis Vaccine Initiative[22]	2013	TB	All stakeholders	Global	70
12	BIO Ventures for Global Health and Boston Consulting Group[23]	2006	TB	Private sector	Global	30
13	Hopkins et al[24]	1982	Measles	All stakeholders	Global	3
14	PATH[25]	2002	Immunization	All stakeholders	Global	16
15	Thompson et al[26]	2013	Measles and rubella	All stakeholders	Global	8
16	Nelson et al[27]	2014	Cholera	All stakeholders	Bangladesh	4
17	PATH[28]	2015	Immunization	All stakeholders	Global	4
18	Global Polio Eradication Initiative, McKinsey & Co[29]	2016	Polio	Donor (BMGF)	Global	8
19	Nayagam et al[30]	2016	Hepatitis B	All stakeholders	China	1
20	Global Polio Eradication Initiative, McKinsey & Co[31]	Polio	All stakeholders	Global, Nigeria, Afghanistan, Pakistan	28	Gray literature
21	Tsu and Ginsburg[32]	2017	HPV	All stakeholders	Global	5
22	Tiwari and Richardus[33]	2016	BCG (leprosy)	All stakeholders	Global	21
23	Thompson and Tebbens[34]	2012	Immunization	All stakeholders	Global	8
24	Walker and Lupp[35]	2012	Immunization	All stakeholders	Global	13

BCG indicates Bacillus Calmette–Guérin; BMGF, Bill & Melinda Gates Foundation; ETEC, enterotoxigenic *Escherichia coli*; HPV, human papillomavirus; JE, Japanese encephalitis; TB, tuberculosis.

Table 1. Continued

Type of publication	Phase	Stated objectives and aims
Gray literature	Procurement and delivery	Not specified
Gray literature	Procurement and delivery	"Recommend that Gavi establish a financing policy to subsidize the purchase of vaccines." (p. 3) "Sets forth a comprehensive plan with the objectives of generating important evidence for informed decision-making and creating the necessary environment whereby rotavirus vaccines can join the other EPI vaccines in saving the lives of children in many of the world's poorest countries." (p. 4)
Gray literature	Procurement and delivery	"Outlines a 20-year strategic vision for introducing and sustaining pneumococcal vaccines." (p. 5)
Gray literature	Procurement and delivery	"Determine optimal vaccine financing strategy; priority rank vaccine financing strategies given various value measures." (p. 6)
Gray literature	Procurement and delivery; disease control	Not specified
Gray literature	Procurement and delivery; research and development	"Designed to meet this request [of the WHO Strategic Advisory Group of Experts]." (p. i)
Gray literature	Procurement and delivery	"Provide a useful, evidence-based guide to policymakers in Bangladesh in making decisions about the use of oral cholera vaccines, as well as to the global health community in considering technical and financial support for cholera vaccine introduction." (p. 10)
Gray literature	Procurement and delivery	"Enable upfront, evidence-based decisions about GAVI's future vaccine investments in order to align planning by countries, industry and donors for the introduction of new, priority vaccines." (p. 2)
Gray literature	Procurement and delivery; research and development	"Begin improving data and answering questions about potential impact and costs." (p. 2)
Gray literature	Research and development	"Provide a rationale for the development of ETEC vaccines." (p. 2) "Increase the awareness of biotechnology and pharmaceutical companies in Europe and the United States, as well as companies in emerging markets like China and India, about the opportunities and potential markets that exist for low-cost and effective ETEC vaccines." (p. 2)
Gray literature	Research and development	"Demonstrate that a viable global market exists for new TB vaccines." (p. 7) "Advocate for the portfolio management approach as the most efficient and effective mechanism for facilitating the development of new TB vaccines." (p. 7)
Gray literature	Research and development	"Build the case for private-sector investment in tuberculosis (TB) vaccines or—if existing markets are inadequate to support such investment—reveal gaps where donor involvement may improve the market opportunity." (p. 5) "Develop a deep understanding of the markets … illuminate the potential return on industry investment, the target product files needed to capture these market opportunities." (p. 7)
Peer-reviewed article	Disease control	"Advocate establishing global measles eradication as a goal, to be achieved by accelerated implementation of the World Health Organization (WHO)'s Expanded Programme on Immunisation (EPI)." (p. 1396)
Gray literature	Disease control	Not specified
Peer-reviewed article	Disease control	Not specified
Meeting report	Disease control	"To discuss the investment case for cholera vaccination as a complimentary control and prevention strategy." (p. 1)
Gray literature	Disease control	Not specified
Gray literature	Disease control	"Establish core economic arguments for continuing to invest in eradication." (p. 1) "Offer a forward-looking perspective on the benefits of eradication using updated cost inputs that underlie the Plan." (p. 1)
Abstract	Disease control	"We present the case for a comprehensive scale-up package of HBV interventions … evaluated its impact, cost and return on investment." (p. 1)
Disease control	Not specified	
Peer-reviewed article	Disease control	"Draws on the insights of the expert contributions of the preceding papers to construct a compelling case for urgent investment in cervical cancer prevention." (p. 70)
Peer-reviewed article	Disease control	"Review systematically the literature … and to assess this information on its applicability for defining a Leprosy Elimination Investment Case (LEIC) based on Eradication Investment Case guidelines." (p. 2)
Peer-reviewed article	Disease control	"Report on the final proposed content for investment cases and the insights from the stakeholder consultation process." (p. 1)
Gray literature	Disease control	Not specified

