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Review of Literature on Factors Affecting Private Sector Investment in Global Health R&D

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EPAR Technical Report #345

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December 5, 2017

Executive Summary

The share of private sector funding, relative to public sector funding, for drug, vaccine, and diagnostic research & development (R&D) differs considerably across diseases. Private sector investment in overall health R&D exceeds $150 billion annually, but is largely concentrated on non-communicable chronic diseases (Jamison et al., 2013) with only an estimated $5.9 billion focused on diseases that primarily affect low and middle-income countries (LMICs) (West et al., 2017b).[1]

It would be easy to conclude that private sector investment choices simply reflect the most profitable use of funds or the most comfortable risk-return tradeoffs, especially considering the high opportunity cost of capital earning large returns in high-income country (HIC) markets. There are, however, examples of privately funded R&D, blended financing, and public-private partnerships targeting diseases in LMICs. The detailed story, therefore, is likely more complex, with possibilities at the margin for catalyzing more private sector investment by increasing returns, lowering risk, or overcoming institutional disincentives for private R&D funding.

We look more closely at these nuances by examining the evidence for five specific disincentives to private sector investment: scientific uncertainty, unstable policy environments, limited revenues and market uncertainty,

Price, information & market power: influences on private sector global health R&D investment

- Low or uncertain LMIC product prices relative to prices in the U.S. or other HICs limit private global health R&D investment
- LMIC market data gaps further hinder revenue forecasting and reduce firm or product market entry
- Though revenues from global health R&D may be low or uncertain, costs are often high, sunk and incurred upfront with certainty
- Relatively strong downstream market power may make it cheaper to purchase (license) rather than produce internally (conduct R&D)
- Proprietary science and LMIC health science data gaps represent further barriers to private global health R&D (e.g., data science, bioengineering)

[1] In this paper, we use the term global health R&D to refer to R&D that targets diseases primarily affecting low- and middle-income countries (LMICs) while overall health refers to R&D that targets any disease, both in LMICs and in high-income countries.

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high fixed and sunk costs, and downstream rents from imperfect markets. Though all five may affect estimates of net returns from an investment decision, they are worth examining separately as each calls for a different intervention or remediation to change behavior.

Our goal of examining these separate components of private sector investment decisions in global health R&D is made challenging by the scarcity and unevenness of publicly available information. Our strategy, therefore, both for painting as full a picture as possible and having confidence in our findings, is to reference - and check against – multiple sources. An earlier report (West et al., 2017b) draws on consultations with over two dozen experts on global health R&D from multiple sectors and case studies of leading examples of venture capital investments and innovative finance. In this report we conduct an expansive review of the grey and published literature that allows us to analyze overlaps and differences in the investment challenges highlighted by expert consultations and by academic and industry research.[2]

Our review draws on literature from five primary academic search databases, five supplemental search databases, ten private pharmaceutical company websites, and twelve philanthropic and public organizations involved in health R&D worldwide. The literature reviewed focuses primarily on global health R&D, but in order to capture factors possibly influencing private sector "non-investors" we did not limit results to health R&D specific to LMICs. The searches yielded 285 sources that discuss private investment in 47 individual diseases that we use to extract information on company characteristics, research and development characteristics, and potential market returns. All sources were published in the past 15 years, relate to private sector R&D investments targeting either drugs, vaccines, or diagnostics, and include findings on R&D at any point from pre-clinical research through Phase III clinical trials.[3]

We coded the resulting sample of literature using a framework derived from public goods theory and theories of private firm behavior, which includes five disincentives hypothesized to inhibit private sector investment in global health R&D, though not all equally unique to R&D for LMICs: *Scientific uncertainty*; *Uncertain, unstable, or weak policy environments*; *Limited revenues and market uncertainty*; *High fixed and sunk costs*; and *Downstream rents from imperfect markets*. Some of these factors are more frequently cited than others, as summarized below:

- *Scientific uncertainty (seldom mentioned)*: Uncertainty surrounding the results of scientific research is rarely discussed as a primary factor deterring private investment in global health R&D, although some sources provide estimates for the probability of success for medical product research when describing private sector investment decisions. Only four studies emphasize the complexity of research, access to existing research and the limited volume of existing knowledge as specific factors influencing private R&D investment decisions.

- *Uncertain, unstable, or weak policy environments (frequently mentioned)*: Geo-political risks and

[2] An upcoming report relies on publicly disclosed industry-reported financial data.

[3] Stages of clinical trials as defined by the WHO: "Phase I: Clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects). Phase II: Clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety. III: Studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely. IV: Studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use" (*WHO: http://www.who.int/ictrp/glossary/en/#TrialPhase*).

unstable macroeconomic and policy environments are widely cited in industry reports as deterrents to private sector investment in global health R&D, but most sources offer little specificity. Uncertainty in returns stemming from the regulatory environment, regulatory costs, and weak or uncertain intellectual property (IP) protections are among the more commonly cited policy challenges for private health R&D, rather than more general macroeconomic volatility.

- *Limited revenues and market uncertainty (frequently mentioned)*: Considerable evidence points to limited market potential (i.e., low expected revenues) to explain underinvestment in diseases affecting LMICs. However only two sources cite small market size as a deterrent to private investment – most others highlight pricing (low and/or uncertain LMIC prices) as the major deterrent to private R&D. The interaction between competition and expected revenue streams also appears in the literature: eight sources report on how low (high) prices are deterring (incenting) private R&D investment, depending on the treatment. Four additional sources look at prices and willingness-to-pay across high- and low-income countries, suggesting that companies assume different prices for the same drug when estimating potential future revenues across different markets. Incentives to invest in R&D targeting diseases prevalent in the U.S. and other high-income countries are higher given the ability to set prices at what the market will bear, relative to prices in LMICs which may be lower, regulated, or unknown.

- *High fixed and sunk costs (often mentioned)*: Multiple studies mention costs though only five specify the high fixed and/or sunk costs of global health R&D in private investment decisions. Clinical trial costs, specialized equipment, subject area expertise, and payments for access to previous research via royalties or other IP payments, are "sunk" to the extent that these investments are difficult to repurpose. The reviewed literature presents a range of cost estimates for bringing a drug to market between $802 million and $2.2 billion. However, critiques of the most widely cited cost-estimate studies emphasize the "constructed nature of R&D cost estimates" (Light & Warburton, 2011, p. 47) and the degree to which cost estimates may be inaccurate, and depend heavily on assumptions and available data.

- *Downstream rents from imperfect markets (often mentioned)*: Theory predicts that the nature of the health R&D industry creates incentives for large firms with downstream capacity to increasingly move resources out of R&D, if they are able to purchase rights to the results of upstream R&D at lower cost than producing those R&D outputs themselves. Upstream competition can make it more profitable for large firms with a downstream presence to purchase patent rights rather than invest in their own R&D, which Roy & King (2016) note is a common industry practice. Five sources describe private R&D efforts to improve the efficacy or effectiveness of existing treatments — so-called "me-too" drugs — as examples of private investors' preference to secure downstream rents rather than invest in new health R&D ventures. In other cases policy incentives may favor downstream private investment, or public and philanthropic funding may be subsidizing or crowding out upstream research in ways that discourage private funding. Three sources suggest limited patent windows may encourage private firms to divert their resources towards marketing rather than additional R&D, in order to maximize profits during the period of exclusivity (Love, 2005).

We find some corroboration between expert opinions as reported in West et al. (2017b) and the current review of literature. West et al. (2017b) offer six main explanations for limited global health private sector R&D: *Limited Markets for Certain Diseases* (illnesses that affect small numbers), the *Cost of Drug Development* (long development cycle), *Geo-political Risks* (risks to long-term investments and revenue streams), *Macroeconomic Difficulties* (recession, exchange rate, and interest rate risks), *Poor Health Governance* (difficulty in products reaching intended beneficiaries), and a *Lack of Systematic Data* (evidence on what works). In our review of literature there is common mention of the challenge of limited markets, though the literature reviewed is clear

that in the revenue calculation, LMIC pricing is the primary disincentive (even in cases where the LMIC market size is large), especially relative to drug pricing in the U.S. and other HICs. We also find a common lament in the literature that limited information is available about LMIC markets, making revenue (and in some cases cost) forecasts difficult. Other factors cited by experts in West et al. (2017b) including *Geo-political Risks*, *Macroeconomic Difficulties*, *Poor Health Governance*, and a *Lack of Systematic Data*, are less frequently cited in the literature we reviewed as the key determinants of private sector investment decisions – although all broadly relate to private firms' perceptions of risks and potential revenues associated with R&D investments.

Largely absent from factors highlighted in expert consultations but frequently mentioned in the literature is the effect of an imperfectly competitive market structure that creates economic incentives downstream relative to upstream R&D. This structure potentially grants larger pharmaceutical firms enough market power to buy or license R&D below a competitive market price (rather than conduct their own R&D) and enough market and regulatory authority to sell final products above a competitive market price. We find evidence that the current health R&D market structure is characterized – and likely constrained - by specialization, high entry costs, regulatory rents and privately held information; a result of both the nature of disease research and the policy environment. In a perfectively competitive market, in a situation where the vast majority of private investment is flowing into HIC health R&D, at some point the marginal return to a dollar invested in global health R&D would exceed the marginal returns to further HIC health R&D investment (so long as global health R&D was at all profitable). But in an imperfectly competitive market this threshold may not be realized.

The attractiveness of licensing upstream research rather than conducting R&D internally is likely to increase as more computing and data analysis occur in biotech companies relative to the physical science labs of traditional pharmaceutical companies. Customer and market data collected remotely, via social media, through internet searches, or through other means (utility payments, bank transactions, etc.) contain information that has commercial value by informing market opportunities. And as the industry evolves further from a "chemical compound configuration" to a "biotech/biopharmaceutical configuration" resting on "sophisticated informatics and big data infrastructure," (R&D Magazine, 2016), the potential to easily share market, customer, and health knowledge expands, but so does the opportunity to monopolize it, depending on the policies and other incentives facing private investors.

To the extent that health science and market data are more limited for global health R&D, there is reason to speculate that as the industry evolves an even smaller share of investment will be directed at diseases prevalent in LMICs. Both industry experts and the literature lament the limited market data available to better assess potential market outcomes – yet despite potential industry-wide gains, there is no clear incentive for any individual firm within this sector to either fund or contribute to such a data service.

Though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions), evidence of effectiveness is mixed. While we find 42 sources suggesting that some combination of policy tools had a positive impact on catalyzing private R&D funding for diseases more prevalent in LMICs, 11 sources report mixed results, and 3 sources report negative impacts of policies.

Table of Contents

1. Introduction

Private sector spending on overall health research and development (R&D) exceeds $150 billion annually, with about $5.9 billion focused on low and middle income countries (LMICs) - though estimates vary depending on the source and definition of what constitutes R&D (West et al., 2017b; Chapman et al., 2016; EvaluatePharma, 2016; Jamison et al., 2013). Though the majority of health R&D funding worldwide comes from private sources, the share of private relative to public sector funding for R&D differs considerably across diseases.

Most private investment targets non-communicable chronic diseases (Jamison et al., 2013), with much less devoted to the so-called "neglected diseases[4]" primarily afflicting LMICs (Chapman et al., 2016). Pedrique et al. (2013) studied 49 neglected diseases in five disease categories—malaria, tuberculosis, diarrheal diseases, neglected tropical diseases (WHO definition), and other neglected diseases—finding that R&D investment in these diseases has traditionally been relatively low as compared to research for diseases that affect high-income countries: from 2000 to 2011 only 4% of approved new drug compounds were for neglected diseases, even as these diseases represent an estimated 12% of the global health burden. Moreover, Pedrique et al. (2013) find that public organizations were involved in 54% of the products in clinical development for neglected diseases, compared to 23% by the private sector, 15% by the philanthropic sector, and 8% by a mix of sponsors. More recently, and adopting a wider lens of R&D that includes basic research, product discovery, and preclinical development (and a definition of neglected disease that is quantitatively different from Pedrique et al.'s (2013) definition but shares the same spirit), the 2016 G-Finder report finds that of total neglected disease R&D spending in 2015, the public sector contributed 63%; the philanthropic sector, 21%; and the private sector, only 16%, or $471 million in 2015 (Chapman et al., 2016).

The composition, as much as the amount, of private sector funding for health R&D is of interest because disease morbidity and mortality (measures of the global burden of disease) make clear that while there are certainly problems with access to current drugs and vaccines, there are also knowledge gaps in upstream research, especially for diseases concentrated in LMICs where historically private funding has been low. Part of the obvious explanation for relatively low levels of private sector funding of global health R&D is simply that LMICs are a less lucrative market than high-income countries (HICs). Another part of the explanation is that knowledge generated by R&D has public good characteristics of both being re-usable ("non-rival consumption") and difficult to charge users for ("non-excludability"), the latter making it difficult to recoup investments without some sort of patent protection.

Nonetheless, there are examples of privately funded R&D, blended financing and public-private partnerships targeting diseases in LMICs, and in the presence of well-functioning intellectual property rights regimes it may be possible to effectively minimize the "public goods problem" (i.e., effectively overcoming the non-excludability public goods characteristic of R&D products via patents). There is also some evidence that multinational corporations may be investing more in recent years compared to the past in order to explore other disease areas in large emerging markets (Aeras, 2014). Hence it bears examining whether the simple explanations for current levels of private sector funding – high costs, low or uncertain returns, and non-excludable benefits - hold generally, as a step in identifying the most promising opportunities to catalyze

[4] Defined in the Policy Cures G-Finder reports as diseases that "disproportionally affect people in developing countries," which have a "…need for new products," and for which a market failure exists, "i.e., there is insufficient commercial market to attract R&D by private industry" (Chapman et al., 2016). The 2016 G-Finder report defines neglected diseases as HIV/AIDS, TB, malaria, diarrhoeal diseases (rotavirus, cholera, *Shigella*, *E. coli*, giardia, others), kinetoplastids (Leishmaniasis, sleeping sickness, Chagas disease, others), dengue, bacterial pneumonia, meningitis, helminth infections (schistosomiasis, filariasis, onchocerciasis, hookworm, tapeworm, intestinal roundworms, whipworm, other), typhoid, salmonella, hepatitis C, leprosy, meningitis, trachoma, rheumatic fever, Buruli ulcer, leptospirosis, Ebola, and Marburg.

additional private sector investment in global health R&D. To this end, we develop a framework for thinking about the factors that drive the estimated returns on private sector investment in global health R&D (summarized in detail in Appendix C), and use this framework for organizing our evidence search.

Our goal of examining the separate components of private sector investment decisions in global health R&D is made challenging by the scarcity and unevenness of publicly available information. To have confidence in our findings, therefore, our approach is to reference - and check against – multiple sources with trade-offs in objectivity, contextual relevance, and scope. An earlier report (West, 2017b) uses expert opinion to explore factors influencing private investment in global health R&D – via interviews which are valuable for being contemporary and contextual. The current report draws on an expansive review of the grey and published literature to examine similar themes – and the consistency with which different factors are cited - as reported in industry and government reports and scholarly publications. And an upcoming report summarizes detailed company-specific findings drawing on private company 10-K filings, which offer rich data from the subset of R&D companies who file annual financial reports with the Security and Exchange Commission (SEC). Each information source has strengths and weaknesses, and focuses on a slightly different set of questions. Together these reports provide the most comprehensive view of private sector global health R&D investment drivers to date.

Table 1: Strength of data sources on private investment in global health R&D

	Scope and scale *(sample size & breadth)*	**Objectivity** *(unbiased sample & review)*	**Contextually relevant**
Expert Opinion	Low	Low	High
Literature Review	Medium	Medium	Low
SEC 10-Ks	High	High	Medium

The purpose of this paper is to provide a broad review of the evidence on key market, regulatory, policy and other factors that have affected private sector incentives for global health R&D investment. We do not report on the outcomes of that funding, as assessing the efficiency or effectiveness of private sector investment funds requires largely proprietary data on costs and benefits that are unavailable and that did not appear with any consistency in the literature we reviewed. We do, however, distill any available evidence on the effectiveness of policy incentives for stimulating private sector investment and partnership models that may reflect opportunities for a more efficient distribution of funding and research activity across public and private sectors and across research phases (from preclinical research to Phase III clinical trials).

The paper is organized as follows. As background, we outline a simple theoretical model based on the assumption that private sector actors seek to maximize the present value of net benefits from their investments. This model allows us to break out the components of R&D investment decisions, and generates five hypothesized challenges underlying private sector incentives to invest in global health R&D: scientific uncertainty, unstable policy environments, limited revenues and market uncertainty, high fixed and sunk costs, and other market failures (namely downstream rents from imperfect markets). We then outline our methods for creating a database to assess the broader support for these propositions, describe this database, and present our findings. We include investments in the development of health products - drugs, vaccines, and diagnostics - in our definition of global health R&D, and exclude investments in health & IT system processes or the quality or delivery of health-related services and products. We limit our analysis to health product R&D from preclinical research through Phase III clinical trials, as these upstream research phases are relatively more likely to generate global public goods benefits, and thus may be more likely to see weaker incentives for private investment. We follow with additional details on information from the reviewed literature on policy incentives and partnerships, a potential response to some of the financing challenges discussed. We conclude with an assessment of the evidence on the broader alignment of theory, 15 years of published and grey literature, and expert consultation.

The resulting paper provides a relatively comprehensive, large sample, check on common assumptions and claims surrounding the drivers of low private sector funding for health product R&D of importance to developing countries. An important contribution of this paper is the creation of a repository of 285 reports, analyzed to provide estimates of costs, probabilities to market, and other seldom-assembled data surrounding private sector health product R&D.

1.1 Factors Influencing Private Sector Investment in Global Health R&D: Five Propositions on Disincentives

The economic literature provides theoretical bases for understanding why public and philanthropic funding comprises a greater share of global health R&D than private funding, particularly at pre-clinical and early clinical phases and particularly for diseases most prevalent in low-income countries. We briefly discuss these theories below, and refer the reader to Appendix A for a fuller treatment of the assumptions underlying which factors may determine private sector investment in terms of scientific uncertainty and policy uncertainty, delayed or small financial returns, high costs, and market failures.

One of the most fundamental barriers to providing global health R&D through markets is that the outcome of health R&D – knowledge - has public good elements of both "non-excludability" and "non-rival consumption". Private incentives for making knowledge investments thus depend at least in part on the degree to which the public good arising from those investments can be charged for. The use of knowledge is not inherently physically "excludable," but can to varying degrees be legally protected (e.g., via patents) to secure a revenue stream. Additionally, certainly the knowledge and to some extent the products (i.e., new vaccines, drugs, and diagnostics) of biomedical R&D can confer non-rivalrous benefits to the global public at low cost, for instance in terms of improved health via the benefits of a vaccine that accrue to the unvaccinated. In this case the scientific discovery leading to the vaccine is a public good, and even with patent protection the full value of its benefit flow will not translate into private revenues because the unvaccinated beneficiaries do not pay for their reduced exposure to the virus. Nor does the investor realize any direct revenue streams from multiplier effects due to disrupted transmission chains of infectious diseases that yield improved school attendance or increased economic productivity. Hence, because the external benefits cannot be privately captured, less than the socially optimal amount will be privately produced.

Private firms are expected to make strategic economic decisions based on the expected net present value of an investment, prioritizing those with the highest return. For private sector health R&D investment decisions, the expected net present value of a given stream of research depends on the potential for market revenues (including the market size, pricing, and uncertainty and time delays associated with future revenues), and the costs incurred at each stage of R&D prior to bringing a product to market. Once these calculations are made, the private sector investor then compares the possible returns to a given health R&D investment to the possible returns from other uses (including non-R&D uses) of the same investment funds. Ultimately when R&D is undertaken, a *priori*, theory suggests that profit maximization motives would lead the private sector to invest in R&D for market-oriented products targeting diseases with higher potential for financial returns.

It would then be easy to conclude that private sector investment choices simply reflect the most profitable use of funds or the most comfortable risk-return tradeoffs, especially considering the high opportunity cost of capital earning large returns in high-income country (HIC) markets. In contrast, public and philanthropic funding sources might fund R&D for a greater variety of diseases, factoring in social returns (e.g., herd immunity and other spillover benefits not captured in market prices) as well as private returns. There are, however, examples of privately funded R&D, blended financing, and public-private partnerships targeting diseases in LMICs. The detailed story, therefore, is likely more complex, with possibilities at the margin for catalyzing more private sector investment by increasing returns, lowering risk, and institutional responses to the public good traits of R&D.

We look more closely at these nuances by examining the evidence for five specific disincentives to private sector investment: scientific uncertainty, unstable policy environments, limited revenues and market uncertainty, high fixed and sunk costs, and downstream rents from imperfect markets. Though all five may affect estimates of net returns from an investment decision, they are worth examining separately as each calls for a different intervention or remediation to change behavior.