Figure 2. Classification of investment cases by vaccine types, authors or affiliations, and decade of publications. The number of vaccine types (n = 17), authors (n = 19), and the total count (n = 30) are not equal to the total number of investment cases (n = 24) because multiple vaccines from Gavi's Vaccine Investment Strategy published in 2008 (n = 4) and in 2013 (n = 3) and from Thompson et al[26] (n = 2) were counted separately.

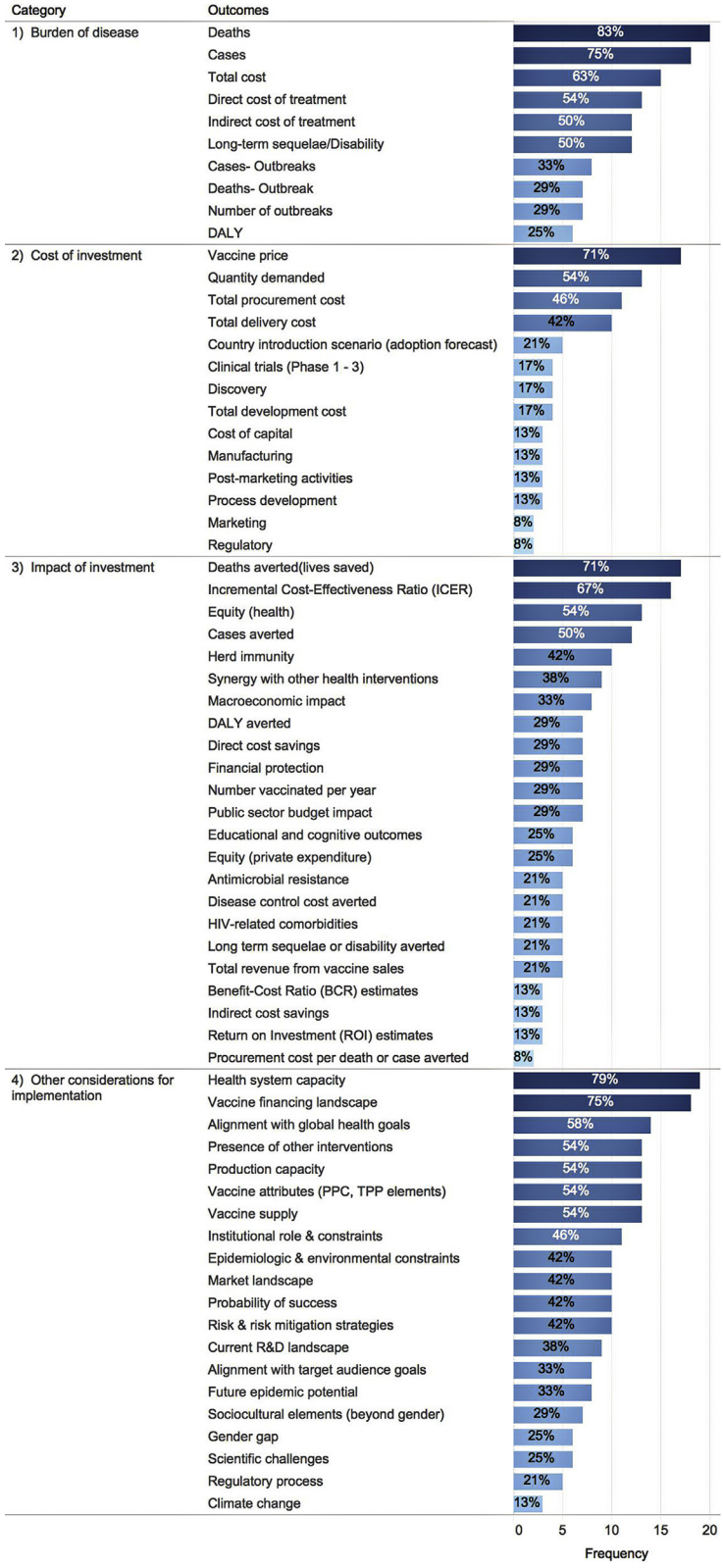


commitment was considered to be critical when signaling potential push funding for clinical trials and pull mechanism that allows guaranteed volumes when the product becomes available. These investment cases were authored by Product Development Partnerships (PDPs) such as Aeras, PATH Malaria Vaccine Initiative, Tuberculosis Vaccine Initiative, and BIO Ventures for Global Health.[20-23] The PDPs are nonprofit organizations that work to fill the research and development gap for products for use in low- and middle-income countries by engaging partners, supporting and conducting clinical trials, and managing the portfolio or intellectual property issues.[37] The Bill & Melinda Gates Foundation funded 6 investment cases related to PDPs included in this review.