1. *Scientific Uncertainty.* In the case of global health R&D **a private investor's calculations of returns on investment will vary with disease-specific scientific uncertainty**, i.e., how likely a stream of research investments will yield a marketable product. Financial returns to a private R&D investment are primarily realized once the products developed reach the market (though knowledge is generated - and patents may be purchased - at earlier stages). Hence the uncertainty surrounding the likely success of upstream research efforts to yield a marketable product may substantially discourage investment.

2. *Uncertain, Unstable, or Weak Policy Environments*. Like scientific uncertainty, **unstable or weak policy and regulatory environments (both where the R&D occurs and where the final products are sold) and macroeconomic instability can further discourage investment in global health R&D**, especially where geo-political risks may represent substantial disincentives to investors. R&D that is focused on diseases in countries where it is more difficult to realize a return on investment, either because **health systems are underdeveloped**, or **property rights are poorly protected** may be particularly prone to below socially optimal levels of provision by the private sector as the ability to recoup investments may be compromised and insufficient to ensure a secure revenue stream.

3. *Limited Revenues and Market Uncertainty*. In addition to uncertain policy environments and macro-economic conditions, LMIC **market size and demand is uncertain**. Consumer awareness of health treatments, access to products and guidance, and ability to pay is limited in many low-income settings. Moreover, estimating demand in health care markets is confounded by who pays - the patients, third party insurers, or various public or philanthropically funded subsidy mechanisms (e.g., GAVI or the Global Fund). And despite the potential for knowledge and its products, such as vaccines, to have far reaching value, few of these spillover benefits be captured in private sector prices or translate into increased revenue projections for a private sector firm trying to decide whether or not to invest in the development of a vaccine.

4. *High Fixed and Sunk Costs.* In contrast to revenues, **many costs - and in particular initial (start-up) costs - are incurred with certainty and regardless of whether the** research is successful or not (hence they are "fixed" or invariant to output). Costs vary by the phase of R&D (from pre-clinical to clinical trials), and include fixed costs, such as lab equipment and space, variable costs in the form of researchers and materials, and regulatory compliance costs. Clinical trial costs, specialized labs and equipment, subject area expertise, and royalties or other IP payments are "sunk" to the extent that they are difficult to repurpose which further reduces the contestability of markets, and increases the costs of shifting to different areas of global health R&D.

5. *Downstream Rents from Imperfect Markets.* Lastly, **the market for global health R&D is not a competitive one** with low costs of entry and exit, homogenous products, large numbers of buyers and sellers, and perfect information. Global health R&D bears little resemblance to a perfectly competitive market where dollars and resources will simply flow according to relative profit margins. Rather, information and access to knowledge varies across investors and investment portfolios, products are highly specialized and entry costs can be very high. These industry traits give rise to different degrees of market power, and when there is less competition downstream than upstream it can be "cheaper to

buy than make," i.e., private firms can buy patents at below competitive market prices, and below the expected cost to produce new R&D. Private investors can earn an above market return from these mid-phase exchanges when market power is asymmetric, and may not invest in R&D in the absence of other incentives – such as public or philanthropic partnerships - that favorably shift or pool costs and risks.

2. Methods

2.1 Literature Review Methods

We conducted a literature review of published and unpublished literature for evidence on the proposed challenges to private sector investment in global health R&D. Appendix B provides a detailed review of the literature search, including a table with the search terms and the number of results found from each database or webpage, broken down by search string or search method. During the initial search, we gathered 708 academic articles and grey literature sources that discussed private sector investment in R&D on a drug, vaccine, or diagnostic.

To be included in the review, a source had to meet these four criteria:

- Discuss information about R&D on a drug, vaccine, or diagnostic;
- Discuss R&D at any point between initial research through Phase III clinical trials;
- Discuss investment by a private organization;
- Be published in the last 15 years.

After screening, we retained a total of 285 unique sources, including 131 sources from the peer-reviewed literature database searches and 154 sources from the grey literature searches. We then systematically coded the content of each of these 285 sources using a customized review framework capturing basic information about the source, R&D characteristics mentioned, investment characteristics, factors that influenced investment decisions, and evidence of financial and other returns.

We developed a data extraction form to capture as much information as possible on private sector investments in global health R&D and distinguish these investments from general health R&D investments worldwide. As summarized in Box 1, we collected information on company characteristics, disease and research characteristics, and information on potential market returns. For a full description of the data extraction framework, see Appendix C.[5]

Box 1: Information extracted from studies

Company characteristics	Research characteristics	Potential market returns[6]
Company characteristics	Disease studied	Willingness to pay
Company profits, costs, revenues	Phase of research	Existing policies & regulatory framework
Investment characteristics	Product characteristics	Return on investment
Value of investments	Technical feasibility	Net sales growth rate
Partnership type	Product competitors	R&D investment incentives
	Burden of disease	Estimated costs involved

[5] Some sources had relevant information on more than one drug, vaccine, diagnostic, illness, policy, or program. In such cases, we distinguished particular information by entering data on more than one line. Therefore, some sources appear multiple times in the review framework.

[6] Where the literature reported monetary amounts in different currencies and years, we converted the currency to 2016 US dollars (USD), using the country or region specific GDP deflator to account for inflation to 2016. We then used the average local currency unit per US dollar in 2016 to convert that amount to USD.

In section 3, we present descriptive characteristics of the literature reviewed. We report first on the distribution of diseases and product types mentioned across the 285 sources (Appendix E presents available information on estimates of potential market demand for the R&D products discussed, and Appendix F reports evidence of efficacy and cost-effectiveness of these products as presented in the literature). We then summarize key characteristics of the various private companies represented in the literature, including briefly presenting information on the types of partnerships described (further information on partnerships is reported in Appendix G).

2.2 Analytical Methods

We conducted both qualitative and quantitative analysis of the data extracted from the 285 sources. For each hypothesized disincentive, i.e.: scientific uncertainty, unstable policy environments, limited revenues, high fixed and sunk costs and downstream rents from imperfect markets, we identified a set of indicators for which at least some data were available through our coding framework. Where possible we summarize quantitative evidence supporting or refuting the hypotheses; otherwise we summarize conclusions drawn from the literature providing qualitative evidence relating to each presumed disincentive to private sector R&D investments. Appendix D provides details on indicators for each hypothesis.

Though we are examining the individual components of investment decisions in five separate hypothesized disincentives, they are obviously related: scientific uncertainty affects costs, policy and market uncertainty affect demand, etc. They are nonetheless worth examining separately as each calls for a different intervention or remediation to change behavior. For example, scientific uncertainty affects costs and estimated revenues through the time and likelihood to discovery and price of expertise. Reducing scientific uncertainty would likely involve more and better information sharing among researchers, whereas addressing the capital costs of initiating R&D efforts would potentially require new financing options.

The individual components, however, are not always neatly separated in the literature, and instead may bundle two or more disincentives, as for example: “Vaccine candidates with high development costs, significant scientific risks and uncertain markets (e.g., no significant industrialized country market) may require both push and pull mechanisms to motivate rapid product development” (Batson, Meheus, & Brooke, 2006, p. 222). When it was clear that the source was predominantly focused on one challenge, we counted it once under the dominant corresponding proposition. When equal weight was given to multiple factors, the source would be counted under each of those hypotheses. Beyond this general protocol, we made the following coding decisions:

- Code “scientific uncertainty” ONLY if it is mentioned in isolation of costs or as the driver of costs;
- Code “costs” whenever costs in general are mentioned as a primary investment challenge, but also code specifically for fixed costs or disease or company specific costs that cannot be repurposed (i.e. are “sunk”)
- Code “downstream rents” whenever the article mentioned factors broadly related to the organization of the health R&D industry, including “upstream rents” deliberately created through IP protection to create R&D incentives and that can support monopoly pricing, though our primary interest is in specific mention of imperfect markets including non-marginal cost pricing and monopsony power, which can result from asymmetric market power, not patent policy.

The number of counts, therefore, should not be equated with the magnitude of the investment challenge, as much as the narrowness or breadth of what is included. They do reflect, however, relative attention in the literature to factors affecting private sector investment. The evidence related to each of the five hypothesized disincentives is presented in section 4.1.

In addition to reviewing evidence related to the five disincentives to private global health R&D investment, we also analyzed evidence of the effects of various policy incentives seeking to promote expanded private global health R&D. Incentives include push mechanisms, such as public research funding and R&D tax credits, as well as pull mechanisms, such as advanced purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions. We identified 56 sources reporting on impacts of these policies on private global health R&D spending; this evidence is presented in section 4.2.

Finally, the highly specialized nature of some R&D can also give rise to market efficiencies from firms forming partnerships allowing them to specialize in those activities in which they have lower relative costs of production. Thus, in order to more fully understand private sector investment in global R&D, we also explore private sector investments in collaboration with public and philanthropic partners. For example, a product-development partnership (PDP) or other form of public-private partnership (PPP) may be established to undertake R&D through a contractual arrangement that lowers the upfront costs to pharmaceutical companies, so that private firms will invest in diseases they ordinarily would not. Appendix G summarizes our findings on the role of partnerships in supporting private sector investments in global health R&D. We start by exploring private-to-private partnerships, followed by information on the role of public-private partnerships and then present findings on public-private partnerships by disease, by research phase and by funding amounts. These data are not comprehensive, but rather represent estimates based on the 285 studies in this review.

3. Descriptive Characteristics of the Literature Reviewed

3.1 Diseases and Product Types

The 285 studies included in this review covered 47 individual diseases. Noting that some sources may mention more than one disease, Table 2 shows frequency of studies by major disease category, with much of the private health R&D funding literature comprised of studies on infectious diseases (28 percent of all studies reviewed), chronic diseases including cancer (16 percent) and antibacterial/antimicrobial resistance (6 percent). Malaria (8 percent), HIV/AIDS (6 percent), and tuberculosis (5 percent) make up the majority of R&D studies within infectious diseases, while other neglected or neglected tropical diseases account for 16 percent of all studies reviewed and preventable diseases account for 6.5 percent.

Table 2: Number of sources that mention each disease or type of disease[1]

Infectious Diseases	Number of Sources
Viral Diseases	
HIV/AIDS	17
Ebola	4
Hepatitis C	4
Rotavirus	4
Hepatitis B	2
Influenza	2
Bacterial Diseases	
Tuberculosis	15
Meningitis	2
Pneumococcal Disease	2
Parasitic Diseases	
Malaria	23
Chagas Disease	6
Dengue Fever	4
Onchocerciasis (River Blindness)	4
Trypanosomiasis (Sleeping Sickness)	3
Schistosomiasis	3
Chronic Diseases	
Pain/Inflammation	3
Diabetes	2
Inflammatory Bowel Disease	2
Degenerative Diseases	
Cancer[1]	43
Alzheimer's Disease	4
Inherited Diseases	
Cystic Fibrosis	2
Drug-Resistant Diseases	
Antibacterial/Antimicrobial Resistance	18
Multidrug-Resistant Pathogens	3
Other	18
No Specific Disease Mentioned[2]	153
Total	343[3]

1. Specific cancers mentioned (number of sources): Cervical cancer (6), melanoma (2), acute myeloid leukemia (1), lung cancer (1), mesothelioma (1), pediatric (1)
2. Some sources did not mention any specific disease but instead discussed health R&D in general or for types of diseases
3. Some sources discuss more than one disease.

It was common for studies to include multiple diseases or disease types[7] as follows: general R&D (104 sources), neglected diseases (17), vaccine R&D (6), neglected tropical diseases (5), rare diseases (5), central nervous system diseases (3), cardiovascular disease (2), developing country R&D (2), infectious diseases (2), orphan drugs (2), diseases of intermediate prevalence (200,000-1,000,000 patients) (1), diseases of the poor (1), emerging infectious diseases (1), immunological diseases (1), microbiome disorders (1), noncommunicable diseases (NCDs) (1), neurological diseases (1), pathogens (1), sexually transmitted infections (STIs) (1), Type II & Type III diseases (1).

Table 3 describes the products by development phase for drugs, vaccines and diagnostic tools. The most studies were for pharmaceutical drug R&D, followed by vaccine R&D. There is relatively little published literature on private funding for diagnostic tool R&D. We also found relatively limited information in the private R&D funding literature on the number of competitors for products, evidence of clinical efficacy, and

[7] Terminology taken verbatim from sources.

evidence of cost effectiveness, though a targeted search for market and product characteristics, or effectiveness could yield more information (available data are summarized in Appendix E and F).

Table 3: Product types by development phase (number of sources)

Product	Number of Sources	Pre-clinical	Phase I	Phase II	Phase III	Product Competitors	Evidence of Efficacy	Evidence of Cost Effectiveness
Drug	125	86	85	89	84	3	11	6
Vaccine	65	43	46	45	42	6	9	5
Diagnostic	3	1	3	3	3	0	0	0
Multiple	92	85	76	77	78	0	2	3
Total	285	215	210	214	207	9	22	14

Note: Stages of clinical trials as defined by the WHO: "**Phase I**: Clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety. **Phase II**: Clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety. **Phase III**: Studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions.

3.2 Characteristics of Companies

We compiled available data on private sector company characteristics reported in the literature including the size of companies, annual sales, annual profit, the ratio of R&D investments to sales, and the number of employees. Table 4 shows the wide range in company size, with most papers reviewed reporting on the activities of a small number of large companies working in global health R&D - mostly based in high income countries, though two sources mention Chinese companies and four mention Indian companies.

Table 4: Company characteristics by number of sources

		Number of Sources
Annual Sales	$257 - $41,533 (in 2016 USD millions)	14
Annual Profit	$100 - $44,179 (in 2016 USD millions)	7
Ratio of R&D Investments to Sales	0.06-0.26	14
Number of Employees	17 - 127,600	25
Most Frequently Discussed Company	1. AstraZeneca	31
	2. GlaxoSmithKline	17
	3. Merck	15
Most Frequent Company Location	1. United Kingdom	49
	2. United States	30
	3. Japan	15
	3. Sweden	15

While not exhaustive, our literature search was able to provide some illustrative information on the median and range of investments by research stage and for total investments (Table 5). Private companies and public/philanthropic investors both contribute to private sector global health R&D, with estimates ranging from single investments of less than $500,000 to collective PhRMA member investments of $35 billon in a given year. The median amount invested by private companies and public/philanthropic groups was $335 million and $126 million, respectively. Note that the amounts presented vary in terms of number of years of investment and/or may also represent total investments by multiple private companies.

Table 5: Median and range of investments by research phase and sector (2016 USD millions)

	Median dollars invested	Range	Description of minimum investment	Description of maximum investment	Number of sources
Pre-Clinical					
Private Company	$23.33	$8.3-$11,172	Contribution by one private company over five years to fund range of projects	Total PhRMA[1] member preclinical R&D spending in single year	9
Public / Philanthropic[2]	$8.08	$0.2-$570	Contribution from nonprofit to support preclinical work on malaria drug	All basic research funding directed towards malaria from non-industry sources	26
Clinical					
Private Company	$188	$27.9-$21,846	Initial payment by private company for exclusive rights for HPV therapy	Total PhRMA member Phase I-Phase III R&D spending in single year	13
Public / Philanthropic[2]	$8.55	$1.65-$211	Funding from Cancer Vaccine Acceleration Fund to support clinical development for cancer drugs	Grant from Bill and Melinda Gates Foundation for malaria vaccine development	8
Overall					
Private Company	$335	$1.01-$35,816	Amount of private sector contributions and pledges to TBVI between 2010-2012	Total overall PhRMA member Preclinical – Phase III R&D spending in single year	80
Public / Philanthropic[2]	$126	$0.350-$22,993	Funding for The Synaptic Leap's Schistosomiasis project by the WHO and the Australian government	Federal R&D expenditures in 1996	42

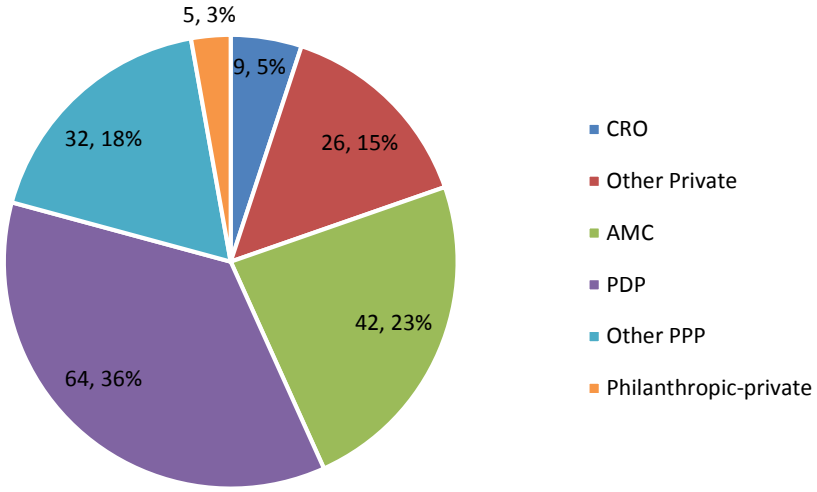
[1] Pharmaceutical Research and Manufacturers of America

[2] These are public or philanthropic grants or investments that support private sector collaboration or PPPs that are partially funded by the private sector.

We define a PPP as any kind of agreement between a private for-profit firm and a public organization in which both private and public organizations have collective decision making authority (Buse & Harmer, 2007). As anticipated, the literature review revealed that partnerships between two or more private firms (private partnerships), or between private firms and philanthropic organizations (philanthropic-private partnerships) or public institutions (public-private partnerships, or PPPs) are common across all phases of preclinical and clinical research. Philanthropic organizations are also often involved in PPPs. A product-development partnership (PDP) is a different type of partnership that is organized specifically to develop a product. Whereas PPPs can be short-term collaborations, PDPs for global health are permanent organizations that drive product development for the "advancement of public health rather than commercial gain" (Moran et al., 2010). Most PDPs involve public, philanthropic, and private for-profit organizations. Philanthropic-private partnerships are partnerships between private philanthropic organizations and private for-profit firms that do not include any

public sector partners. A partnership with an academic medical center (AMC) involves both an academic and private for-profit partner, and AMCs can be involved in PPPs and PDPs as well. AMCs generally provide research rather than funding. Contract Research Organizations (CROs) are private firms that conduct research, usually defined by a contract with a pharmaceutical company. In our review PDPs and other PPPs (excluding PDPs and AMCs) accounted for over 50% of all partnership types, while private partnerships (private-private), contract research organizations (CRO), philanthropic-private partnerships, and academic medical centers (AMC) accounted for the remainder.

Figure 1: Proportion of sources that mention a partnership by type of partnership.



Note: The Other PPP category includes PPPs that are not PDPs or AMCs. The total number of sources reporting on partnerships is 178.

At the company level, Table 6 lists the pharmaceutical, biotech, and vaccine companies mentioned in the literature reviewed, as well as one contract research organization, that were in some type of partnership. Of the 51 companies that were listed by name in this review, 31 were involved in at least one PPP. Of these, 19 were involved in a PDP and nine partnered with an academic medical center. Five companies were listed as both involved in a PDP and partnering with an AMC. Four companies had at least one partnership with a contract research organization. Sixteen companies in our review did not report any involvement in partnerships.

Further discussion of evidence on the effectiveness of partnerships seeking to promote private sector global health R&D investment is provided in Appendix G.