Discussion

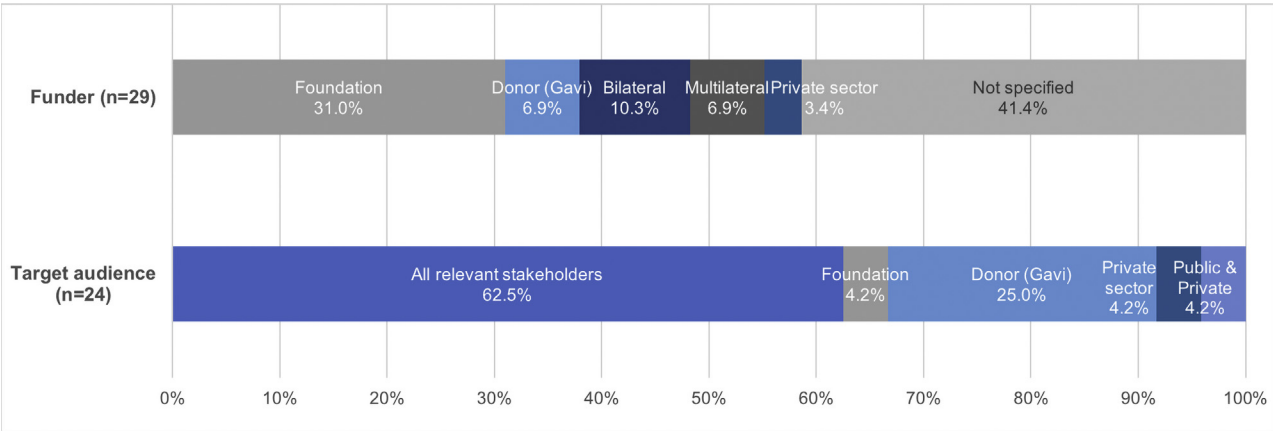
Although investment cases present considerable heterogeneity in terms of objectives, outcomes, and target audiences, a broad categorization provides insights on overarching information needs across stakeholders. The 4 broad categories of outcomes could be used to standardize the definition and content of investment case, enhancing transparent communication of key information for decision making. Such need is identified in earlier efforts by Walker and Lupp[35] that aimed to "systemize the elements, advance a core methodology and ensure that appropriate review is conducted" through the development of "Guide to Preparing an

Figure 3. Percent of all investment cases that contain a specified outcome. The percentages refer to the percent of all investment cases (n = 24) in the review. The frequency refers to the number of investment cases that contain a specified outcome. The largest possible number is 24.