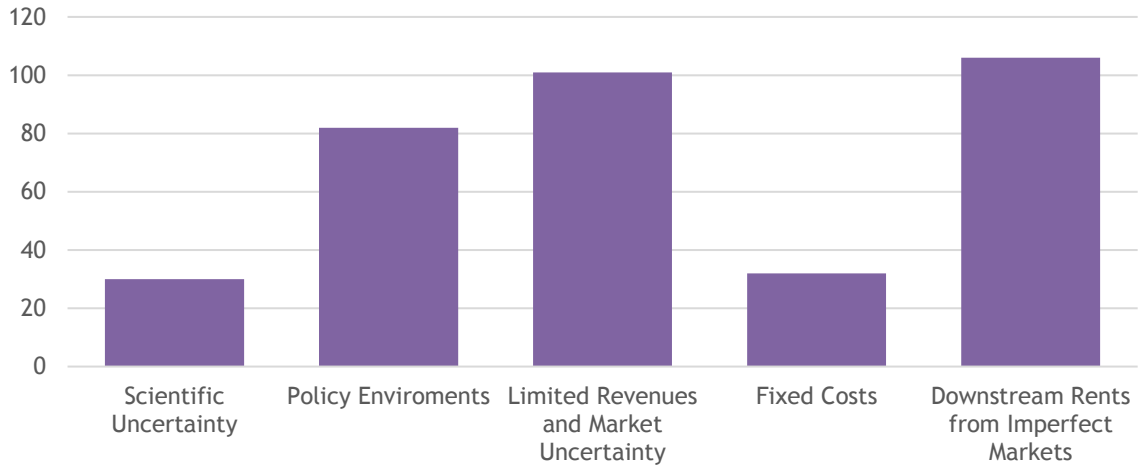
Table 6. Partnerships by company

Company	Public Private Partnership (PPP)	Product Development Partnership (PDP)	Partnership with Academic Medical Center (AMC)	Partnership with Contract Research Organization (CRO)
Pharmaceutical Companies				
Abbott	Y	Y		
AbbVie	Y	Y		
Anacor	Y	Y		
AstraZeneca	Y	Y	Y	Y
Bayer Healthcare	Y	Y		
Bristol-Myers-Squibb	Y	Y		
Celgene Global Health	Y	Y		
Charles River Laboratories				Y
Daiichi Sankyo	Y		Y	
Eisai	Y	Y	Y	
Emergent BioSolutions	Y			
GlaxoSmithKline	Y	Y	Y	
Johnson & Johnson	Y	Y	Y	
Merck	Y	Y		
Novartis	Y	Y		
Pharco Pharmaceuticals	Y	Y		
Presidio	Y			
Roche	Y	Y		Y
Rusnano	Y			
Sanofi	Y	Y		
Takeda	Y	Y	Y	
Biotech Companies				
Aurora Biosciences/Vertex Pharmaceuticals	Y			
CellFree Sciences	Y		Y	
CureVac	Y			
Lentigen	Y	Y		
Shanghai H&G Biotechnology Ltd	Y			
Shantha	Y		Y	
Vertex Pharmaceuticals	Y			
Vaccine Companies				
Crucell	Y	Y		
GeoVax	Y		Y	
Serum Institute of India	Y	Y		
Contract Research Organizations				
Covance				Y
Total	31	19	9	4

4. Results from the Literature

For each of the 285 articles reviewed, we coded any mention of an investment challenge according to which of the five hypothesized disincentives it was most closely associated with. Noting that each source may discuss more than one factor that promotes or hinders drug, vaccine, or diagnostic R&D, *Figure 2* summarizes the number of sources that mention factors across the five propositions. Scientific uncertainty was mentioned least often in the literature, though it is arguably one of the most narrowly defined categories and mentions of costs associated with this uncertainty appear elsewhere. Policy environments include any sort of regulations or mention of weak property rights. Factors related to limited revenues were mentioned often, perhaps because this category includes mention of pricing, market size, overall revenue and disease burden – of which only the incidence is expected to matter to profit maximization, though the morbidity of the disease can affect willingness to pay, all else equal.[8] Costs were mentioned in over 100 documents, but only mention of high up-front costs or the costs associated with specialized investments or activities that are "sunk" appear here. Examples of text coded into this category include: "Moderna will use upfront payment to fund portion of GMP manufacturing facility for purpose of personalized cancer vaccine manufacturing" and Sanofi spent €350 million on a dedicated manufacturing plant for dengue fever vaccine." Factors associated with the possibility of downstream rents were mentioned often perhaps given the breadth of this category that includes references to buying patents, consolidation, market power, imperfect markets, and monopoly or monopsony pricing (pricing outputs or inputs above marginal cost).

Figure 2: Number of sources that discuss various factors that influence private sector investment



Note: The count for "fixed costs" in Figure 2 includes only documents explicitly referencing high fixed or sunk costs. All other source counts reflect an accounting of all mentions of hypothesized disincentives to private sector global health R&D investment in the literature reviewed, using criteria as described in Appendix C. Totals may differ somewhat from counts reported elsewhere in the report using narrower criteria.

We use this literature to first explore evidence relevant to the five hypothesized disincentives to private sector global health R&D investment (4.1) and then to report on policy incentives (4.2) and partnerships (Appendix G) that may be a response to some of these challenges.

[8] We assume private sector investors and firms are primarily commercially oriented, even though we recognize that corporate social responsibility and other non-purely profit motives exist.

4.1 Findings for the Five Hypothesized Disincentives to Private Sector Global Health R&D

The findings presented in this section are restricted to the 285 reviewed and coded articles, published and unpublished, that surfaced through the search strings across multiple databases and websites, and met the screening criteria. For each presumed disincentive, the indicators selected from the database and presented in the tables and figures are summarized in a text box.

4.1.1 Proposition 1: Scientific Uncertainty

The degree of scientific uncertainty inherent to successful health R&D outcomes – both the efficacy and safety – will affect costs and time to market and varies by disease. And while breakthroughs for molecular biomarkers for certain diseases can generate multiple new potential therapies, each can require years of expensive translational research and still have a substantial likelihood of failure. The degree to which this uncertainty is a disincentive is likely to depend on investors' risk/return preferences and ability to manage these risks against a portfolio of investments. While scientific uncertainty is theorized to affect investment choices, it was not emphasized in expert consultations on the drivers of private sector investment in health R&D (West et al., 2017b).

Indicators of Scientific Uncertainty

- Probability of successful R&D
- Scientific factors that influence R&D investment
  - Product studied
  - Phase of research

Probability of Successful R&D

We summarize probabilities reported in the literature of a medical product advancing successfully through Phase III of clinical research and development (Table 7). Several sources report the probability of advancing successfully through Phase III only, while others report the probability throughout the length of preclinical or clinical trials.

Table 7: Estimates of the probability of success, through clinical research approval

Product Studied	Phase of Research	Partnership Type	Probability of Success	Source
Drug R&D	Preclinical - Approval			
		Public-Private Partnership, Product-Development Partnership, Partnership with CRO	0.08	Banerjee, 2012
		Public-Private Partnership	0.21	Barton & Emanuel, 2005
		Only non-partnership R&D studied	0.22	Di Masi et al., 2003
	Phase I - Approval			
		None specified	0.11	Tufts, 2015
		None specified	0.18*	DiMasi. et al., 2010
		None specified	0.26	Abrantes-Metz et al., 2004
		None specified	0.30	Hirsch & Schulman, 2013
	Phase III - Approval			
		None specified	0.71	Adams & Brantner, 2010
New Chemical Entity (NCE) R&D	Preclinical - Approval			
		None specified	0.22**	Pronker et al., 2011
Vaccine R&D Infectious Diseases	Preclinical - Approval			
		None specified	0.06	Pronker et al., 2013

Sexually Transmitted Infections		Public-Private Partnership	0.22	Dodet, 2014
Vaccine & Drug R&D	Phase I - Approval	None specified	0.20	Waye et al., 2013
Tuberculosis	Phase III - Approval	Public-Private Partnership	0.85	Aeras, 2014
Orphan Drug R&D	Phase II - Approval	Partnership between large pharmaceutical firms and smaller biotechnology firms	0.93	Kumar Kakkar & Dahiya, 2014
Alzheimer's, diabetes, arthritis, lupus R&D	Preclinical - Approval	Public-Private Partnership	0.05	NIH, 2014b

Notes: All probabilities taken from associated paper
* Clinical approval success rate in the U.S. for self-originated drugs
** Provides a large range, drawing from 7 articles, Average 22%, range 7%-78% depending on the study

Three sources further break down the probability of regulatory success by individual phase of clinical research. One source, in reference to general biopharmaceutical drug research and development, reports a 75% success rate for Phase I, 48% for Phase II, and 71% for Phase III (Adams & Brantner, 2010). The second source, discussing research and development for Tuberculosis drugs, reports 20% for preclinical, 33% for Phase I through Phase IIA, 33% for Phase IIB, and 85% for Phase III (Aeras, 2014). The third source, again discussing general biopharmaceutical research and development for drugs, reports 81% for Phase I, 58% for Phase II, and 57% for Phase III (Abrantes-Metz, Adams, & Metz, 2004).

Kumar Kakkar & Dahiya (2014) report that orphan drugs have a 93% probability of regulatory success in Phase III, as compared to 88% for non-orphan drugs. Orphan drugs are defined by the FDA as those which treat conditions affecting fewer than 200,000 individuals in the U.S. (FDA/CDER, 2012), and by the European Medicine Agency Committee for Orphan Medicinal Products as "a life-threatening or chronically debilitating condition the prevalence of which is not more than 5 in 10,000" (Kumar Kakkar & Dahiya, 2014, p. 231). This higher probability of success is thought to be driven by the various incentives acquired through orphan drug designation.

Other Scientific Considerations

Four other sources mention scientific factors as a concern, with three specifically citing increasing scientific complexity as a major factor in investment decision-making (Table 8).

Table 8: Sources mentioning scientific challenges of R&D

Scientific Factor	Research Phase	Research Focus	Source
Complexity	Preclinical-Phase III	General drug R&D	Fernandez et al., 2012
Complexity	Preclinical	General Precompetitive R&D	Williams et al., 2012
Complexity	Preclinical	Vaccines	Yaqub et. al., 2012
Access to research	Preclinical	Vaccines	GSK, 2013
Existing Knowledge	Preclinical	Orphan Drugs for rare diseases	Heemstra et al., 2009

The underlying scientific uncertainty of successful R&D outcomes is fundamental to risk-return calculations. Heemstra et al. (2009) posit that disease-specific scientific output is a contributing factor in translating orphan disease research to drug development. They find that rare diseases with a greater amount of related research

(measured by number of scientific publications), and less scientific uncertainty, are more likely to progress to orphan drug development. Fernandez, Stein, & Lo (2012) claim that as biomedical science advances, the complexity of research grows, requiring increased resources, funding, time, and consequently, risk. Plotkin et al. (2015, p. 297) write that "Vaccine development is facing a crisis for three reasons: the complexity of the most challenging targets, which necessitates substantial investment of capital and human expertise; the diminishing numbers of vaccine manufacturers able to devote the necessary resources to research, development, and production; and the prevailing business model, which prioritizes the development of vaccines with a large market potential."

We found only limited mention of differing scientific challenges across diseases and products. Yaqub & Nightingale (2012) report that despite funding ($961 million USD in 2007), the presence of an adequate market, and public support, HIV vaccines have not been developed due to difficulties in scientific experimentation. Diseases such as HIV, malaria, and tuberculosis face scientific barriers including limited and/or weak animal models and high to extreme genetic variation in virus/infection type, both of which can increase costs and experimentation time. The authors conclude by remarking that "the limited production of new vaccines does not necessarily indicate a lack of social concern, demand or funding. It also reflects a difference in difficulty of such a degree that some therapeutics and prophylactics may be beyond easy reach" (p. 2149).

But there is an argument that it is not the inherent complexity of science that is driving uncertainty and costs, but rather imperfect input and output markets that allow companies to monopolize knowledge. Williams et al. (2012), discussing precompetitive research, note that as scientific research and development becomes more complex, vast bodies of scientific knowledge are being stored in different companies. They argue that pharmaceutical firms should become more open to sharing data and discoveries, in order to alleviate challenges in drug development due to the complex understanding of human disease processes, thereby reducing the risk and time associated with scientific uncertainty. In these cases, imperfectly competitive markets may compound the risk and cost associated with scientific uncertainty.

4.1.2 Proposition 2: Uncertain, Unstable or Poor Policy Environments

Challenges in the policy environment include the effects on private investment for diseases prevalent in populations concentrated in countries with poor health delivery systems or health governance (which may limit delivery and access to markets), and uncertain regulatory environments (which may weaken IP, support fraud, or affect the time and probability to market). These factors were also mentioned in the West et al. (2017b) expert consultations under "macroeconomic difficulties" and "higher geopolitical risk," which can likewise contribute to weaker demand and market volatility. Eighty-two sources cited policy factors as relevant to private sector investment, but most offered little specificity.

Indicators of Market and Policy Uncertainty
- Estimated regulatory costs:
  - Health systems & governance
  - Regulatory uncertainty

Poor Health Delivery Systems & Poor Health Governance

Type II and Type III diseases[9], prevalent in low-income countries, are also those with populations likely vulnerable to poorly funded health delivery systems. Several sources mention the challenges present in vaccine R&D including that "the larger companies already supplying vaccines for the global market attached

[9] According to the WHO, "Type I diseases are incident in both rich and poor countries, with large numbers of vulnerable populations in each, Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries, and Type III diseases are those that are overwhelmingly or exclusively incident in developing countries" (WHO, 2012c)

little or no commercial value to markets in developing countries, citing the slow uptake and lack of funding for such cost-effective products as hepatitis B and Haemophilus influenzae type B vaccines" (Batson & Ainsworth, 2001, p. 723). For instance, in India, a country that manufactures vaccines and has a Universal Immunization Program, only about 60% of children receive basic vaccines, attributed variously to a "huge and diverse population, spread over various geographical terrains in the country; drought, floods, a large migrating population and problems with the cold chain system" (Gupta et al., 2013, p. B48). In another example, pneumonia and diarrhea together account for almost half of all child deaths around the world despite there being highly cost-effective interventions that have been around for several decades (Rudan et al., 2007). Rudan et al. (2007) estimate that by using existing cost-effective health technology "up to two-thirds of deaths in children under 5 years of age could be prevented today" (p. 57).

Uncertain Regulatory Environments

One source (PhRMA, 2016) reports industry-aggregated costs for 2014. Using annual member surveys, PhRMA (2016) reports the aggregate figure for regulatory compliance costs for PhRMA members at approximately $2.78 billion for the year. This represents 5.1% of the overall reported cost across all PhRMA members for developing a new product. PhRMA lists this cost under the "approval" phase of development, occurring between the time a company applies for New Drug Application (NDA)/Biologic License Application (BLA) and when a decision is made to accept or deny the application.

In addition, uncertain regulatory environments in LMICs may delay product approval. Rezaie et al. (2012) studied the biopharmaceutical market in China, India, Brazil, and South Africa and found that health product regulation was a common challenge facing local firms that performed R&D. These challenges were rooted in different causes for each country. For example, the authors describe the regulatory process in India as fragmented, while in Brazil and South Africa regulators appeared to be lacking experience. The main problem reported for China was corruption within the regulatory system. The results of these challenges across all countries studied were delays in approving clinical trials (ibid).

In addition to accelerating the review and approval process to cut down on regulatory costs (Theuretzbacher, 2012; Chataway, 2010), other regulatory issues mentioned included the need for increased regional regulatory cooperation to benefit LMICs (Freeman, 2013), the involvement of regulatory agencies in public-private partnership (PPP) decision making (Goldman, 2012), and the inclusion of cost-effective measurements in the regulatory approval process (Hall et al., 2010). Additionally, Chataway (2010) reports that high regulatory costs associated with Phase III clinical trials limits small and emerging market firms. Though small firms may be innovative, some authors argue that the high regulatory costs limit the direct impact small firms can have on developing health products (Chataway, 2010).

Where intellectual property is not enforced, LMICs become doubly disadvantaged from low-income markets and undercutting rights that discourage private R&D for diseases not also prevalent in countries where patent protection generates some monopoly rents. Sheer size, however, may either override lower incomes and uncertain IP regimes, or may lead companies to engage in advocacy to improve IP. As Qui et al. (2014) observe, "For private investors, the best solution is to increase the firm's profit expectation of R&D" (Qui et al., 2014, p. 8) by lobbying for and actively contributing to the creation of practical and effective IP strategies against global competitors.

4.1.3 Proposition 3: Limited Revenues and Market Uncertainty

Limited revenues from small or low-income markets with limited willingness or ability to pay (even where there is a high burden of disease) and forecasting challenges estimating future market demand given the time to development and third-party subsidies may be one of the primary obstacles to private sector investment. This proposition stems from the basic assumption that the private sector is interested in maximizing private returns, and from expert consultations that mention both "Limited Markets for Certain Diseases" and "A Lack of Systematic Data" as barriers to private sector R&D investment (West et al., 2017b).

Indicators of Limited Revenue & Market Uncertainty

- Numbers of individuals affected
- Disease type
- Price of existing treatment
- Price/WTP of therapy
- Product type
- Is there a partnership involved in development?

Findings on Limited Revenues

The papers reviewed commented on limited markets, but did not directly discuss market size. Many papers, however, discussed disease prevalence and the need for diagnostics, drugs and vaccines to prevent or treat global health diseases and conditions. Table 9 presents the number of individuals affected per year by a disease as reported by the literature[10], where "affected" generally refers to deaths, infections, or spread (new cases or infections). The estimates in Table 9 do not proxy market size, because the individuals affected by disease may not be the ones paying directly for the products, will have different levels of access, and will have differential rates of uptake. They do help to evaluate the significant unmet potential demand, though estimates vary depending on the source. Appendix C summarizes a number of FIND reports on actual or potential market size to provide some estimates of the quantity and revenues currently for diagnostics, drugs and vaccines for tuberculosis (TB), malaria, HIV, vaccine preventable diseases (in India) and Hepatitis C. Given current demand, these markets may be relatively small compared to more profitable commodities. For example, for malaria worldwide, the actual market volume for rapid diagnostic tests was 314 million, while approximately 200 million people were infected with malaria in 2013 (Table 9).

Table 9: Number of individuals affected by selected diseases worldwide per year

Disease	Number of individuals affected	Comment	Source
Infectious Diseases			
Viral Diseases			
Ebola	14,000		Arnold & Pogge, 2015
Hepatitis C	140,000,000	130-150 million people have chronic hepatitis C infections and about 500,000 die each year	DNDi, 2016a
	150,000,000		DNDi, 2016b
Herpes	4,117,000,000	Number of people with disease in 2012	Gottlieb et al., 2016
	417,000,000	417 million prevalent infections in 2012 among 15-49 year olds	Gottlieb et al., 2016
HIV/AIDS	33,000,000		Hecht & Gandhi, 2008
	2,700,000	2.7 million people became infected with HIV in 2007, 2 million people died of AIDS	IAVI, 2008

[10] A more comprehensive, methodologically-uniform dataset on disease prevalence is provided through the Lancet's Global Burden of Disease Study 2015, in particular the *Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015* which can be found here: http://thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)31678-6.pdf

Disease	Number of individuals affected	Comment	Source
	2,000,000		IAVI, 2015a
	See describe	3.3 million children under 15 infected, 3.1 in Sub-Saharan Africa; 900 new cases each day	DNDi, 2013
Influenza	350,000	14 million infected in industrialized countries, 350,000 deaths worldwide	Johnson & Johnson, 2009a
	500,000	About 500,000 people die of the flu every year	PATH, 2008a
Rotavirus	111,000,000		Light et al., 2009
Bacterial Diseases			
Chlamydia	131,000,000	New infections in 2012	Gottlieb et al., 2016
Gonorrhea	78,000,000	New infections in 2012	Gottlieb et al., 2016
Pneumococcal disease	14,500,000	About 14.5 million episodes of serious pneumococcal disease occur annually resulting in about 826000 deaths in children up to 5.	Sanofi, 2014
Syphilis	5,600,000	New infections in 2012	Gottlieb et al., 2016
Tuberculosis	1,400,000	1.4 million people died from tuberculosis infections in 2011	Eisai, 2015b
	1,800,000	1.8 million people die a year from TB with 9 million new cases per year	Li & Garnsey, 2014
	2,000,000		Aeras, 2006
	8,700,000	In 2011, an estimated 8.7 million people fell ill with active TB, a third of these cases undiagnosed and untreated	Aeras, 2014
	8,700,000	WHO estimated 8.7 million new cases in 2011; 1.4 million deaths	Treatment Action Group, 2013
	9,000,000	9 million people developed TB in 2013	TBVI, 2015b
	9,000,000	9 million people developed TB in 2013	TBVI, 2015d
	12,200,000	10.4 million new cases & 1.8 million deaths in 2015	Aeras, 2015
Parasitic Diseases			
Chagas	8,000,000		Eisai, 2011d
	8,000,000		Eisai, 2013
Dengue fever	390,000,000		Sanofi, 2015f
Filariasis	150,000,000		Eisai, 2015a
Malaria	630,000	Malaria killed 630,000 in 2012	Eisai, 2015a
	655,000		PATH, 2012
	800,000	Malaria kills close to 800,000 individuals per year, most of whom are children under 5 in sub-Saharan Africa	PATH, 2011
	800,000		PATH, 2009
	1,000,000		PATH, 2008b
	198,000,000	198 million people were infected with malaria in 2013	Eisai, 2015a
	198,000,000	198 million people were infected with malaria in 2013 and an estimated 584,000 deaths, primarily young children from developing countries	MMV, 2015b
	207,000,000	207,000,000 infected in 2010 (627,000 deaths)	Årdal & Røttingen, 2015
	250,000,000	250 million people were infected with malaria in 2006, nearly 1 million of them died	Eisai, 2011c

Disease	Number of individuals affected	Comment	Source
	250,000,000	Between 300-500 million people infected per year with malaria and over 1 million deaths	MMV, 2006
	500,000,000	Leading cause of death for children under 5 in sub-Saharan Africa	DNDi, 2005
Onchocerciasis	25,000,000	25 million affected worldwide, 6 million have debilitating symptoms, 270,000 suffer blindness	DNDi, 2014a
Schistosomiasis	200,000,000	200 million people in Africa suffer from schistosomiasis, with more than 200,000 dying each year	Merck KGaA, N.D.
Trichomoniasis	143,000,000	New infections in 2012	Gottlieb et al., 2016
Chronic Diseases			
Alzheimer's	44,000,000	44 million people worldwide live with dementia	AstraZeneca, 2015a
Cancer (cervical)	500,000	Almost 500,000 new cases of cervical cancer are reported each year	Batson et al, 2006
	200,000	80% of new cervical cancer cases occur in women from developing countries; 200,000 deaths per year from cervical cancer	Brooke. et al., 2007
	490,000	490000 are diagnosed each year with cervical cancer; 249000 deaths every year	Cottingham & Berer, 2011
Inherited Diseases			
Cystic fibrosis	70,000		Lott, 2014

A few sources mentioned market size as a primary constraint on investment: “The high cost of drug development, together with the estimated low return on investment (due to very small patient populations), has discouraged the pharmaceutical industry from developing drugs for rare diseases, despite the huge medical need” (Fischer et al., 2005, p. 845). And “the market for antibiotics is not sufficiently profitable to incentivize companies to maintain an R&D pipeline that could meet the present and future threat of antibiotic resistance” (Nwokoro et al., 2016, p. 2). Cottingham & Berer (2011) also observe that while the hormonal contraceptive market was worth $6.2 billion in 2008, it was relatively low in contrast to the global market for cardiovascular diagnostics and therapies at $111 billion in 2006, and that such estimates have an impact on which medicines are developed and how they are marketed.

Many more sources mentioned a limited “market” – where “market” refers to potential revenue, not necessarily number of beneficiaries – as the reason that private companies did not invest in diseases that primarily affect low-income countries (Nwokoro et al., 2016; Woodson, 2016; WHO, 2010; Batson et al., 2006; Batson & Ainsworth, 2001). Several sources describe returns that vary broadly across R&D categories. Meadows et al. (2015) report that diagnostics do not have as much of a return on investment as therapeutics: “Diagnostic development is typically more rapid than for therapeutics, although with significantly lower returns” (p. 10). Nutt & Aldridge (2014) on the other hand, find that in the EU, very low reimbursed prices for mental health treatments could signal to investors not to persist with product development even if there are some valuable incremental innovations in late development. They report that several leading companies have withdrawn R&D in mental disorders, and predict “If incremental advances now in late development fail to access reimbursement at reasonable prices, investment in further product development for these mental illnesses could dry up altogether” (p. 19). Additionally, White et al. (2011) finds that “The current economic model does not favor antibacterial development and the antibacterial market does not support ‘blockbuster’ returns on investment as other types of therapeutic agents, particularly those prescribed for chronic illness” (p. 1950).

Other sources describe challenges of limited revenues in driving R&D for pharmaceutical markets specifically for low-income countries. Woodson (2016) notes that "biotechnology and pharmaceutical companies will not develop new medicines to target DoP [Diseases of the Poor] if they cannot recoup their R&D expenses, and as a result, there is less R&D and medicines for DoP" (p. 1410). "One of the challenges of development is that technology specifically designed to address the problems of poor countries is not developed, both because the public interest of rich countries in subsidizing such technology is low or heavily discounted and because there are no private incentives, given that the markets in which the technology would be sold are thin and small" (WHO, 2010, p. 10). Plotkin et al. (2015) observe that "there are many infectious disease targets for which vaccines are both badly needed and feasible but which are not being developed owing to either a lack of governmental prioritization or a lack of incentives because the market has been considered too small to justify the capital investment, to allow development costs and reward the required investment risk. They are not attractive to major manufacturers because the anticipated revenues would be small" (p. 298). The literature suggests that prevalence and numbers of potential consumers (market size), is less determinative than willingness and ability to pay. Accordingly, a high burden disease in a low-income country may still be an unattractive investment for the private sector.

Berndt et al. (2007) emphasize the lack of economic incentives for vaccine developers to pursue neglected disease R&D: "Biotechnology and pharmaceutical ('biopharmaceutical') firms that operate under a profit-maximizing business model are likely reluctant to invest in R&D for such diseases if they fear they may be unable to sell a vaccine at prices that would cover their risk-adjusted costs. Two sources discuss differences in willingness to pay in high-income versus low-income countries for products with existing treatments. DND*i* (2016a) notes that the treatment for hepatitis C has prices of up to $84,000 per course of treatment, but estimates the willingness-to-pay in low income countries at around $300. Cottingham & Berer (2011) similarly contrast the high-income country price for a three-shot HPV vaccine ($360) with the estimated willingness-to-pay in the poorest Latin American and Caribbean countries ($15).

Two additional sources discuss willingness to pay (WTP) for products *without* existing treatments. Based on tiered pricing for public and private markets in Brazil, China, India, Kenya, Russia, South Africa, Thailand, UK, and USA, Hecht & Gandhi (2008) estimate willingness-to-pay in a private market (including all individuals aged 16-49 years) for an HIV/AIDS vaccine ranges from ($10, $50, and $100 for low-, middle-, and high-income countries respectively), while the range for a public market is $2-50 ($2, $10, $50 for low-, middle-, high-income countries respectively). A report from Aeras (2014) concludes the willingness to pay for a TB vaccine is more than $4 in high-income countries as classified by the World Bank (countries with a GNI per capita of $12,476 or more). However, "in poorer countries, respondents struggled with the price, but most thought that in one way or another countries would find the resources to fund the immunization strategy – ideally with external help but, in extremis and over a longer period, without it" (Aeras, 2014, p. 36).

Willingness to pay and prices vary by market and were scarce in the literature, but several sources reported on estimated costs per treatment, suggesting the lower bound of a price necessary to cover investment funding, in the absence of subsidies or other third-party interventions. Just as markets with high prevalence but low WTP may constrain revenues, the literature confirms that markets that are limited in size but with a large enough WTP may be sufficiently attractive to generate private investment. Batson et al., 2006 note that the expected market for HPV vaccines in high-income countries was enough incentive to develop a vaccine. And "as long as there is a sizable market for ARVs in high-income countries, pharmaceutical companies will remain interested in developing innovative products, such as long-acting agents, for HIV-1 infection" (Lange & Ananworanich, 2014, p. 9).

Table 10 summarizes evidence on the prices of therapies or preventative vaccines as described in the R&D funding literature.

Table 10: Evidence on the prices and WTP of drug therapies, diagnostics and vaccines (2016 USD)

Income Level	Product Type	Disease	Price (2016 USD)	WTP (2016 USD)	Description	Source
High Income						
	Drugs	Hepatitis C	$ 84,000		Per treatment course for Hepatitis C drugs. Current drugs cost $84000 in US, $7500 in Brazil, and $900 in India	DNDi, 2016b
		HIV/AIDS	$ 11,394		In 2000, best discount was US$10,349 for first line ARVs for HIV/AIDS, but Indian companies started marketing generic versions for US$350	Cottingham & Berer, 2011
		Tuberculosis	$10,138		A second-line TB drug can cost about $10,000 in developed countries	Li & Garnsey, 2014
	Diagnostics	Breast Cancer	$ 3,039		Per treatment course	Meadows et al., 2015
		HIV/AIDS	$ 11,394		In 2000, best discount was US$10,349 for first line ARVs for HIV/AIDS, but Indian companies started marketing generic versions for US$350	Cottingham & Berer, 2011
	Vaccines	HIV/AIDS		$ 61.76	Mean dollars per dose for HIV/AIDS vaccine. High-income = private market WTP; low-income = public market WTP	Hecht & Gandhi, 2008
		HPV	$ 360		In US, three-shot vaccination for HPV costs $360, even at a price of $15 for three doses would represent major budgetary challenge for world's poorest countries	Cottingham & Berer, 2011
Middle and Low Income						
	Drugs	Hepatitis C	$ 294		Per treatment course for Hepatitis C	DNDi, 2016a
		Hepatitis C	$ 900-7,500		Per treatment course for Hepatitis C. Current drugs cost $84000 in US, $7500 in Brazil, and $900 in India	DNDi, 2016b
		HIV/AIDS	$ 385		In 2000, best discount was US$10,349 for first line ARVs for HIV/AIDS, but Indian companies started marketing generic versions for US$350	Cottingham & Berer, 2011
		Malaria	$0.13-2.68		$.13, $.14, $2.68; Cost for chloroquine, suphadoxine-pyrimethamine, and kinin respectively for 7 day treatment	

Income Level	Product Type	Disease	Price (2016 USD)	WTP (2016 USD)	Description	Source
	Vaccines	HPV	$ 34		In US, three-shot vaccination for HPV costs $360, Mexico negotiated a price of $34 for 3 doses	Cottingham & Berer, 2011
		Hepatitis B	$25.63		Prior to Shantha, Merck and GSK held a monopoly on Hepatitis B vaccines. Most Indian families could not afford them.	
		HIV/AIDS		$ 29	Mean dollars per dose for HIV/AIDS vaccine. High-income = private market WTP; low-income = public market WTP	Hecht & Gandhi, 2008
		Tuberculosis	$0.10-0.20		TB BCG (childhood) vaccine per dose.	Li & Garnsey, 2014
		Tuberculosis		$ 4.50	Market study presented a proposed $4 vaccine price - okay for wealthier countries, but in the majority of countries at least one respondent thought it was too high and could not be met with in-country health budgets	Aeras, 2014

Trouiller (2002) observes that "Developed countries offer viable market incentives for research and development through individual purchasing power and purchasing through government-run health insurance programs… With public spending on drugs at around $239 per head per annum in countries belonging to the Organization for Economic Cooperation and Development (OECD), the pharmaceutical industry has a strong incentive to develop drugs for this market. By contrast, most developing countries spend less than $20 per year and per head on all health programs (less than $6 in sub-Saharan Africa, including drug expenditures)(p. 2191).

Some sources argue that competition from cheaper generics pose a threat to revenue streams (Chakma et al., 2011; Cottingham & Berer, 2011). Also, several sources (DNDi, 2016a; DNDi, 2016b; Li & Garnsey, 2014; etc.) identify high costs of certain products in developed countries, and use this to either point to the inability of developing countries to pay the same prices, and the potential need for differential pricing schemes (charging high prices in those countries with greater ability to pay). For example, the Hepatitis C drug sofosbuvir costs consumers $84,000 in the U.S., $7,500 in Brazil, and $900 in India (DNDi, 2016b). Several sources also report that companies allow generic manufacturers to produce and distribute their products in low-income countries (Johnson & Johnson, 2012), sometimes charging royalties (Lange & Ananworanich, 2014).

Unsubsidized Willingness to Pay

Intermediaries between sellers and buyers of medical products can complicate the demand forecasts essential to long term investment decisions. In many high-income countries there are private insurance providers as well as government institutions that pay for drugs, vaccines, and diagnostics. For example, the government of France negotiated a reduced price of $47,000 (down from $84,000) for a new Hepatitis C medicine (DNDi,

2016a). Many LMICs also have some government subsidized health care. The Indian government, for example, provides some subsidized health care, although more than 75% of health spending is paid privately, and drugs account for over 70% of out-of-pocket costs (Balarajan, Selvaraj, & Subramanian, 2011). Out-of-pocket expenses for health care are proportionately higher for low-income countries (50%) as compared to middle-income (30%) or high-income (14%) countries (Mills, 2014). Additionally, there are many development agencies and philanthropic organizations that fund health programs in LMICs, including the Bill and Melinda Gates Foundation, UN, World Bank, Gavi, and the Global Fund. These organizations contributed $35.9 billion to health programs in LMICs in 2014 (Dieleman et al., 2015). Gavi claims to have supported the immunization of over 277 million children between 2011-2015 (Gavi, 2016).

Public-private funding partnerships also have been created that can subsidize global health R&D costs. For example, Holmes et al. (2013) describes a public-private funding partnership subsidizing R&D costs for infectious diseases that disproportionally affect poor populations: "In a three-way fund matching partnership, five of Japan's biggest pharmaceutical companies, the Japanese government and the Bill and Melinda Gates Foundation committed US$100 million, for 5 years, to malaria, tuberculosis, neglected tropical diseases and HIV research" (p. 894). We explore the broader role of public, private and philanthropic partnerships in greater detail below.

Nine sources in our review specifically mention the role of subsidies for ensuring broad access to drugs, vaccines, or diagnostics. The breakdown of diseases each R&D effort is addressing is provided in Table 11.

Table 11: Information on subsidies for drugs, vaccines, or diagnostics

Disease and Type	Product Type	Partnership	Comment	Source
Type 1				
HPV	Vaccine	None Specified	GAVI subsidies to governments are necessary providing HPV vaccine through the public health system.	Batson et al., 2006
Type II				
HIV	Prevention vaginal ring	Yes	Janssen Global Public Health group, in collaboration with International Partnership for Microbicides (IPM) will help improve access for patients in resource-limited and emerging markets	Johnson & Johnson, 2014a; Johnson & Johnson, 2014c
Meningitis	Vaccine	Yes	The Bill and Melinda Gates Foundation awarded a grant to PATH to partner with the WHO to develop a vaccine and provide it for $0.40 per dose	Brooke et al., 2007; Widdus, 2010
Hepatitis B	Vaccine	None specified	GSK made HBV vaccines available in low-income countries for one-ninth the price charged to industrialized countries; often coupled with high-volume, long-term contracts	Stéphenne, 2011
Type III				
Malaria	Drug	Yes	Agreement with DND*i* for Sanofi-Aventis to sell the product at cost to public health structures of countries affected and to international organizations and NGOs	DNDi, 2005

Disease and Type	Product Type	Partnership	Comment	Source
Type II &Type III				
Type II and Type III diseases	Vaccine	Yes	The advance market commitment (AMC) may help introduce new products to developing countries but there are mixed opinions about whether the AMC does enough	WHO, 2012b
N/A				
	Vaccine	None Specified	The Indian Government has a Universal Immunization Program, but full coverage for basic vaccines is about 60%	Gupta et al., 2013

We found little information specifically mentioning the challenge of forecasting revenues in markets that had typically or previously been subsidized (though GSK (2011) acknowledges a plan to sell a product at marginal cost, and recoup R&D spending through the Health Impact Fund). Hecht & Gandhi (2008) use a demand-forecasting model to estimate that an AIDS vaccine would generate a revenue of at least $1 billion annually in a private market model comprised of adults aged 16-49 years who are willing and able to pay for the vaccine, but exclude other potential buyers such as firms who would purchase the vaccine as part of their employee healthcare benefits. Four sources (DND*i*, 2016c; Meadows et al., 2015; Chakma et al., 2011; Cottingham & Berer, 2011) report a market price for existing vaccines, drugs, or diagnostics. Most relevantly, in a market study commissioned by Aeras (2014), respondents were presented with a proposed $4 vaccine price, which was a "price barely worthy of discussion" (Aeras, 2014). However, in a majority of the eight countries where the 86 interviews were held, at least one respondent believed that the $4 vaccine price would be too high. In poorer countries, respondents struggled with the price, but believed that it could be possible for countries to find the resources to fund an immunization strategy.

4.1.4 Proposition 4: Fixed and Sunk Costs

The costs of drug development were commonly mentioned in expert consultations (West et al., 2017b), and in particular, the fixed costs of R&D entering a new product market are assumed to be a limiting factor to private sector investment. This is especially true when these costs are highly specialized and have limited resale (repurposing) in the event of failure. The cost of pharmaceutical development, "can be calculated by adding up the market value of resources used in each phase of development, including labor, supplies, equipment and overhead allocations" (Waye, Jacobs, & Schryvers, 2013, p. 1496). In our review many of the studies that mentioned the cost of R&D cited DiMasi, Hansen, & Grabowski (2003, 2016), who examine data from pharmaceutical companies to estimate the cost of R&D.

Indicators of Sunk Costs

- Overall costs of R&D
- Capital costs
- Success rate
- Study period

Findings on Overall Costs of Health R&D

The most recent research from DiMasi et al. (2016) listed prior studies and analyses of pharmaceutical R&D costs from 2003-2012 (Table 12), ranging from $802 million (DiMasi, 2003) to $2.2 billion (O'Hagan & Farkas, 2009). DiMasi et al. (2016) estimate that the average out-of-pocket cost (actual cash outlays) per approved new compound is $1.4 billion (2013 USD) and that when adding in the costs of capital (i.e., the opportunity cost of large sums of money invested in long-term R&D rather than invested in generating short-term market returns) the total pre-approval cost estimate approaches $2.6 billion (2013 USD).

Table 12: Prior studies and analyses of out-of-pocket pharmaceutical R&D costs

Study Period	Clinical Success Rate	Real Cost of Capital	Cost Estimate (2013 USD)	Study
First-in-humans, 1983-1994	21.5%	11.0%	$802 million	DiMasi et al. (2003)
First-in-humans, 1989-2002	24.0%	11.0%	$868 million	Adams & Brantner (2006)
Company R&D expenditures, 1985-2001	24.0%	11.0%	$1.2 billion	Adams & Brantner (2010)
First-in-humans, 1990-2003 (large molecule)	30.2% (large molecule)	11.5%	$1.2 billion	DiMasi & Grabowski (2007)
2000-2002 (launch)	8.0%	NA	$1.7 billion	Gilbert et al. (2003)
2009 (launch)	NA	NA	$2.2 billion	O'Hagan & Farkas (2009)
2007	11.7%	11.0%	$1.8 billion	Paul et al. (2010)
In clinical development, 1997-1999	10.7%	11.0%	$1.5 billion	Mestre-Ferrandiz et al. (2012)

Source: DiMasi et al. (2016)

DiMasi's 2003 study has been cited more than 4,500 times, but there is some debate over these R&D estimates. In particular, Light & Warburton (2011) suggest that DiMasi et al.'s (2013) $802 million estimate overstates actual R&D costs. Among other issues, Light & Warburton point out that the authors report the mean cost, even though the median was 74% of the mean due to a few very expensive drugs. Another point of contention is the decision to include the cost of capital in the overall cost estimate, which Light & Warburton (2011) identify as making up a full 50% of the estimated $802 million cost. The cost of capital is defined as the expected revenue that could have been generated by investing in the stock market rather than in an R&D project (DiMasi et al., 2013). The authors, citing Engelberg (1982), argue that these opportunity costs should not be added to out-of-pocket costs since doing R&D is a regular cost of business for industries that require innovation. Light & Warburton also critique problems with sampling and data, including the costs of discovery, not counting special tax provisions as tax savings, inflating trial costs and time, and overstating corporate R&D risk. They find that "based on independent sources and reasonable arguments, one can conclude that R&D costs companies a median of $43.4 million per new drug"; their analysis serves to highlight the "constructed nature of R&D cost estimates" (Light & Warburton, 2011, p. 47). This critique highlights the high degree to which assumptions and available data drive variability in R&D cost estimates.

Fixed and Sunk Costs of Health R&D

Twelve sources (AstraZeneca, 2015d; Barton & Emanuel, 2005; Burrill, 2012; Hirsch & Schulman, 2013; Light & Warburton, 2011; Macarron et al., 2011; Merck KGaA, 2012; NIH, 2014b; Padhy & Gupta, 2011, Seib et al., 2017; White et al., 2011; Wilson, 2010) cite cost as a key factor in private global health R&D investment decisions.

Of these, four sources estimate the cost of upfront expenditures. These costs ranged from about $280 million for building new manufacturing capacity for rotavirus vaccines (Light et al., 2009) to $1.4 billion for investments such as property, manufacturing sites, and equipment (AstraZeneca, 2017). Additionally, Keith et al. (2013) reported that the lower bound estimate for the cost of building a manufacturing site for biologically derived vaccines is $625 million and Plotkin et al. (2015) reported that the average capital investment for a new vaccine is $760 million. Although Wilson (2010) did not provide specific dollar estimates, he stated that fixed costs account for the bulk (60%) of the total cost of vaccine production. These estimates show major costs associated with new equipment and buildings when expanding R&D efforts.

Some of the sources cite the large disease-specific cost of development. For example, Sanofi (2014) specifies that there is no investment in manufacturing infrastructure needed for pneumococcal disease vaccine. Light et al. (2009) describe the need for development of a rotavirus vaccine, and Sanofi (2015f) similarly call for investment in a dengue vaccine. For antibacterials, White et al. (2011) state that many companies have "abandoned the field" due to increased costs, among other development factors.