DALY indicates disability-adjusted life-year.

Figure 4. Distribution of funders and target audiences of the investment cases. Although the total count of target audience adds up to 24, the total count of funders is 29 because the categories are not mutually exclusive.



Eradication Investment Case." Another example is a list of generic contents proposed by Thompson and Tebbens[34] for investment cases for global management of infectious diseases. To facilitate decision making at local and global levels, investment cases are expected to demonstrate the current knowledge and future trend of the disease, provide information about the cost of the proposed investment and its impact on the populations at risk, and address practical concerns regarding health system capacity, financing needs, and other implementation barriers.

Nayagam et al,[30] Nelson et al,[27] and the International Vaccine Institute's case study in Bangladesh[18] contain similar types of information as global investment cases with more country-specific information for all 4 categories. As there is an increasing need for domestic resource mobilization for vaccine procurement and delivery in countries that are transitioning out of Gavi support, more information such as budget impact of the proposed investment and alternative financing mechanisms is likely to prove useful for the countries to develop strategic plans for increasing and sustaining access to vaccines.

Consistent reporting of the key assumptions in health and economic impact models will be required to facilitate the discussion of the model outputs and comparison across vaccine investments as well as those in other areas of the health sector. Model assumptions could drive differences in the value of outputs,

Table 2. Funders of investment and their data needs.

By phase	Procurement and delivery	Research and development
Funders	*External sources* Gavi Bilateral donors Multilateral donors Development banks Other donors (foundations and NGOs) *Internal sources* National governments Local governments Local foundations and NGOs Private firms	Private firms National governments Bilateral donors Multilateral donors Foundations
Type of funding	Grant Concessional loans Nonconcessional loans Tax revenues Insurance Innovative financing mechanisms (climate financing)	Grants Cost-sharing Debt financing Equity fund Innovative financing mechanisms (advanced market commitment, blended capital, Bill and Melinda Gates Foundation's program-related investments)
Funders' data needs	Demand and price forecast that predicts total procurement and delivery cost All potential funding sources Projection of funding by funder and by cost types Global and country-level funding gap Incremental costs for the existing health system Considerations for financial sustainability at the country level (comprehensive multiyear strategic plans and cost-effectiveness estimates)	Demand and price forecast that predicts market revenue potential In-depth analysis of major drivers of revenue Signals of donor commitment that could bring push or pull funding Product development strategies and approaches that increase cost efficiency (ie, portfolio management approach) Considerations for development hurdles (funding need for clinical trials and support for vaccine purchase in low- and middle-income countries)

NGO indicates nongovernmental organization.

and transparent presentation of analytical choices is needed for interpretation of the results and comparative analyses that guide resource allocation and priority setting. A clear reporting will also help stakeholders to assess the predictive accuracy of the models and potential implementation gaps. Key findings from this review could inform standardization of investment cases and development of a general framework such as the WHO Full Public Health Value Propositions for Vaccines.[38]

The major objectives of investment cases are to provide information for decisions or advocate for a specific goal or agenda. Some investment cases (n = 9) explicitly state their advocacy goals, whereas others assume the role of carriers of information (n = 12). Nevertheless, it is challenging to determine whether they are impartial carriers of information given potential benefits of vaccine development and introduction that will be provided for the authors of the investment cases. In many cases, examination of additional sources is needed to understand the contexts in which investment cases are developed and the influence and nature of stakeholders. The need for discernment arises especially when those who have direct interest in the development of certain vaccines also serve the role of providing scientific evidence for decision making, as seen in value dossiers or some economic evaluations published by vaccine manufacturers. Investment cases should ideally state their aims, intended audience, and funding source clearly, and link the type of outputs generated to the decision-making needs of their audience. Monitoring and tracking of the final decisions on proposed investments will add to our knowledge of the role of investment cases in decision making concerning vaccine introduction and development decisions.