Barton & Emmanuel (2005) suggest that, among other factors, the growing size of clinical trials and increasing clinical development costs may have contributed to the declining number of new products since the mid-1990s. Hirsch & Shulman (2013) mention that clinical development costs can be prohibitive and that rising costs are creating an unsustainable business model. Munos & Orloff (2016) suggest that the current pharmaceutical R&D model is antiquated – "Innovative drugs might exist, but not all can be developed because the R&D infrastructure is too costly. The availability of new technologies and the application of those technologies to clinical research have not yet bent the cost curve in the industry setting" (p. 3).

4.1.5 Proposition 5: Downstream Rents from Imperfect Markets

The specialized nature of health R&D products, high costs of entry and development, and imperfect information leading to scientific and market uncertainty all contribute to imperfectly competitive markets that allow companies to exercise market power in the pricing of inputs and outputs. Patents, for example, are designed to deliberately confer a stream of monopoly rents as an incentive for costly R&D. But when there is less competition downstream than upstream it can be cheaper to "buy rather than make" if downstream firms with market power can buy patents at below competitive market prices, and below their own expected cost to produce. Private investors can earn an above market return from these mid-phase exchanges when market power is asymmetric. Another reputed consequence of patents is that the limited window of exclusivity encourages firms to divert resources into marketing, and away from further R&D.

Indicators of Downstream Rents

- Existing products?
- Does/will this product have IP protection
- Who owns the IP for this product?

One common measure of market competition is the number of substitutes available to consumers, which to some degree depends on current IP protection. Few of the expert consultations explicitly noted that private investment in R&D was limited because downstream rents or marketing returns were higher, but they did note that lack of systematic data, which is a factor that often weakens competition, was also a challenge.

Findings on Competitor Products

Thirty sources mention that products already exist that have been approved by a regulatory body and are on the market as treatments for the disease of R&D interest. Of those, five sources mention TB; four mention malaria; three mention HIV/AIDS or hepatitis C; two mention cancer, onchocerciasis, or sleeping sickness; and one source mentions each of the following diseases: Chagas, dengue fever, hepatitis B, bacterial infections, central nervous system diseases, elephantiasis, mycetoma, pneumococcal disease, psoriasis, rotavirus, or schistosomiasis. Of the existing treatments, two sources that mention hepatitis C note the product as having low cost-effectiveness, and one that mentions the HPV vaccine as having mixed cost-effectiveness results. Fifteen sources describe R&D efforts to improve the efficacy or effectiveness of existing treatments, two sources focus on improving dosing or delivery, and six sources describe efforts to make an alternative to an expensive treatment. Twenty-three sources explicitly state that there is no existing product that has been approved and is available in the market for the treatment under consideration (Table 13).

Table 13: Sources noting no existing product for the treatment of R&D interest.

Disease		Product	Number of Sources
Auto-Immune Diseases			
	Neuromyelitis Optica (NMO)	Drug	1
Infectious Diseases			
Viral Diseases			
	Dengue Fever*	Vaccine	1
	Ebola	Vaccine	3
	Hepatitis C*	Drug	1
	HIV/AIDS	Vaccine	4
Bacterial Diseases			
	Malaria	Vaccine	3
	Tuberculosis	Vaccine	2
Degenerative Diseases			
	Alzheimer's	Drug	1
	Cancer	Drug	2
Inherited Diseases			
	Batten Disease*	Drug	1
	Cystic Fibrosis	Drug	2
Other			
	Neglected Diseases	Drug	1
	Diseases of intermediate prevalence (200,000 – 1,000,000 patients)	Drug	1
Total			23

*There has since been a product approved for this disease

Findings on IP Protection in Private Funding for Global Health R&D

Eighteen patents were described in the literature we reviewed. Private companies owned 14 of these patents (Table 14). However, the sample may not be representative of trends in the broader health R&D sector - one source, for example, reports 56% of malaria patents from 1993-2013 were owned by non-industry and seven patents were owned by PPPs (Årdal & Røttingen, 2015).

Table 14: Number of sources that list a patent per disease and sector.

Disease	Philanthropic	Private	Public	Mixed
Infectious Diseases				
Viral Diseases				
Hepatitis B		1		
Hepatitis C		1		
HIV/AIDS		2		
Influenza		1		
Rotavirus		1		
Bacterial Diseases				
Pneumococcal disease		2		
Tuberculosis		1		1
Parasitic Diseases				
Malaria		1		
Schistosomiasis			1	
Degenerative Diseases				
Cancer		4		
Inherited Diseases				
Cystic fibrosis				1
Total	1	14	1	2

Patent rents depend on IP enforcement and market size, both of which favor HICs. "The value of a patent is determined as much, and sometimes more, by the size of the disease market than the novelty of a patent

holder's invention" (Love, 2005, p. 259). This may incentivize private companies to invest in "me-too" drugs, which are drugs that offer relatively minimal benefits over existing treatments. The marketing monopoly created by the patent also incentivizes private companies to spend large amounts of money in marketing, "and even to skew the research process with an eye to marketing opportunities once a drug is approved" (Love, 2005, p. 259).

Of the 35 diseases mentioned in this review, four report open-source data sharing (HIV/AIDS, malaria, schistosomiasis, and tuberculosis).Two other sources mention open source in the context of precompetitive R&D, bacterial infections, and neglected diseases, and one source each mentions Alzheimer's, diabetes, arthritis, lupus, diseases of the poor, neglected tropical diseases (NTDs), elephantitiasis, onchocerciasis, Type II, and Type III diseases. The WHO reports that while open source initiatives are useful for advancing pre-competitive research, they are not effective in producing finished health products (WHO, 2012a).

Without information on premiums of downstream product pricing above marginal cost, or upstream below competitive market (monopsony) purchasing of patents, the attention to market power along the value chain is difficult to assess from the literature. But Roy & King (2016) describe the practice of purchasing other companies or products to acquire IP rights as a common industry practice. They report that Gilead Pharmaceuticals purchased Pharmasset for $11 billion for the right to produce sofosbuvir, an effective Hepatitis C drug. Pharmasset reportedly spent $271 million to in total R&D expenses, which included sofosbuvir and other (many failed) drugs, from 2003-11. Gilead expected an approximately $20 billion annual market, and purchased Pharmasset after sofosbuvir had completed Phase II clinical trials. Gilead is considered an "acquisition and regulatory specialist in drug development for hepatitis C", and the company spent an additional $880 million for Phase III clinical trials for sofosbuvir, which gained regulatory approval in December 2013 (Roy & King, 2016, p. 1).

The World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) took effect in 1995 and required all members to institute a minimum 20-year patent term for medicines (Moon, Bermudez, & Hoen, 2012). This agreement was designed to prevent "free riding" from countries that benefit from medical products without contributing to the burden of financing health R&D. Moon et al. (2012) argues that this system effectively handles the free rider problem, but also "can block access to medicines for a large proportion of the population." Angeli (2013) examines the impact of the TRIPS agreement on the Indian pharmaceutical industry. This study reports that the implementation of TRIPS increased biopharmaceutical innovation in India and that Indian companies that had foreign business partners were more successful at increasing their innovation as compared to those that did not have foreign partners (Angeli, 2013). This study also reports that "Indian firms in most instances lack the financial resources to undertake the costly patenting process" (p. 287).

Royalties

Some PPP/PDPs report receiving royalties for research and some report offering R&D products royalty free. For example, the Novartis Institute for Neglected diseases claims that any resulting drugs will be available to low-income countries without royalties while the institute hopes to receive revenue for products from high-income countries (Normile, 2013) and WHO (2014) reports that the Biomedical Advanced Research and Development Authority (BARDA) does not require any royalties for antibacterial R&D that is produced through their partnerships. In contrast, the Infectious Disease Research Institute uses royalties for adjuvants that it has patented to fund R&D for tuberculosis and leishmaniasis (GHTC, 2013). Additional sources that mention PPPs or public/philanthropic organizations that receive royalties are the Cystic Fibrosis Foundation that receives royalties from Vertex Pharmaceuticals after contributing to the development of a Cystic Fibrosis drug

(Willyard, 2016), and the Johns Hopkins Brain Science Institute that will receive royalties from Eisai for contributing to preclinical research on neurological diseases (Eisai, 2011b).

Five sources note that royalties have been or will be paid to produce a product. Three of these sources report that a public or philanthropic organization owns the IP rights and receives royalties from firms that produce the product (one for neurological diseases, one for cystic fibrosis, and one for general R&D). Two of the sources report that a private firm owns the IP rights and receives royalties from generic manufacturers. One of these sources is for HIV/AIDS drugs and includes multiple companies. The other source is from GSK, noting that the company will not file for IP rights in least developed countries, whereas they will grant licenses to generic manufacturers in lower middle income countries (GSK, 2014b).

Novartis Institute for Neglected Diseases claims that any resulting drugs will be available to developing countries without royalties (Normile, 2003). "The royalties and other funds from IDC [Immune Design Corporation] have helped support IDRI's [Infectious Disease Research Institute] programs, and IDC's clinical safety data relating to the adjuvants have been vital in IDRI's ability to accelerate the development of vaccines for tuberculosis and leishmaniasis, two diseases with an immense burden in LMICs" (GHTC, 2013, p. 7).

Critiques of IP and Monopolization of Market Information

The literature also provides some evidence to suggest that although patents and other IP policy tools can effectively incentivize private investment, the current structure of patents may not be achieving its original intended outcomes. In HICs the result is an increasing diversion from R&D to marketing: Industries' "emphasis on marketing [is] disproportionately high compared to its research efforts… Companies spend almost twice as much on promotion as they do on R&D" (Naci et al., 2015, p. 4). Similarly González, Macho-Stadler, & Pérez-Castrillo (2016) observe that "if a pharmaceutical company can only adopt one of the two types of innovation processes due, for instance, to budget constraints, it may happen that the firm has an incentive to seek a me-too drug although R&D activities oriented to search for a radical innovation are socially superior" (p. 287). This is again echoed by Naci et al. (2015): "Much of the increase in pharmaceutical expenditures has been due to the increasing investment in me-too medicines, rather than the small minority of clinically superior medications" (p. 2). For moving into LMICs, "However, a major theme expressed by the PPPs is that they use patents to protect themselves. Several PPPs worry that other organizations could prevent them from working on projects or steal their IP if they do not proactively patent their technology." (Woodson 2016, p. 1416).

4.2 Findings on Policy Incentives

Some governments and international organizations have enacted policies designed to increase private sector investment in health R&D, often for limited to diseases that disproportionately burden low-income populations or affect a small number of individuals and therefore do not have a large market. Incentives include push mechanisms, such as public research funding and R&D tax credits, as well as pull mechanisms, such as advanced purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions. While we counted 42 sources that regarded these policies as having a positive impact on private R&D funding (see for example Seib et al., 2017; Kostyanev et al., 2016; Fehr, Thürmann, & Razum, 2011; Stéphenne, 2011; Berndt et al., 2007; Young, 2006), 11 sources reported mixed results (Willyard, 2016; Outterson et al., 2015; Daems, Maes, & Nuyts, 2013; Freeman & Robbins, 2013; Hughes-Wilson et al., 2012; GSK, 2011; Kesselheim, 2011; Sampat & Lichtenberg, 2011; Wilson, 2010; Hecht, Wilson, & Palriwala, 2009; Barton & Emanuel, 2005) and three sources reported negative results (Reid & Balasegaram, 2016; Light & Warburton, 2011; Light, 2005).

Table 15 summarizes incentive mechanisms described above and the frequency in which they are mentioned in the sources reviewed. We found that the most common incentive mentioned was public research funding,

followed by advanced purchase commitments, and then orphan drug programs. A number of other innovative financing mechanisms were referenced, including FDA Fast-Track program, prizes for the completion of successful R&D, and stage-based debt/equity mechanisms. We coded for sources that mentioned patent buyouts as an incentive to invest in R&D, but did not find any discussion of this mechanism in the literature reviewed.

Table 15: Incentives to invest by number of sources

Types of reported incentives	Number of sources
Public Research Funding	30
Advanced Purchase Commitment	14
Orphan Drug Program	13
Priority review vouchers	10
R&D Tax Credits	10
Other Push Program Incentives	7
Wild Card Patent Extensions	2
Patent Buyouts	0
Other Innovative Financing Mechanism	19

Notes: "Other Push Program Incentives" include fellowships, bonds, innovations funds, and pharma-cost sharing; "Other Innovative Financing Mechanism" includes prizes, FDA Fast Track program, stage-based debt/equity mechanisms, WHO prequalification, and market exclusivity extensions.

4.2.1 Public Research Funding

28 sources indicated that public research funding helped advance private sector R&D through achieving milestones such as moving from one clinical phase to another, or cited the success of the program or initiative as a reasoning to find more sustainable funding (Seib et al., 2017; AstraZeneca, 2016h; NIH, 2016; TBVI, 2016; AstraZeneca, 2015j; Kostyanev et al., 2015; NIAID, 2015; TBVI, 2015b, 2015d; AstraZeneca, 2014c, 2014e, 2014f, 2014g; Geohegan-Quinn, 2014; Johnson & Johnson, 2014d; NIH, 2014b; Uniting to Combat NTDs, 2014; Eisai, 2013; Holmes, 2013; Årdal & Røttingen, 2012; AstraZeneca, 2012; Goldman, 2012; Theuretzbacher, 2012; Williams et al., 2012; Fehr et al., 2011; Bond, 2001; Merck KGaA, N.D.; OSDD, N.D.). For example, Seib et al. (2017) note that the Biomedical Advanced Research and Development Authority (BARDA) has resulted in 23 medical products in the last nine years. Evidence from AstraZeneca (2014e) suggests that funding from the Medical Research Council (MRC) in addition to private sources has helped support the Manchester Collaborative Centre for Inflammation Research (MCCIR) in publishing 37 papers in scientific journals since the Center was formed. And Kostyanev et al. (2016) believe that the Innovative Medicines Initiative's New Drugs for Bad Bugs (ND4BB) public-private partnership has benefited from public investment in that "public sector financing… has created a highly ambitious research agenda to combat a major global public health threat. The need for rapid concerted action has driven the funding of seven topic areas, each of which will add significantly to progress in the fight against ABR" (p. 294).

One source discussed the trade-offs with the use of public research funds for global health R&D. Daems et al. (2013) believe that direct public funding could be a "powerful mechanism," but could "work against the objectives of timeliness and efficiency" (p. 10). For example, if the recipient company knows that all the costs would be funded *a priori* there is no incentive to work in the most cost-efficient manner. Asymmetric information - where the sponsor does not know as much about the chances of success as the company - could further increase the risk of "picking the wrong horse" (Daems et al., 2013, pp. 10-11).

Reid & Balasegaram (2016) expressed similar concerns about the efficiency implications of publicly-funded pharmaceutical R&D, arguing that the public is "effectively paying twice for the same product: first through public investment in medical R&D, and second through high prices" (p. 656). They also believe that

governments should encourage incentives and models for R&D that "do not put innovation and access into conflict" (p. 656).

4.2.2 Advance Purchase Commitments

Seven papers cited advance purchase commitments (APCs, also known as advance market commitments or AMCs) as having the potential to incentivize investment in R&D (Seib et al., 2017; Keith et al., 2013; WHO, 2012b; Stéphenne, 2011; Berndt et al., 2007; Batson et al., 2006; McGuire, 2003). In the context of vaccine R&D, Keith et al. (2013) states that experience has provided evidence on the value of the advance purchase commitment mechanism, including "reduced uncertainty for donors and suppliers regarding supply and demand; vaccine-specific prioritization and funding; clearly defined product profile; and an estimated 20 million children immunized to date" from the APC for pneumococcal conjugate vaccines. An analysis by Berndt et al. (2007) concluded that vaccines generated by APCs would be cost-effective based on the World Bank's benchmark of $100 spent per DALY saved. Stéphenne (2011) believes that APCs, along with tiered pricing, could put existing resources to the best use to incentivize private investment in vaccine R&D.

Daems et al. (2013) cite positive and negative aspects of APCs: while an APC might create a market for a drug or vaccine and reward successful innovations, "innovators remain in a position of economic dependence because they will have made large investments during a protracted period of more than a decade" (Daems et al., 2013, p. 13). In the meantime, there may be a change in the political environment and no guarantee that sponsors will follow through with their commitment if they are incentivized to obtain the product at the lowest possible price.

Finally, two sources conclude that APCs may not be effective in increasing vaccine R&D innovation. Light (2015) states that advanced commitments encourage late-stage development, but not research to discover new vaccines or drugs. Light & Warburton (2011) argue that APCs are also flawed because they are structured around the "mythic costs of R&D" and do not fulfill the intent of rewarding the discovery of new vaccines for LMICs (p. 47).

4.2.3 Orphan Drug Programs

Four papers contend that the orphan drug programs through the FDA and the European Union have increased health R&D funding (Fehr et al., 2011; Kesselheim, 2011; Barton & Emanuel, 2005; Fischer et al., 2005). Barton & Emanuel (2005) argue that the Orphan Drug Act encourages development for small markets and that between 2001 and 2005 the act has generated 217 new products. Kesselheim (2011) posit that the Orphan Drug Act induced "success in making increased resources available for rare disease drug development" (p. 469). In a survey soliciting views from experts in academia, industry, international organizations, national governments/parliaments, NGOs, and PPPs, Fehr et al. (2011) found that 61.4% of experts responded that they believed orphan drug laws were either very effective (7.1%) or effective (54.3%).

Four sources had mixed conclusions about orphan drug program outcomes (Daems et al., 2013; Hughes-Wilson et al., 2012; Heemstra et al., 2009; WHO, 2012b) Heemstra et al. (2009) suggest that although current orphan drug development programs have increased the volume of biomedical research, it may not be enough for exceptionally rare diseases and other economic incentives would be required. Hughes-Wilson et al. (2012) also acknowledge the increase in treatments for rare and serious conditions after the European Orphan Medicinal Products Regulation was enacted in 2000. However, they believe that there are some flaws in the system, for example companies may work the system to receive orphan designation and request a higher price point even though it may primarily be prescribed for a non-rare condition. To combat these issues, Hughes-Wilson et al. (2012) suggest that "at the time of pricing and reimbursement, each new orphan drug is evaluated against

several criteria, which is believed to also help frame a more structured dialogue between manufacturers and payers, with the involvement of the treating physicians and the patients" (p. 5).

4.2.4 Priority Review Vouchers

Three papers conclude that a priority review voucher (PRV) had a positive impact on private sector health R&D spending (Daems et al., 2013; Robertson et al., 2012; Young, 2006). Young (2006) states that a PRV could be worth more than $300 million to the sponsor of a potential blockbuster drug, the value of having the medication enter the market about a year earlier, describing PRVs as a "win-win" in terms of serving as an incentive for neglected diseases and getting a blockbuster drug to consumers a year sooner (p. 694). Daems et al. (2013) concur that PRVs are valuable because they may be able to bring a product with a major market potential to market earlier than normal, but the value is difficult to predict and could vary with a company's R&D pipeline depending on the pipeline's breadth, composition, and level of diversification.

In contrast, a WHO report on Research and Development to Meet Health Needs in Developing Countries (2012b) expresses doubts on the effectiveness of the PRV mechanism as an incentive to meet the needs of LMICs. WHO (2012b) states that the PRV incentive does not address IP management, does not de-link drug prices from the cost of R&D, nor does it have any impact on affordability or access. However, the WHO also mentions that "the scheme is clearly complementary and consistent with existing incentive mechanisms" (p. 60). Similarly, other research has found through conversations with pharmaceutical companies that the chance to earn a PRV could keep existing development projects going but that there would be long term risk costs that are not accounted for in the design of the PRV. However, they also find that PRVs are useful to PDPs as leverage when the PDPs negotiate with pharmaceutical companies to secure partners and finding commitments (Bill and Melinda Gates Foundation, 2016).

4.2.5 R&D Tax Credits

Four papers discuss the impacts of R&D tax credits on private R&D investment (Li & Garnsey, 2014; Fehr, 2011; Anderson, 2009; Barton & Emanuel, 2005). Anderson (2009) argues that the success of the Orphan Drug Act shows that a tax credit for neglected diseases could work. While a tax break would still "not make research on neglected diseases profitable, or indeed even fully cover the costs of such work, it would allow a profitable company to offset a portion of its expenses in the near-term earnings horizon," and "allow companies to expand their efforts" (Anderson, 2009, p. 1755). Fehr et al. (2011) found in their surveys that when asked about the effectiveness of tax credits for rare diseases, 62.3% of respondents stated that they believed tax credits to be very effective (14.5%) or effective (47.8%).

There are also mixed opinions on R&D tax credits for neglected diseases from three sources (Daems et al., 2013; WHO, 2012b; Kesselheim, 2011). The WHO (2012b) notes that claims by U.S. pharmaceutical companies under the Research and Experimentation Tax Credit represent only 3% of total domestic expenditures by the industry on R&D, showing that it may not be a powerful incentive. Daems et al. (2013) found evidence that there was a positive and statistically significant change in R&D spending in the pharmaceutical industry after the tax credit went into effect, however because of the low commercial value of neglected disease products, the tax credit on sales would have little impact.