In the future, stakeholders will benefit from a more extensive review and comparative analysis that include investment cases for other health interventions outside the field of vaccines and immunization programs. Although our scoping review was limited to investment cases in the field, our insights could help to inform more harmonized approaches to investment cases that may benefit the broader health sector by increasing transparency and comparability of information presented for decision making, advocacy, and planning.

Investment cases are not a kind of analysis on their own but a compilation of outcomes from other analyses. Although measurement and reporting of each outcome should follow the existing good practice guidelines and reference cases in the field, such as the WHO guide to CEA,[39] the International Decision Support Initiative reference case,[40] or the International Society for Pharmacoeconomics and Outcomes Research Good Practices,[41] an umbrella reference case could be developed to provide guidance on choosing among the existing guidelines for each outcome. The umbrella reference case should present specific conditions in which investment cases are used for priority setting by local-, national-, and global-level decision makers and donor organizations. To be used for priority setting, the investment case should include some measure of the efficiency of the intervention corresponding to the decision problem on the basis of the results from CEA or BCA. Opportunity costs and trade-offs of the proposed investment should also be made clear. Such an umbrella reference case could be developed by agencies such as WHO that produce global standards and reference materials.

In brief, our recommendations on the harmonization of investment cases include the following points:

- Standardized definition and content based on 4 categories (burden of disease, cost of investment, impact of investment, and other considerations for implementation);
- Consistent reporting of the key assumptions in health and economic impact models used for investment cases;
- Transparency in stating aims, intended audience, and funding sources of investment cases;
- Tracking of the final decisions on proposed investments;
- Extensive review and comparative analysis of investment cases in the health sector;
- Further harmonization could benefit from development of an umbrella investment case that provides:
  - guidance on choosing among the existing guidelines and reference cases for each outcome;
  - endorsement that investment cases be used for priority setting and that they incorporate efficiency measures such as those based on CEA or BCA; and
  - guidelines for assessing opportunity costs and trade-offs of the proposed investment (ie, investment on other health or nonhealth sector interventions).

Despite the valuable insights it provides, this review is not free of limitations. First, the lack of a clear definition on what an "investment case" constitutes in the field made it necessary to limit the results to self-described investment cases, value propositions, or business cases. Some health and economic impact modeling articles, including return-on-investment analysis,[9] demonstrate the similar characteristics as some of the self-described investment cases, but were excluded from the review on the basis of the predetermined eligibility criteria.

Also, heterogeneity across investment cases posed numerous challenges for literature search, data extraction, and analyses. The definition of categories and outcomes from different investment cases had to be carefully reviewed to see whether they compare with other investment cases. Frequency-based identification of outcomes does not account for length or depth of analysis, and, more importantly, extracting individual outcomes may obscure the overall picture of each investment case.

The review does not include investment cases generated for internal decision making by private sector stakeholders; such studies are likely to exist but are not publicly available. We expect that these types of investment cases focus more on markers of profitability (eg, internal rate of return) that ensure accountability to shareholders than public health outcomes alone. It is also expected that they will provide additional insights on implementation considerations such as payment mechanism, competitor landscape, and intellectual property. Being able to incorporate such studies may give a more comprehensive understanding of the use of investment cases in vaccine development and introduction.

Conclusions

This scoping review describes the aims, target audiences, and funding sources of investments and categories of information that are critical to decision making for investments on vaccines and immunization programs. The findings from the review have implications for resource mobilization and allocation for the broader health sector. A global-level effort to harmonize investment cases as a body of work will effectively inform decisions by increasing transparency and comparability of data presented for the proposed investments.

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Supplemental Materials

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REFERENCES

1. Health and development: why investing in health is critical for achieving economic development. International Monetary Fund. https://www.imf.org/external/pubs/ft/health/eng/hdwi/hdwi.pdf. Accessed November 15, 2017.
2. A healthier humanity: the WHO investment case. WHO/DGO/CRM/18.2. World Health Organization. http://www.who.int/about-us/planning-finance-and-accountability/financing-campaign/investing-global-investing-local. Accessed October 1, 2018.
3. Strengthening primary health care through community health workers: investment case and financing recommendations. Johns Hopkins University, the Office of the UN Special Envoy for the health-MDGs, the World Bank, Partners in Health, Last Mile Health, the Clinton Foundation, ALMA, and the governments of Ethiopia and Liberia. http://www.who.int/hrh/news/2015/CHW-Financing-FINAL-July-15-2015.pdf. Accessed March 15, 2018.
4. Nurturing the health and wealth of nations: the investment case for breastfeeding. Global Breastfeeding Collective. http://www.who.int/nutrition/publications/infantfeeding/global-bf-collective-investmentcase.pdf?ua=1. Accessed July 8, 2018.
5. The investment case for noncommunicable disease prevention and control in Mongolia. UN Interagency Task Force on NCDs. http://apps.who.int/iris/bitstream/handle/10665/259627/WHO-NMH-NMA-17.55-eng.pdf?sequence=1. Accessed December 22, 2017.
6. Guidance note: investment cases. Global Financing Facility. https://www.globalfinancingfacility.org/guidance-note-investment-cases. Accessed December 22, 2017.
7. Global vaccine action plan 2011-2020. World Health Organization. http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/. Accessed September 25, 2017.
8. Manheim D, Chamberlin M, Osonde OA, Vardavas R, Moore M. Improving decision support for infectious disease prevention and control: aligning models and other tools with policymakers' needs. https://www.rand.org/content/dam/rand/pubs/research_reports/RR1500/RR1576/RAND_RR1576.pdf. Accessed December 22, 2017.
9. Ozawa S, Clark S, Portnoy A, Grewal S, Brenzel L, Walker DG. Return on investment from childhood immunization in low- and middle-income countries, 2011-20. *Health Aff (Millwood)*. 2006;35(2):199–207.
10. Immunisation—a healthy return on investment. Gavi, The Vaccine Alliance. https://www.gavi.org/library/audio-visual/infographics/immunisation—a-healthy-return-on-investment/. Accessed July 8, 2018.
11. Stansfield C, Dickson K, Bangpan M. Exploring issues in the conduct of web searching and other online sources for systematic reviews: how can we be systematic? *Syst Rev*. 2016;5(1):191.
12. Gavi Alliance investment case: accelerating the introduction of pneumococcal vaccines into Gavi-eligible countries. Gavi's PneumoADIP at JohnsHopkins University. http://www.nitag-resource.org/uploads/media/default/0001/01/8252ac0af32f9f93a979e8a017335e25e2d6bd08.pdf. Accessed November 15, 2017.
13. The Africa Measles Partnerships. Measles investment case submitted to the Executive Board Global Alliance for Vaccines and Immunization. Published April 20, 2004.
14. Accelerating the introduction of rotavirus vaccines into Gavi-eligible countries. PATH's Rotavirus Vaccine Program (PATH, World Health Organization, Centers for Disease Control and Prevention). http://www.nitag-resource.org/uploads/media/default/0001/01/ea8101072b609db7271b4a6fe0b1886e338a889e.pdf. Accessed November 15, 2017.
15. History of vaccine investment strategy—Gavi vaccine investment strategy: executive summary. Gavi, The Vaccine Alliance. https://www.gavi.org/about/strategy/history-of-vaccine-investment-strategy/. Accessed July 8, 2018.
16. World Health Organization and United Nations Children's Fund. *Eliminating serogroup A meningococcal meningitis epidemics as a public health problem in Africa: an investment case for the GAVI Alliance*. 2008.
17. An investment case for the accelerated introduction of oral cholera vaccines. Seoul: 2011. International Vaccine Institute. http://www.ivi.int/?page_id=12479&uid=816&mod=document&pageid=1. Accessed November 15, 2017.
18. Country investment case study on cholera vaccination: Bangladesh. International Vaccine Institute. http://www.ivi.int/?mod=document&uid=819&page_id=12479. Accessed November 15, 2017.