4.2.6 Wild-card Patent Extensions

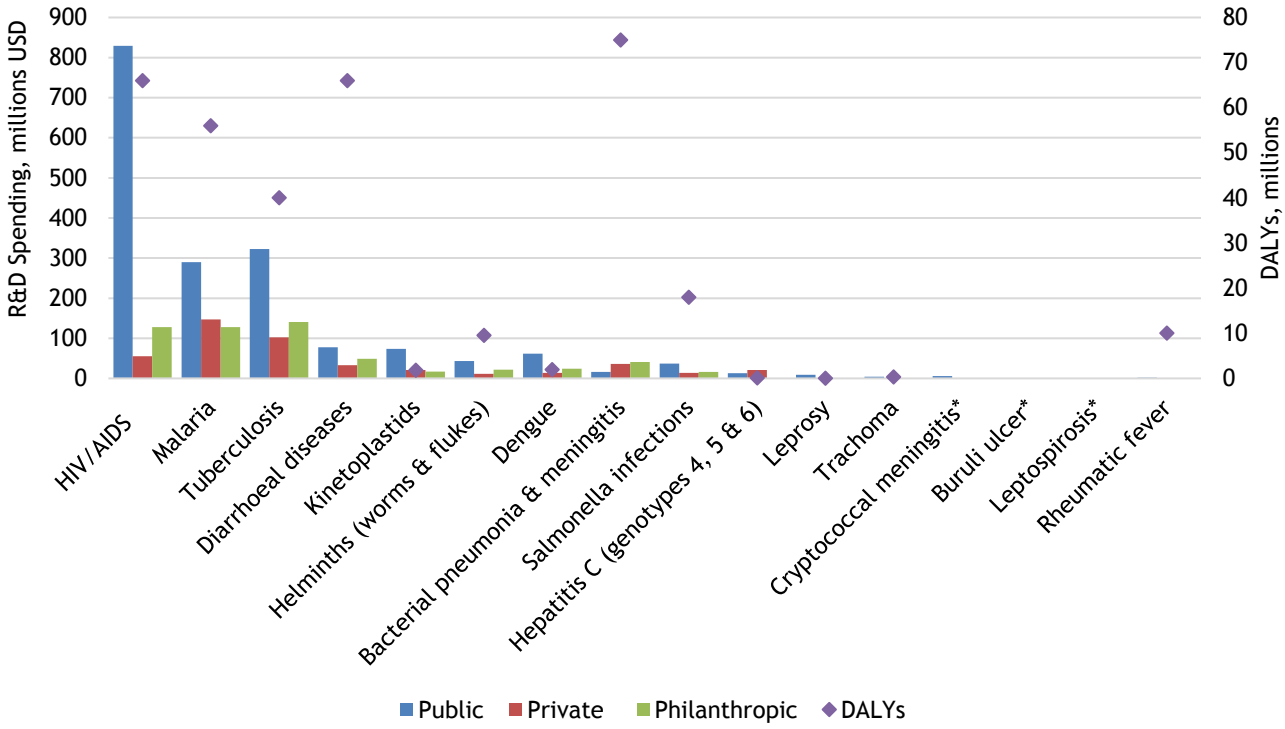
Two sources discuss wild-card patent extensions (Batson & Ainsworth, 2001; Kesselheim & Outterson, 2010). The World Bank AIDS Vaccine Task Force commissioned a study to ascertain the barriers to investment on AIDS vaccines, summarized by Batson & Ainsworth (2001). The authors report on pharmaceutical company views about different mechanisms that might stimulate investment. One finding was that "transferable patents were

supported, particularly by pharmaceutical firms with large, profitable portfolios" (Batson & Ainsworth, 2001, p. 725). Kesselheim & Outterson (2010) describe wildcard patents as linking "development to supplementary market exclusivity rights that could be transferred to other drugs" (p. 1691). They estimate that ten wildcard parents could cost as much as $40 billion; concluding that the high cost and shifting of funds among disease categories regardless of market signals might be more damaging than beneficial (Kesselheim & Outterson, 2010).

5. Concluding Remarks and Messages from the Literature Review

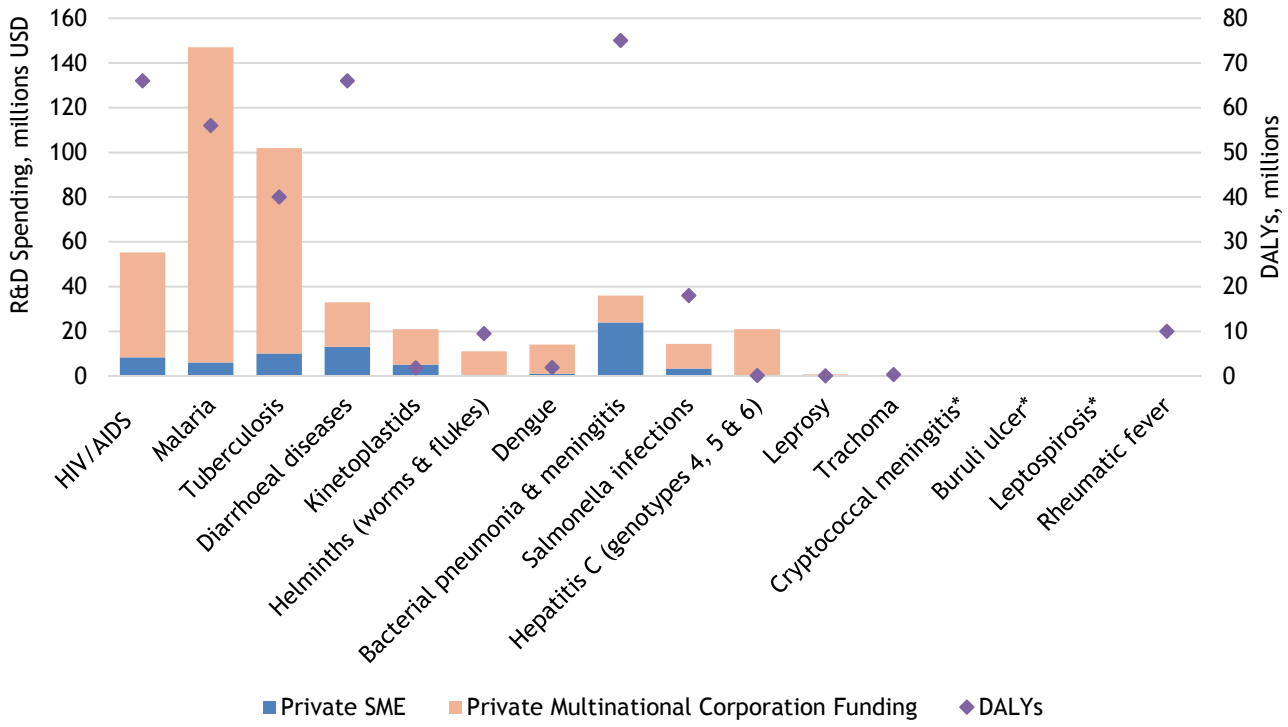
Despite the private sector's overwhelming share of all health R&D spending, the sector trails the public and philanthropic sector in funding "neglected" diseases, prevalent in LMICs (Figure 4). "Global public and philanthropic investments for neglected disease R&D were $2.4 billion purchasing power parity- adjusted dollars in 2010, which is roughly 1% of total global health R&D investments" (Røttingen et al., 2013, p. 16). Figure 4 demonstrates that DALYs remain high relative to funding levels for several classes of neglected diseases, and that fully addressing the burden of disease is likely outside the capacity of public and philanthropic funding alone. In isolation, however, this is a humanitarian, not an economic, motivation.

Figure 4: Public, private, and philanthropic neglected disease R&D spending and DALYs, 2015



Source: Chapman et al., 2016
* Information on 2015 DALYs not available

Figure 5: Private neglected disease R&D spending and DALYs, 2015



Source: Chapman et al., 2016
* Information on 2015 DALYs not available

Developing countries shoulder 90% of the global disease burden, and yet only 10% of medical R&D focuses on diseases that primarily affect these countries (Tideline, 2017). Our assumption is that relatively low private sector investment levels in global health R&D reflect a calculated assessment of the highest investment return based on expected net present value. The economic argument for catalyzing additional private sector dollars stems from the "public good" aspects of global health R&D. To the extent that producing R&D knowledge is non-rival in consumption, the incremental costs of serving additional beneficiaries is low, including additional spillovers from higher productivity, herd immunity, etc. Yet this production process is long and often specialized, and once biopharmaceutical companies have invested in the R&D necessary to develop vaccines, governments and international organizations can use their powers as dominant purchasers and arbiters of intellectual property rights to keep prices close to marginal cost. Because the largest part of the industry's expenditures lies in the initial R&D cost (while the variable costs of production are typically relatively modest), near marginal cost pricing likely implies negative total profits from the investment, thereby deterring industry from investing in the first place (Kremer, 2002). Further, if additional private sector investment is limited by knowledge gaps or phases of excessive risk that other investors may have a greater tolerance for (in exchange for the social returns they seek), understanding those challenges could potentially reveal where levers exist.

We find some corroboration between expert opinions as reported in West et al. (2017b) and the current review of literature. There is common mention of the challenge of limited markets, though the literature reviewed is clear that in the revenue calculation, LMIC pricing is the primary disincentive (even in cases where the LMIC market size is large), especially relative to drug pricing in the U.S. and other HICs. We also find a common lament in the literature that limited information is available about LMIC markets, making revenue (and in some cases cost) forecasts difficult. Other factors cited by experts in West et al. (2017b) including *Geo-political Risks*, *Macroeconomic Difficulties*, *Poor Health Governance* are less frequently cited in the literature as the key

determinants of private sector investment decisions – although both broadly relate to private firms' perceptions of risks and potential revenues associated with R&D investments.

A *Lack of Systematic Data* from the expert consultations surfaced in various forms throughout the review. Customer and market data collected remotely, via social media, through internet searches, or through other means (utility payments, bank transactions, etc.) contains information that has commercial value by informing market opportunities. When such information is held privately, markets become less competitive and less efficient. When choosing where to invest the next dollar, the uncertainties associated with LMIC markets, relative to HICs, appears to be more of an issue than the relative revenue across markets. And as the industry evolves further from a "chemical compound configuration" to a "biotech/biopharmaceutical configuration" resting on "sophisticated informatics and big data infrastructure," (R&D Magazine, 2016), the potential to easily share market, customer, and health knowledge expands, but so does the opportunity to monopolize it, depending on the policy and other incentives facing private investors.

Otherwise, of the remaining challenges articulated by the expert consultations only two are arguably unique to LMICs: *Geo-political Risks* (risks to long-term investments and revenue streams) and *Poor Health Governance* (difficulty in products reaching intended beneficiaries). These concerns were often mentioned but infrequently specified in our review of literature. We note, however, that this may be more a function of our indicator choice as these challenges are more difficult to code and quantify than are revenues and costs. West et al. (2017a) cite a WHO report noting that "counterfeit and substandard" medical products are increasingly being circulated in many countries, and that this is a result of "weak and ineffective medicine regulatory systems and poorly managed medicine supply chains that prevail in many countries" (Kohler & Baghdadi-Sabeti, 2011). This source suggests that corruption in the pharmaceutical supply chain is present in every country, but it is more prevalent in low-income countries. While corruption may be an impediment to many individuals in low-income countries in receiving quality medical products, our review uncovered no evidence that fraud or corruption impacts health R&D. Interviewees also raised "clear rules and metrics" in this category, which is a policy and regulatory issue (West et al., 2017a).

We found some evidence that it is not simply costs, but rather the high sunk costs of basic R&D where uncertainty and risk is highest. These sunk costs are the specialized pre-clinical science and materials or clinical activities with no or low resale in the event of a product failing to reach the market. "More than two-thirds of the total cost, in both dollars and time, of the discovery and development of new drugs is embedded in the clinical testing phase" (Rosenblatt, Boutin, & Nussbaum, 2016, p. 1671).

Imperfect Markets Leading to Downstream Rents was largely absent from factors highlighted in expert consultations as a disincentive to upstream R&D, but more frequently mentioned in the literature. Asymmetric market competition potentially grants larger pharmaceutical firms enough market power to buy or license R&D below a competitive market price (rather than conduct their own R&D) and enough market and regulatory authority to sell final products above a competitive market price. In a perfectively competitive market, in a situation where the vast majority of private investment is flowing into HIC health R&D, at some point the marginal return to a dollar invested in global health R&D would exceed the marginal returns to further HIC health R&D investment (so long as global health R&D was at all profitable). But in an imperfectly competitive market this threshold may not be realized, since differential opportunities for economic rents along the value chain from R&D to the final product will affect investor choices.

Our take-away from the literature is that the current global health R&D market structure, driven by specialization, high entry costs, and privately held information is fundamentally a result of both the uncertain and complex nature of disease research and the evolved policy and regulatory environment around consumer safety and IP. Scientific information and market knowledge are the essential inputs that give rise to market

power. Based on our review we suggest that proprietary scientific information plays a generally positive role in creating incentives for private sector global health R&D, but that proprietary market information – especially moving forward with enormous data repositories and especially for LMICs – may create more downstream rents that have the counter effect.

As reported by R&D Magazine's 2016 global funding forecast, the cost to develop a new drug, often exceeding $1 billion per new chemical entity, is rising, and the time to market can stretch to 12 years. The response to the slow, costly and risky nature of health R&D has often been restructuring and mergers and acquisitions (M&A). In principle licensing agreements and mergers and acquisitions have at least some potential to overcome challenges to private investment in global health R&D via economies of scale or scope. In a 2006 analysis of M&A in the pharma-biotech industry, the authors found that for larger firms mergers are a "response to patent expirations and gaps in a company's product pipeline, which lead to excess capacity of the fixed marketing resources. For smaller firms, mergers are primarily an exit strategy in response to financial trouble" (Danzon, 2006). At least according to these two sources published ten years apart, as the health R&D industry evolves, the advantage of large firms is moving farther downstream. In a study of the determinants of drug success in clinical trials, Danzon (2006) finds that:

> "We find some evidence that focused experience is more valuable than broad experience ("diseconomies of scope across therapeutic classes"). Products developed in an alliance have a higher probability of success in the more complex late stage trials, particularly if the licensee is a large firm. Thus although larger firms enjoy economies of scale in experience for the complex trials, smaller firms can tap into this expertise through licensing agreements." (Danzon, 2006, pp. 14-15)

Though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions), evidence of effectiveness is mixed with several sources suggesting that these tools had positive impacts on R&D funding, some sources reporting mixed results, and a few sources reporting negative impacts. These policy incentives do not address asymmetries in market power that make it increasingly more attractive to "buy" than "make." The attractiveness of licensing upstream research rather than conducting it internally is likely to increase as more computer-based aspects of R&D occur in biotech companies relative to the physical science labs of traditional pharmaceutical companies. To the extent that health data are more limited for global health diseases, there is reason to speculate that as the industry shifts more R&D to biotechnology even less will be directed at diseases prevalent in LMICs. Both industry experts and the literature lament the limited market data available to better assess potential market outcomes – yet despite potential industry-wide gains, there is no clear incentive for any individual firm within this sector to either fund or contribute to such a data service.

Insufficient data to inform drug effectiveness, investment returns, and infrastructure costs all contribute to scientific uncertainty and market uncertainty. Mechanisms to collect, manage, and make publicly available all scientific and financial data could address this, as could changes to patent rules possibly requiring alternative incentives to recoup R&D costs. The case for better information sharing has also been made outside of the literature we reviewed: "A global observatory on health R&D is needed because our understanding of what health R&D is undertaken, and where, by whom, and how, is very scarce, and such knowledge is necessary to improve priority setting and coordination for health R&D" (Røttingen et al., 2013, p. 1286). As Røttingen et al. (2013) emphasize: "Health R&D funders, both public and private, should be able to access appropriate and accurate information about health R&D inputs, processes, and outputs. To achieve this aim, national, regional, and global monitoring of health R&D must be strengthened" (p.1306).

The literature review highlights pricing (market revenue) and risk and uncertainty as the primary disincentives to more private sector investment in R&D for diseases prevalent in LIMCS. To that list we add the evolving complexity and specialization in the R&D markets that appear to be leading to more competition upstream (where creating scientific knowledge can be patented) and more concentration downstream (where market information can be bought and kept privately). To the extent that profit is reasonably the primary motivation of the private sector, the outcome may be more health R&D, but it is unclear that it will be in neglected disease R&D. If the goal is promoting private sector interest in LMIC markets, our recommendation is to focus on information access: consider alternative mechanisms to patents (that are time limited, have distorting incentives, and are unevenly enforced in LMICs) for rewarding scientific innovation and knowledge, and undertake efforts to make market information fully public.

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Appendix A. Theoretical Foundations: Factors Driving Private Sector Investment in Global Health R&D

Central to this paper's framework is the recognition that health R&D has public good elements of both "non-rival consumption" and "non-excludability." Knowledge that can be used repeatedly and that is costly to exclude from non-payers is likely to be under-provided by markets relative to the socially optimal level (Samuelson, 1954). The knowledge leading to new drugs, vaccines, and diagnostics that is, at some stage, applicable across different countries and regions, is health R&D that can also be considered a global public good (GPG) (Stiglitz, 1999).

Nelson (1959) and later Arrow (1962) were among the first to argue not only that the social returns to research investment exceeded the private returns realized by individual firms, but also that scientific and technical knowledge have large and far-reaching marginal social benefits at low marginal cost. The products (i.e., new vaccines, drugs, diagnostics, and knowledge) of biomedical R&D can confer almost completely non-rivalrous benefits to the global public, for instance in terms of improved health via the benefits of a vaccine that accrue to the unvaccinated. Global public goods may be especially vulnerable to under-provision in the absence of difficult-to-realize coordination across multiple potential beneficiaries, and across multiple potential funders (Kaul, 2012; Cepparulo & Giuriato, 2016) and given widespread disparities in resources across potential beneficiaries and providers (Oerlemans & Meeus, 2001). The products of the knowledge developed through research are also subject to under provision, because of the external benefits and spillovers which cannot be privately captured. Vaccinations lead to multiplier effects for the broader economy as they disrupt transmission chains of infectious diseases throughout the community. Pivotal work on the value of vaccination by Canning and Bloom (Canning et al., 2011; Bloom, Canning, & Shenoy, 2012) demonstrates the economic benefits from vaccination through improved school attainment, economic productivity, and social functioning throughout the life course. Research has also shown that increased child survival through vaccination catalyzes fertility declines, possibly creating opportunities for economic growth (Bärnighausen et al., 2014).

Ultimately, however, private incentives for making knowledge investments depend at least in part on the degree to which the public good arising from those investments can be charged for – that is, whether the good is either physically "excludable" (e.g., whether a drug offers lifelong protection or must be re-administered) or legally protected (e.g., via patents) sufficiently to ensure a secure revenue stream. Biophysical excludability is low for knowledge, such as a discovery of a genetic code that can be shared at low cost with other researchers, or the health benefits to households arising from herd immunity following the introduction of a vaccine. But, holding constant the biophysical characteristics of the product, excludability rises with legal property rights protection, and the degree to which *de facto* property rights approach *de jure* property rights. Greater legal excludability of goods produced as a result of R&D will increase the financial returns of those R&D investments. R&D that is focused on diseases in countries where it is more difficult to realize a return on investment, either because potential beneficiaries are low-income, health systems are underdeveloped, or property rights are poorly protected may be particularly prone to below socially optimal levels of provision by the private sector.

Investment in health R&D is theorized to involve a calculation of the 'expected' net present value (NPV) accounting for the technical, economic, and regulatory uncertainties of moving an R&D product through each phase to market (Levy & Rizansky, 2014). For any R&D investment decision, return on investment calculations can be financial (e.g., profits from vaccine sales) or social (e.g., spillover benefits from herd immunity). Generally, and to draw some lines for our analysis, private companies are assumed to measure net returns in terms of profitability alone, while governments and foundations are assumed to more likely consider at least some of the aggregate social impacts of investments (Mondiale, 2001). From the private sector perspective therefore Net Present Value can be decomposed into a relatively small set of economic variables including: (i) potential for market revenues; (ii) costs incurred at each stage to market; and (iii) uncertainty and time delays associated with revenues and costs (associated with discounting in benefit-cost calculations). These economic

considerations vary with disease specific scientific uncertainty and the policy and regulatory environment in which the R&D occurs and the market in which the products are sold.

In a simple market, revenues are a function of market size, market share, and consumer willingness-to-pay. Size refers to the number of potential product transactions, which derives from the number of consumers and the transactions per consumer – a distinction to reflect a difference between one-time diagnostic tests compared to vaccines for preventable childhood illnesses or a chronic drug treatment. Consumer willingness to pay is primarily a function of ability to pay (i.e., income), and the price of complementary and substitute goods – the latter of which also reflects market share and any seller's ability to charge a price above marginal cost. Estimating demand in health care markets is confounded by who pays - third party insurers, the patients, or various public or philanthropically funded subsidy mechanisms (e.g., GAVI or the Global Fund).

In contrast to revenues, many costs - and in particular initial (start-up) costs - are incurred with certainty (spent whether successful or not). Costs are presumed to vary by the phase of R&D, and include fixed costs, such as lab equipment and space, variable costs in the form of researchers and materials, and regulatory compliance costs. The initial start-up research costs as well as ongoing development costs of maintenance or updating can be substantial (Barrett, 2003). Subsequent costs are only incurred if successful in the previous phase of research. Depending on how specialized the research is, some of these costs may also be "sunk" with low resale value.

Importantly, financial returns to a private R&D investment (along with any social benefits) are primarily realized once the products developed reach the market (though knowledge is generated - and patents may be purchased - at earlier stages). Consequently financial returns may be heavily discounted depending on risk and time delays: the probability of getting a product to market is conditional on the probabilities of successfully getting through each phase in the R&D process. The more numerous and risky the phases of research, or the greater the time lag between expenditures and returns, the greater the discounting. Present value accounts for the often very long time lag between cost expenditures and market returns via discounting those returns by the real opportunity cost of capital over time (Echeverria & Beintema, 2009). The time to market is a function of the stage of science and the complexity of the pathogen or genetic code, and regulatory requirements and processes (Rawlins, 2004). Introduction of new drugs, diagnostics and vaccines in LMICs may require additional regulatory approval in each country (Aeras, 2014; Rezaie et al., 2012), which can incur significant time delays and regulatory costs that might deter private investment in diseases afflicting large populations distributed across multiple national regulatory systems.

In addition to affecting the clinical costs of research and getting a product approved for the market, the policy or regulatory environment also affects expected revenues arising through patents that grant temporary exclusive rights to R&D discoveries. Private financing for public goods, including global health, will be limited without intellectual property (IP) rights to protect the necessary R&D investment. While the IP model works to incentivize investment in high-income countries where the markets are strong enough to support R&D costs, IP rights may be of limited effectiveness in incentivizing R&D for diseases that are endemic to low-income countries because of market factors (WHO, 2010). Conversely, temporary market exclusivity can support monopoly pricing in markets without strong competition policies or government or other monopsony power for purchasing products. Further, the limited window for exclusivity can incentivize private suppliers to channel resources within this time frame towards marketing at the expense of additional R&D (Lopert, 2016).

Imperfect markets mean that potentially profitable R&D investments may not undertaken because of high fixed and other sunk costs, imperfect information and uncertainty, funding diverted to marketing to maximize limited windows of market exclusivity, or crowding out by public or philanthropic funders. Entry of new firms to exploit these potentially profitable opportunities may be occurring but at a slower pace than a market with

lower costs of entry, more homogenous consumers and providers, better information (i.e. more classically competitive), and/or less activity from the public and philanthropic sector.

Appendix B. Literature Search Methods

We systematically searched the literature for studies discussing factors that influence private sector investment in global health research and development for vaccines, drugs, and diagnostics. We first used a Boolean search string to find relevant literature that covered private sector investments or spending in general health R&D in the SCOPUS, PubMed, Google Scholar, Google, CAB Direct, and ScienceDirect databases. We also performed a supplemental search of science and economics databases to find literature not captured in our primary search using Cochrane Library, Web of Science, EconLit, PAIS, and LILACS. The Boolean search string for initial literature searches was as follows: (invest OR financ* OR spend OR fund OR spillover) AND (private OR industry OR business) AND health AND (research OR development) AND (vaccine OR drug OR diagnostic).

To capture unpublished information from private industry sources, we performed further searches through private company webpages beginning with the top ten private sector investors in global health R&D identified by the 2014 Access to Medicines Index. These private companies are GlaxoSmithKline (GSK), Johnson & Johnson, Merck KGaA, AbbVie, Novartis, Takeda, AstraZeneca, Merck & Co, Sanofi, and Eisai. When possible we used the same Boolean search string through the search function of the companies' webpages; when search functions would not allow the full search string we searched for the phrase "research and development" instead. We also used this same search methodology for philanthropic and public organizations involved in global health R&D that had been identified through our database search. These organizations – mentioned in the broader review of the literature - include: Program for Appropriate Technology and Health (PATH), World Health Organization (WHO), Medicines for Malaria Venture (MMV), Drugs for Neglected Disease Initiative (DND*i*), Global Health Technologies Coalition (GHTC), Global Health Investment Fund (GHIF), the National Institutes of Health (NIH), International AIDS Vaccine Initiative (IAVI), National Institute of Allergy and Infectious Diseases (NIAID), Center for World Health & Medicine at St. Louis University, Tuberculosis Vaccine Initiative (TBVI), and Aeras. The below table provides details on the search.

Table B1: Detailed Search Results by Database/Webpage and Search String/Search Method

Type of Database	Database	Retrieved for Further Review	Search Results	Results Reviewed	Search String
Primary	SCOPUS	29	3,743	150	Boolean search string
	PubMed	77	3,052	920	Boolean search string
	Google Scholar	31	47,900	400	Boolean search string
	CAB Direct	25	772	375	Boolean search string
	Science Direct	43	83,988	900	Boolean search string
	Total primary sources:	**205**			
Supplemental	Cochrane Library	0	34	34	Boolean search string
	Web of Science	5	689	50	Boolean search string
	EconLit	3	123	50	Boolean search string
	PAIS	3	348	50	Boolean search string
	LILACS	0	101	50	Boolean search string
	Total secondary sources:	**11**			
Private Investors	GSK	18	367	170	Boolean search string
(using search string)	Johnson and Johnson	15	172	70	Boolean search string
	Merck KGaA	10	295	230	Boolean search string
	AbbVie	2	9	9	Boolean search string
	Novartis	7	Not listed	30	Boolean search string
	Takeda	4	28	28	Boolean search string

Type of Database	Database	Retrieved for Further Review	Search Results	Results Reviewed	Search String
	AstraZeneca	17	490	290	"research development"
	Merck & Co	8	99	60	"research and development"
	Sanofi	13	80	187	Boolean search string
	Eisai	11	113	113	Boolean search string
	Total:	**105**			
Private Investors	GSK	8	-	-	Targeted searching
(using targeted search)	Johnson and Johnson	13	-	-	Targeted searching
	Merck KGaA	9	-	-	Targeted searching
	AbbVie	4	-	-	Targeted searching
	Novartis	14	-	-	Targeted searching
	Takeda	1	-	-	Targeted searching
	AstraZeneca	52	-	-	Targeted searching
	Merck & Co	37	-	-	Targeted searching
	Sanofi	33	-	-	Targeted searching
	Eisai	27	-	-	Targeted searching
	Total:	**198**			
Philanthropic and Public Organizations	PATH (MVI)	10	69	69	Boolean search string
	WHO	16	3,140	290	Boolean search string
	MMV	21	263	170	Boolean search string
	DNDi	14	480	200	"research and development"
	GHTC	-	Not listed	50	"research and development"
	GHIC	-	10	10	"research and development"
	NIH	9	Not listed	180	Boolean search string
	IAVI	16	84	84	"research and development"
	NIAID	14	133	133	Boolean search string
	Center for World Health & Medicine	3	Not listed	N/A	No search function; targeted searching and clicking
	TBVI	10	71	71	"research and development"
	Aeras	10	29	29	Boolean search string
	Total:	**123**			
Other	N/A	66			Other sources include sources found from other sources or individuals
	TOTAL:	**708**			

Boolean search string: (invest OR financ* OR spend OR fund OR spillover) AND (private OR industry OR business) AND health AND (research OR development) AND (vaccine OR drug OR diagnostic)

Appendix C. Review Framework Questions

- Source Information
    - What is the disease and strain studied?
        - Disease/strain
        - If multiple, describe
    - Is this source general or specific?
    - What type of source is this information from?
    - What is the title of the source?
    - When was the article written/published?
    - How many citations are listed for this article (on Google Scholar)?
    - Is the article peer-reviewed?
    - If yes, where was it published?
    - If no, what organization did the information come from or are the authors affiliated with?
    - Does this source do an evaluation of any sourt?
        - Evaluation? (Y/N)
        - Describe
    - What is the objective of this source?
    - How is monetary information presented?
        - Currency
        - Year of currency
- R&D Characteristics
    - What product is studied in this article?
        - Vaccine? (Y/N)
        - Drug? (Y/N)
        - Diagnostic tool? (Y/N)
        - Describe
    - What stage of research is this study looking at?
        - Preclinical? (Y/N)
        - Phase I? (Y/N)
        - Phase II? (Y/N)
        - Phase III? (Y/N)
        - Describe
    - What are the product characteristics?
        - Product name
        - Number of product competitors
        - Objective of investment
        - Evidence of efficacy on reducing mortality or morbidity? (Y/N)
        - Describe
        - Evidence of cost-effectiveness of product? (Y/N)
        - If yes, what is the measurement of cost-effectiveness in $?
        - If yes, what is the metric used for cost-effectiveness?
        - Describe
- Investment Characteristics
    - What are the characteristics of the company?
        - Name of company
        - Type of company
        - Annual profit
        - Annual sales
        - Value of company
        - Number of employees
        - Country
        - R&D intensity (ratio of R&D investments to sales)
        - Multinational company? (Y/N)
        - Describe

- What amount of money is invested by research stage?
  - Preclinical
    - How much money was invested by the private company?
    - Any partnership with the public/philanthropic sector? (Y/N)
    - How much money was received from the public/philanthropic sector?
    - Any other type of public/philanthropic incentive received? (Y/N)
    - Describe
  - Clinical
    - How much money was invested by the private company?
    - Any partnership with the public/philanthropic sector? (Y/N)
    - How much money was received from the public/philanthropic sector?
    - Any other type of public/philanthropic incentive received? (Y/N)
    - Describe
  - Overall
    - How much money was invested by the private company?
    - Any partnership with the public/philanthropic sector? (Y/N)
    - How much money was received from the public/philanthropic sector?
    - Any other type of public/philanthropic incentive received? (Y/N)
    - Describe
  - Are there any non-monetary R&D contributions provided by the private companies?
    - Non-monetary contribution? (Y/N)
    - Describe
  - What type(s) of partnerships are involved?
    - Public-private partnership (PPP)? (Y/N)
    - Product development partnership (PDP)? (Y/N)
    - Partnership with academic medical center (AMC)? (Y/N)
    - Partnership with contract research organization (CRO)? (Y/N)
    - Other?
    - Describe
    - Is the source introducing or proposing a new partnership, initiative, or policy? (Y/N)
    - Is this source analyzing an existing partnership, initiative, or policy? (Y/N)
    - What is the name of the partnership, initiative, or policy?
    - Describe
    - Is the tone positive or negative (supportive or critical)? (Pos/Neg)
    - Describe
  - What stage is partnership happening?
    - Preclinical (Y/N)
    - Phase I (Y/N)
    - Phase II (Y/N)
    - Phase III (Y/N)
    - Describe
  - What are the incentives to invest?
    - Public research funding (Y/N)
    - R&D tax credits (Y/N)
    - Other push program (Describe)
    - Priority review vouchers (Y/N)
    - Wild-card patent extensions (Y/N)
    - Patent buyouts (Y/N)
    - Orphan drug program (Y/N)
    - Advance purchase commitment (Y/N)
    - Other innovative financing mechanisms (Y/N)

        - Describe
- Potential Factors that Influence Investment Decisions
    - Does this source focus on factors that influence drug R&D?
        - Policy factors (Y/N)
        - Economic factors (Y/N)
        - Organizational factors (Y/N)
        - Other factors (Y/N)
        - Describe
    - What are the estimated costs involved?
        - Capital costs
        - Labor costs
        - IP costs
        - Regulatory costs
        - Indirect costs
        - Other costs
        - Risk costs (probability of successful R&D)
        - Overall costs
        - Describe
    - What is the (expected) time investment?
        - Development time (years)
        - Approval time (years)
        - Describe
    - Are there product competitors?
        - Number of NCEs approved for the disease
        - Is there already a similar drug? (Y/N)
        - Number of existing treatments
        - Cost of existing treatments
        - Cost-effectiveness of existing treatments
        - Coverage of existing treatments (low to high)
        - Describe
    - What is the technical feasibility for the product?
        - Are there investments in manufacturing infrastructure needed? (Y/N)
        - Level of disruption to current manufacturing (low to high)
        - Describe
    - What is the potential market size of the disease?
        - Burden of the disease
        - Projected burden of diseases (increasing or decreasing)
        - Describe
        - Perceived perception of an epidemic
        - Pandemic potential
        - Describe
        - Geographical distribution of the disease (number of countries)
        - Are there multiple global regions affected by this disease/strain? (Y/N)
        - Describe
        - Number of individuals (worldwide) affected per year
        - Prevalence of this disease in high income countries
        - Prevalence of this disease in low income countries
        - Describe
    - What is the ability/willingness to pay?
        - WTP in Sub-Saharan Africa
        - WTP is South East Asia
        - WTP in Latin America/Caribbean

        - WTP in South Asia
        - WTP in Middle East and North Africa
        - WTP in high-income countries
        - WTP in low-income countries
        - WTP in other regions
        - Describe
        - Are target beneficiaries expected to bear the full costs of the product? (Y/N)
        - Will subsidies be needed to provide the drug/vaccine to those most in need? (Y/N)
        - Describe
        - Is there a national health insurance scheme that would affect this product? (Y/N)
        - Proportion of affected countries that have insurance scheme
        - Describe
        - Estimated market potential (total sales revenue)
        - Describe
    - What policies and regulatory frameworks are in place?
        - Differential pricing? (Y/N)
        - Describe
        - IP protection? (Y/N)
        - Years of protection
        - Who owns the IP for product? (Private/Public/Philanthropic)
        - Open source data sharing for product or research? (Y/N)
        - Describe
- Evidence of Financial and Other Returns
    - What are the returns on investment like?
        - ROI
        - More or less than expected?
        - SROI (social ROI)
        - More of less than expected?
        - Expected ROI for R&D in progress? (low to high)
        - Describe
    - What is the net sales growth rate?
        - Net sales growth rate
        - Describe
    - Will financing continue over the long run with little or no need for reauthorization by governments and others?
        - Sustainability of resource generation (low to high)
        - Describe

Appendix D. Description of Indicators

D.1 Indicators of Scientific Uncertainty

To assess attention to scientific uncertainty as a factor in R&D investment decisions by private companies we coded the literature for indicators related to the risk of moving a medical product through preclinical and clinical trials (*probability of successful R&D*). Scientific uncertainty may arise from the scientific complexity and/or the lack of publicly available scientific baseline information. Reported probabilities from this indicator are expected to reflect, but not be specific to, scientific uncertainty, but instead more broadly indicate the probability of regulatory success through Phase III of clinical trials.

D.2 Indicators of Poor Policy Environments

To evaluate the degree to which private investment relates to the policy environment, we coded for information on regulatory and IP costs with the indicators for regulatory costs (*What are the estimated regulatory costs involved?*) and intellectual property rights (*Does/will this product have IP protection?*). We also coded for whether policy factors, including regulations or treaties pertaining to IP, patenting, and licensing (*Does this source focus on policy factors that influence drug R&D?*).

Lastly, in examining the various "push" and "pull" incentives that may promote drug, vaccine, or diagnostic R&D investments by the private sector, we searched for evidence of specific incentive mechanisms as introduced by Mueller-Langer (2013), including public research funding, R&D tax credits, priority review vouchers, wild card patent extensions, patent buyouts, orphan drug programs, advanced purchase commitments, and other incentives and innovative financing mechanisms.

D.3 Indicators of Limited Revenues and Market Uncertainty

We use information on price, quantity, and global health mechanisms that support the market demand for drugs, vaccines and diagnostics. For quantity, we give a rough indication on potential market size (numbers, not revenue) by reporting on the *numbers of individuals affected by a specific condition or disease* as reported in the literature, recognizing that this measures need, rather than potential market demand, since it is not adjusted for current coverage estimates which are typically less than 100%, and does not take into income and health system constraints that constrain availability and access to services in LMIC.

In a simple market, revenues are determined by prices and quantities, and forecasting demand is based on estimates of willingness to pay (WTP), which is necessarily constrained by income (the prices of substitute and complementary goods, etc.). In the landscape of global public health, however, this calculation is made significantly more complex by the question of who actually pays. For instance, any of the following could directly or indirectly through various intermediaries pay for a therapy, but all would have drastically different demand schedules: individuals, insurance companies, taxpayer funded public programs, philanthropic or other non-governmental organizations, or individual benefactors. Hence for price, we pulled any available data on consumer price, or where available, WTP estimates (for the indicators: *What is the ability or willingness to pay in Sub-Saharan Africa, Southeast Asia, Latin America/Caribbean, South Asia, Middle East and North America, high-income countries, low-income countries, other regions?*). We also coded for cost per person of treatment, recognizing that marginal cost pricing is likely rare *(cost of existing treatments*). To discern the difficulty estimating demand in environments with third-party payers, subsidies, etc., we use the data on the indicators: *Are target beneficiaries expected to bear the full costs of the product? Will subsidies be needed to provide the drug/vaccine to those most in need? Is there a national health insurance scheme that would affect this product? What is the proportion of affected countries that have an insurance scheme*?

D.4 Indicators of Fixed and Sunk Costs

We look at the following indicators: *overall costs of R&D, capital costs*, *research success rate*, and *study period* cited by our sources as affecting R&D investment.

D.5 Indicators of Downstream Market Rents

The specialized nature of health R&D products, high costs of entry and development, and imperfect information leading to scientific and market uncertainty all contribute to imperfectly competitive markets that allow companies to exercise market power in the pricing of inputs and outputs, including legally conferred monopolies in the form of patents. The result may be below above competitive market pricing for final products, but also below competitive market pricing for firms with monopsony power purchasing patents (or acquiring firms holding patents) and/or an inefficient directing of resources away from R&D and into marketing during the limited window of exclusivity. To examine intellectual property rights (IP) we use the indicators: *Does/will this product have IP protection and who owns the IP for this product?* The ownership is coded as public, private, philanthropic, or mixed. We did not code for royalties in our review framework, but do report on comments from the literature.

Appendix E. Estimates of Potential Market Demand from FIND Reports

Disease	Product Type	Location	Market Year	Quantity Demanded	Revenue	Potential or actual	Source
TB	All diagnostics	Worldwide	2006	Not reported	>$1 billion	Actual	TB Diagnostics Market Analysis Consortium, 2015
TB	All diagnostics	Brazil	2012	2.4 million	$17.2 million	Actual	TB Diagnostics Market Analysis Consortium, 2014
TB	All diagnostics	South Africa	2012	9.2 million	$98 million	Actual	TB Diagnostics Market Analysis Consortium, 2015
TB	All diagnostics	China	2012	44 million	$294 million	Actual	Zhao et al., 2016
TB	All diagnostics	India	2013	32.8 million	$70.8 million	Actual	Maheshwari et al, 2016
TB	POC diagnostic	Worldwide	Not reported	30.8 million	$54 million	Potential	UNDP, 2016
Malaria	Microscopy	Worldwide	2013	197 million	Not reported	Actual	Daily, 2016
Malaria	Rapid Diagnostic Test	Worldwide	2014	314 million	$103 million	Actual	Daily, 2016
HIV	Drug	Worldwide	2015	Not reported	$24 billion*	Actual	Tideline Working Paper, 2017**
HIV	Drug	LMIC	2015	Not reported	$1.5 billion	Actual	Tideline Working Paper, 2017
All vaccines	Vaccine	India	2015	Not reported	$500 million	Actual	Moran et al., 2015
Hepatitis C	Drug	Worldwide	2020	Not reported	$20 billion	Potential	MSF, 2016

Note: All quantities and revenues reported are for one-year terms
* The U.S. dominates the market for HIV therapies, accounting for 66 percent of total sales by value. LMIC total sales represent 6 percent of the global ARV market.
**Nature Reviews. “The HIV Therapy Market.” (2016)
Clark and Gohil. “In the crowded HIV market, there is room for innovation.” (2015)
Transparency Market Research. “HIV Market – Global industry analysis, size, share, growth, trends and forecast 2014-2020.” (2014)

Appendix F. Evidence of Efficacy and Cost-Effectiveness of R&D Outputs

While the focus of our literature review was global health R&D financing and the research process rather than on evaluations of the ultimate end-products of the R&D process, we identified 23 documents that report evidence of efficacy of R&D outputs on reducing mortality or morbidity and 18 documents that include information on the cost-effectiveness of specific R&D outputs (Table F1). Of these 37 documents, four include both evidence of efficacy and information on the cost-effectiveness of the product. Three of these four documents focus on specific diseases (Hepatitis B, Hepatitis C, and malaria), while the fourth document reports on multiple diseases. We label documents as reporting on "multiple diseases" anytime two or more diseases are discussed in the document.