19. History of vaccine investment strategy—final report on the VIS (phase II)—November Board Paper. Gavi, The Vaccine Alliance. https://www.gavi.org/about/strategy/history-of-vaccine-investment-strategy/. Accessed July 8, 2018.
20. Investment case for malaria vaccines. PATH Malaria Vaccine Initiative. https://www.malariavaccine.org/sites/mvi dev.mrmdev.co.uk/files/content/resources/files/PublicFinancialRoIMalVax-GHCMay2006-v1_000.pdf. Accessed November 15, 2017.
21. The case for investment in enterotoxigenic *Escherichia coli* vaccines. PATH and BIO Ventures for Global Health. https://www.path.org/resources/the-case-for-investment-in-enterotoxigenic-escherichia-coli-vaccines/. Accessed November 15, 2017.
22. TB vaccine research & development: a business case for investment (draft discussion document). Aeras and Tuberculosis Vaccine Initiative. http://www.aeras.org/pdf/TB_RD_Business_Case_Draft_3.pdf. Accessed November 15, 2017.
23. BIO Ventures for Global Health and Boston Consulting Group. *Tuberculosis vaccine: the case for investment*; 2006. http://pacifichealthsummit.org/downloads/MDR-TB/Tuberculosis%20Vaccines%20The%20Case%20for%20Investment.PDF. Accessed November 15, 2017.
24. Hopkins D, Koplan J, Hinman A, et al. The case for global measles eradication. *Lancet*. 1982;1 (8286):1396–1398.
25. Children's Vaccine Program at PATH. *The case for childhood immunization. Occasional Paper 5*. 2002. https://path.azureedge.net/media/documents/CVP_Occ_Paper5.pdf.
26. Thompson KM, Strebel PM, Dabbagh A, et al. Enabling implementation of the Global Vaccine Action Plan: developing investment cases to achieve targets for measles and rubella prevention. *Vaccine*. 2013;31 (Suppl 2):B149–B156.
27. Nelson CB, Mogasale V, Bari TIA, et al. Considerations around the introduction of a cholera vaccine in Bangladesh. *Vaccine*. 2014;32 (52):7033–7036.
28. Investing in vaccines for the developing world. PATH. https://www.path.org/resources/investing-in-vaccines-for-the-developing-world/. Accessed November 15, 2017.
29. Economic case for eradicating polio. Global Polio Eradication Initiative. http://polioeradication.org/wp-content/uploads/2016/07/EconomicCase.pdf. Accessed November 15, 2017.
30. Nayagam S, Chan P, Zhao K, et al. Investment case for a comprehensive package of interventions against hepatitis B in China. *J Hepatol*. 2016;64 (2):S469.
31. Investment case. Global Polio Eradication Initiative. http://polioeradication.org/wp-content/uploads/2016/07/EconomicCase.pdf. Accessed November 15, 2017.
32. Tsu VD, Ginsburg O. The investment case for cervical cancer elimination. *Int J Gynecol Obstet*. 2017;138 (Suppl 1):69–73.
33. Tiwari A, Richardus JH. Investment case concepts in leprosy elimination: a systematic review. *Lepr Rev*. 2016;87(1):2–22.
34. Thompson KM, Tebbens RJD. Development of investment cases for globally-coordinated management of infectious diseases. *J Vaccines Vaccin*. 2012;3 (8):164.
35. Walker D, Lupp J. Guide to preparing an eradication investment case. http://eic-guidelines.org/Guide%20to%20Preparing%20an%20EIC_Draft%208.pdf. Accessed November 15, 2017.
36. Vaccine investment strategy. Gavi, The Vaccine Alliance. https://www.gavi.org/about/strategy/vaccine-investment-strategy/. Accessed June 21, 2018.
37. Mahoney RT. Product development partnerships: case studies of a new mechanism for health technology innovation. *Health Res Policy Syst*. 2011;9:33.
38. Full public health value propositions for vaccines: executive summary. World Health Organization. http://www.who.int/immunization/sage/meetings/2018/april/1_WHO_FPHVPExecSum_SAGE_Apr2018.pdf. Accessed June 21, 2018.
39. Tan-Torres Edejer T, Baltussen R, Adam T, et al., eds. *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*. Geneva, Switzerland: World Health Organization; 2003.
40. Wilkinson T, Sculpher M, Claxton K, et al. The International Decision Support Initiative Reference Case for economic evaluation: an aid to thought. *Value Health*. 2016;19 (8):921–928.
41. Mauskopf J, Standaert B, Connolly MP, et al. Economic analysis of vaccination programs: an ISPOR Good Practices for Outcomes Research Task Force Report. *Value Health*. 2018;21(10):1133–1149.