Table F1: Documents discussing evidence of efficacy on reducing mortality or morbidity and evidence of cost-effectiveness for specific R&D outputs, by disease/condition

Disease/Condition	Evidence of Efficacy on Reducing Mortality or Morbidity	Evidence of Cost-effectiveness
Malaria	7	2
HIV/AIDS	3	
Chagas	2	
Multiple*	2	11
Herpes	1	
Chlamydia		1
Ebola	1	
Hepatitis B	1	1
Hepatitis C	1	1
Alzheimer's	1	
Cancer	1	1
Mycetoma	1	
Onchocerciasis	1	
Psoriasis	1	
Influenza		1
Total	23	18

Note: 4 studies report on both efficacy and cost-effectiveness
*More than one disease/condition discussed

F.1 Evidence of Efficacy of Health R&D Outputs in Reducing Mortality or Morbidity

Evidence of efficacy is seldom mentioned in the literature we reviewed, perhaps because investment in particular health R&D efforts is discontinued beyond a certain phase without such evidence. Further, information and findings discussed in these documents may be limited because many of the R&D outputs reported on are still in early phase(s) of research (Table 2), and do not yet have evidence from larger Phase III clinical trials.

Table F2: Documents discussing evidence of efficacy on reducing mortality or morbidity for specific R&D outputs, by type of R&D output, disease/condition and stage of research

Disease/Condition	Count	Type of R&D Output	Stage of Research of R&D Product
Malaria	2	Drug	1 preclinical; 1 phase II
Malaria	4	Vaccine	1 phase II; 3 phase III
Malaria	1	Drug and Vaccine	preclinical to phase III
HIV/AIDS	1	Drug	phase I to phase III
HIV/AIDS	2	Vaccine	1 not available 1 phase II to phase III
Chagas	2	Drug	phase I to phase III
Herpes	1	Vaccine	preclinical to phase III
Multiple*	2	Drug	1 phase I to phase III 1 preclinical to phase III
Ebola	1	Vaccine	preclinical to phase I
Hepatitis B	1	Vaccine	preclinical to phase III
Hepatitis C	1	Drug	phase II to phase III
Alzheimer's	1	Drug	phase II to phase III
Cancer	1	Drug and Vaccine	preclinical to phase III
Mycetoma	1	Drug	not applicable
Onchocerciasis	1	Drug	not applicable
Psoriasis	1	Drug	phase I to phase III

Note: No R&D products were described as diagnostic tools.
*More than one disease/condition discussed.

In spite of the relatively limited attention to efficacy, twenty-three of the documents report on efficacy for health R&D targeting at least 13 diseases (Table 2). The largest number of documents focused on R&D targeting malaria (7 documents), followed by HIV/AIDS (3), Chagas disease (2), and two documents focusing on multiple diseases. The remaining diseases reported on include neglected diseases, chronic conditions, and sexually transmitted infections.

Sixteen out of the 23 documents that contain information on efficacy are grey literature from pharmaceutical companies like AstraZeneca, Johnson & Johnson, and DNDi. The evidence from these documents is typically limited to one or two sentences summarizing a key positive outcome of a particular phase of the research process. For example, an AstraZeneca (2015a) document indicates that a new drug "has been shown in Phase I studies to significantly and dose-dependently reduce levels of amyloid beta in the cerebro-spinal fluid of Alzheimer's disease patients and healthy volunteers" (pg.1). Another example is an announcement by Johnson & Johnson of an Ebola vaccine that produced an antibody response in participants that was sustained eight months after immunization (Johnson & Johnson, 2016).

Although the detail in these company briefs is limited, a few provide links to describing how they analyzed the efficacy of the specific health R&D output. The Johnson & Johnson (2016) brief, for example, cites a study in *The Journal of the American Medical Association* that presents data from the Phase I clinical trial that reported that the regimen produced an immune response and was well-tolerated by health volunteers. We did not specifically target evidence of efficacy in our literature searches, and expect a more detailed review of pharmaceutical and clinical studies from different phases in the research process would provide additional evidence.

The remaining seven of 23 documents that contain information on efficacy are peer-reviewed journal articles, though most of the information is as limited as the information in the grey literature. For example, Årdal &

Røttingen (2015) state that a vaccine in development by GlaxoSmithKline against the *Plasmodium falciparum* malaria parasite has shown 50% efficacy in young children, but the authors provide no additional information.

Two articles (Gottlieb et al., 2016; Hall et al., 2010) note that evidence of R&D output efficacy is not a sufficient condition to sustain continued development and investment, and argue that cost-effectiveness considerations as well as the degree of efficacy have to be taken into account for development of the drugs and vaccines to continue. For example, Gottlieb et al. (2016) note that a Phase III vaccine for herpes infection was 20% efficacious and did not justify continued development.

F.2 Evidence of Cost-effectiveness of Health R&D Outputs in Reducing Mortality or Morbidity

We identified 18 documents reporting on cost-effectiveness of health R&D outputs targeting at least 7 diseases. The R&D outputs discussed include vaccines, drugs and diagnostic tools though evidence on efficacy is limited to vaccines and drugs.

Table F3: Documents discussing evidence of cost-effectiveness on reducing mortality or morbidity for specific R&D outputs

Disease/Condition	Count	Type of R&D Output	Stage of Research of R&D Product
Malaria	2	Drug	1 preclinical to phase III 1 preclinical
Multiple*	3	Drug	phase I to phase III
Multiple*	4	Vaccine	5 preclinical to phase III 1 phase I to phase III
Multiple*	1	Vaccine and Drug	not specified
Multiple*	3	Vaccine, Drug, and Diagnostic Tool	preclinical to phase III
Chlamydia	1	Vaccine	preclinical
Hepatitis B	1	Vaccine	preclinical to phase III
Hepatitis C	1	Drug	phase II to phase III
Cancer	1	Vaccine	preclinical to phase III
Influenza	1	Vaccine	preclinical

*More than one disease/condition discussed.

Thirteen of the 18 documents that report measures of cost-effectiveness are published studies, while the remaining 5 documents are grey literature. Cost-effectiveness is measured in several different ways:

- cost per year of life saved (Berndt et al., 2007)
- incremental cost-effectiveness ratio (change in costs/change in quality adjusted life years (QALYS) (Hall et al., 2010)
- cost per dose (DNDi, 2005)
- cost per day (DNDi, 2016)
- cost per year (Chakma et al., 2011)
- reductions to price by reference to other drugs (Tigre et al., 2016)
- time-to-market (years) and costs of development (USD) between new drug development and repositioning (Padhy & Gupta, 2011)

The high cost of drug development has led companies to attempt to lower costs through several means. Drug repositioning, the strategy of exploring drugs that have already been approved for new therapeutic indications, lowers costs by eliminating startup costs associated with new drug development, and by adding value and diversity to the revenue streams of pharmaceutical companies (Padhy & Gupta, 2011). The development of

biosimilars, medical products that are almost identical copies of original products, can reportedly reduce costs by 15% to 40% less than the original products (Tigre et al., 2016).

Several sources discussed the importance of economic modeling and considering cost-effectiveness in developing medical products. The general argument that Hall et al. (2010) put forth is that toxicity and efficacy considerations are no longer sufficient determinants of whether new treatments should be used to treat patients; cost-effectiveness should be considered and used earlier in the drug development process. Decision models are being created and refined by health economists that lead to more informed cost-effectiveness and clinical outcomes. Berndt et al. (2006) detail the process of estimating the cost of vaccines under advance market commitments. These commitments occur when one or more sponsors commit to purchase a vaccine at a minimum price per person for an eligible product up until a certain number of persons are immunized. Sensitivity analysis is conducted to test different effects on cost-effectiveness. Bodrogi & Kalo (2010) discuss three major approaches to economic modeling based on the method of data collection:

- Economic evaluation alongside clinical trials (also known as "piggy-back" analysis);
- Naturalistic pharmacoeconomic studies; and
- Economic modelling on the basis of prospectively collected clinical trial data.

Hwang & Kesselheim (2016) note that the cost of any differences in clinical development costs and profitability of products (once they have been marketed) between vaccines and other pharmaceutical products have narrowed greatly in recent years. They also note that prizes for innovative vaccines have historically been cost-effective like the $20 million prize offered by the Obama administration for a "rapid point-of-care diagnostic test for infections caused by antibiotic-resistant organisms" (pg. 225).

Sources also discuss developing drugs at lower cost, typically through collaborative efforts. MMV and Merck & Co. (2009) discuss development of an antimalarial candidate that can be produced for a lower cost in large quantities while PATH (2008) discusses a collaboration with biotech company LentigenCorporation to create an influenza vaccine at can be produced faster and more economically in larger quantities. DNDi (2005) discuss a collaboration with sanofi-aventis to develop a malaria treatment that reduces cost by combining two active ingredients that are already used in monotherapy and in two-tablet packs. Keith (2013) discusses the formation of the WIPO Re:Search program, a collaboration of efforts to fight neglected tropical diseases and offset costs. This program, established in 2011 by the World Intellectual Property Organization and BIO Ventures for Global Health, launched as a consortium of pharmaceutical companies, NGOs, and research institutes to share resources including access to intellectual property and therefore reduce overall cost. DNDi (2016) also discuss an alternative R&D strategy to deliver affordable treatments to hepatitis C patients while Johnson & Johnson (2012) allow generics producers to replicate and distribute a generic version of their HIV treatment.

Appendix G. Addressing Challenges to Private Investment: Mergers, Acquisitions & Partnerships

G.1 Licensing, Mergers and Acquisitions

As reported by R&D Magazine's 2016 global funding forecast, the cost to develop a new drug, often exceeding $1 billion per new chemical entity, is rising, the time to market can stretch to 12 years, and the mid-2015 stock market decline hurt R&D investment in several pharmaceutical companies (Roche, Novartis, Johnson & Johnson, Merck and Astra Zeneca). The response to these ongoing challenges and the slow, costly and risky nature of health R&D has often been restructuring and mergers and acquisitions (M&A). One illustrative example is Pfizer, whose acquisitions have included WarnerLambert in 2000, Pharmacia in 2002, Coley in 2007, Wyeth in 2009, King in 2010, Hospira 2015, and who are in the process of acquiring Irish Allergan (R&D Magazine, Winter 2016). "Large horizontal mergers were particularly frequent in the late 1980s and 1990s and contributed to industry concentration" (Danzon, 2006). Though growth through M&A by "formerly small – to mid-sized pharma companies like Gilead, Valeant, and Activis" has remained active over the past decade, pharmaceutical acquisitions of biotech and data companies have become more common with 2015 and 2016 record-breaking years in health care mergers and acquisitions (Fisher & Liebman, 2015).

In principle licensing agreements and mergers and acquisitions have at least some potential to overcome barriers to private investment in global health R&D. Such mergers and acquisitions, often justified based on a desire for economies of scale (size) or scope (across products or activities) is relevant to this review in that it impacts private sector investment opportunities and incentives. Many acquisitions have been characterized by layoffs and reduced spending in the merged organization (R&D Magazine, Winter 2016). Similarly, other major pharmaceuticals have also recently cut R&D spending due to industry restructuring (*ibid*). Madsen & Wu (2016) argue that this restructuring allows pharmaceutical companies to "reduce R&D costs and compensate for the reduced earnings from patented drugs" (p. 150).

In a 2006 analysis of M&A in the pharma-biotech industry, the authors found that for larger firms mergers are a "response to patent expirations and gaps in a company's product pipeline, which lead to excess capacity of the fixed marketing resources. For smaller firms, mergers are primarily an exit strategy in response to financial trouble" (Danzon, 2006). "For large firms, a merger did not significantly affect subsequent performance on average, whereas small firms that merged had slower R&D growth than similar firms that did not merge; this suggests that post-merger integration may divert cash from R&D" (Danzon, 2006).

At least according to two sources published ten years apart, as the health R&D industry evolves, the advantage of large firms is moving farther downstream. In a study of the determinants of drug success in clinical trials, Danzon (2006) finds that:

> "returns to a firm's overall experience (number of drugs developed across all therapeutic categories) are small for the relatively simple phase 1 trials, but significantly positive (with diminishing returns) for the larger and more complex phase 2 and phase 3 trials that focus on efficacy and remote risks. We find some evidence that focused experience is more valuable than broad experience ("diseconomies of scope across therapeutic classes"). Products developed in an alliance have a higher probability of success in the more complex late stage trials, particularly if the licensee is a large firm. Thus although larger firms enjoy economies of scale in experience for the complex trials, smaller firms can tap into this expertise through licensing agreements." (Danzon, 2006, pp. 14-15)

Similarly, Fisher & Liebman (2015) concludes that "Despite the claims that it takes billions to bring a drug to market, new technologies such as Molecular modeling and computer assisted drug design and DNA sequencing are allowing research to occur at lower costs, especially in the early stages. A small team of the right scientists, for example, can advance an investigational product into Phase II clinical trials far less expensively today than ever before. This means that Big Pharma companies don't necessarily have an advantage over lean start-ups during the early stages of the product lifecycle."

More selective biotech and data science acquisitions are increasing. "The small firm typically gets cash and/or equity upfront, plus contingent milestone and royalties payments, and may choose to participate in late-stage development and co-marketing, in order to gain experience. In return, the large firm obtains rights to develop and market the new product, retaining the majority of product revenues, with specifics depending on the stage of the deal. We find that inexperienced firms received substantially discounted payments on their first deal, although this discount was not consistent with the post-deal performance of these drugs. However, we find that these first deals are associated with substantially higher valuations from venture capital and public equity markets. This evidence suggests that a deal with an experienced pharmaceutical company validates a start-up company's products, sending a positive signal to prospective investors, and making the deal discount a worthwhile investment for the small firms" (Danzon, 2006).

G.2 Public-Private Partnerships: Crowding Out or Crowding In Private Sector Financing?

Partnerships across industries or across private, public, and philanthropic sectors have been argued to address scientific uncertainty (Dodet, 2014, p. 1626), to mitigate uncertain, unstable or poor policy environments, to create demand, increase revenues and reduce market uncertainties, to offset the high sunk costs of R&D and to incentivize socially beneficial investments rather the pursuit of downstream rents (Daems et al., 2016). This section summarizes our findings on the role of partnerships in supporting private sector investments in global health R&D. We start by exploring private-to-private partnerships, followed by information on the role of public-private partnerships and then present our findings on public-private partnerships by disease, by research phase and by funding amounts. These data are not comprehensive, but rather represent estimates based on the 285 studies in this review.

Today's global health R&D landscape involves many cross-sectoral arrangements and public-private partnerships (PPPs) - combining private sector actors with public or philanthropic partner organizations. Indeed, most companies in this review were involved in partnerships of some form (31 out of the total of 51 companies were involved in at least one PPP), and there was broad mention across the literature of the motivation for partnerships, arising from organizational differences in expertise, capital access, funding motivation or risk-return preferences: "Because the perceived financial risks are often too high relative to the potential economic returns, and the scientific challenges are daunting for many poverty-related diseases and conditions, it is impossible to rely solely on one organization or sector to meet the health needs of LMICs" (GHTC, 2013, p. 6). "In the USA, federal laboratories participated in 7327 cooperative research and development agreements with businesses in 2007" (Pratt, 2012, p. 57).

Particularly when public or philanthropic financing is available, private investors have an incentive to form partnerships that provide capital, specialized knowledge, and/or that favorably shift or pool costs and risks. And the public sector often lacks sufficient resources to provide adequate levels of public goods on their own, leading to partnerships with the private sector (Nishtar, 2004).

Partnerships can serve as a means of risk spreading, with the logic that "a group of organizations can better overcome market deficiencies than a single actor (McQuaid, 2000; Van Ham and Koppenjan, 2001)" (Woodson, 2016, p. 1411). For example, Woodson (2016) observes that since some innovations have high technical risks that prevent them from being economically attractive, other innovations have low monetary returns: "PPPs can circumvent these barriers by spreading the risk of failure over multiple parties and projects (Greve, 2006)" (p. 1411). Louët (2003) reports that early research carried out by public and philanthropic organizations reduce the risks to private investors, allowing pharmaceutical companies to come in after Phase II trials and finish developing a product. MMV (2016) reports that partnerships "de-risk" development and "de-link" R&D costs from drug prices. This same source also reports that the "vast majority" of products in the R&D pipeline that are targeted at malaria are being developed through a partnership between MMV and pharmaceutical

companies. According to the WHO, "partnerships have significantly increased the number of products in development for diseases and conditions that predominantly affect developing countries, and they play an important role in identifying pathways and overcoming bottlenecks in research for neglected diseases" (WHO, 2012b). In another report, the WHO states "Funding through these partnerships has a strong impact on health in developing countries, is operationally efficient and is the only mechanism that stimulates early and sustained involvement of multinational pharmaceutical companies" (WHO, 2010).

Over the course of this review the concept of public-private partnerships (PPPs) or product development partnerships (PDPs) repeatedly emerged as offering potential or partial responses to many of the challenges to private sector investment in health R&D. Product development partnerships in particular (recently reviewed in Tideline 2017) "address the lack of commercial incentive to undertake R&D for vaccines, diagnostics, and drugs for neglected diseases of the developing world. They use public and philanthropic funds to engage the pharmaceutical industry and academic research institutions in undertaking R&D for diseases of the developing world that they would normally be unable or unwilling to pursue independently . . ." (Woodson, 2016, p. 1414) Product development partnerships (PDPs) "…emerged as a non-profit model for addressing [this] gap between the health needs of emerging markets with the funding available to address them" (Tideline, 2017, p.4). "Since the late 1990s, when many NPPDs were created, the pipeline of products addressing the health needs of LMICs has grown substantially—including more than 450 technologies currently in development by the NPPDs contributing to this analysis.5 As of 2013, NPPDs and their partners have contributed to the development, evaluation, and/or introduction of 42 new health products" (GHTC, 2013, p. 4). But models that traditionally depend on donations and government grants are frequently highly restricted and are decreasing in dollar terms (Tideline ibid). The Tideline 2017 report concludes that a PDP can attract investment capital beyond restricted donor and grant funding, citing several examples including PATH, who successfully attracted $25 million in return-seeking investments.

Though we cannot know what private sector funding would exist in the absence of public and philanthropic partnerships, our data allow us to look at types of partnerships by disease, partnerships by research phase and funding levels by stage of research and by disease when partnerships are or are not present.

In this section, we cross tabulate diseases, research stage and funding levels with the type of partnerships involved: whether public-private partnerships (PPP), product development partnerships (PDP), partnerships with academic medical center (AMC), or partnerships with contract research organization (CRO). The first three partnerships (PPPs, PDPs, and AMCs) are all public-private partnerships: PDPs and AMCs are specific types of PPPs. To examine partnerships by research phase we used the database indicator on whether private companies indicated they had partnerships with the public/philanthropic sector during the preclinical and clinical phases of research or overall. We present funding information on specific partnerships where available, using the name of the partnership and include the amount invested by private and public sources by research phase noting that these data cover multiple years and are incomplete. The data we extract represents any partnership and is not restricted to only global health R&D. In order to better understand partnerships' investment in global health R&D, we (1) extract information by disease and if the partnership was explicitly for research in LMIC; and (2) extract investments for PPPs and PDPs that we know were for research and development for products for use in LMICs.

G.3 PPPs by Disease

Of the 35 diseases covered in our review, Table G1 indicates that 20 had at least one Public Private Partnership (PPP), 14 had at least one Product Development Partnership (PDP), eight had a partnership involving an Academic Medical Center (AMC), and one had a partnership involving a Contract Research Organization (CRO). There were no partnerships for 15 of the diseases in our literature review. We found seven

diseases for which there were at least three kinds of different partnerships (cancer, Chagas disease, filariasis, HIV/AIDS, malaria, sleeping sickness, and tuberculosis).

Table G1: Types of public private partnership by disease

Disease	Public Private Partnership (PPP)	Product Development Partnership (PDP)	Partnership with Academic Medical Center (AMC)	Partnership with Contract Research Organization (CRO)
Infectious Diseases				
Viral Diseases				
Ebola	Y	Y		
Hepatitis B	Y		Y	
Hepatitis C	Y	Y		
Herpes				
HIV/AIDS	Y	Y	Y	
Poliomyelitis	Y			
Respiratory Syncytial Virus				
Rotavirus				
Influenza	Y	Y		
Bacterial Diseases				
Chlamydia				
Gonorrhea				
Meningitis	Y	Y		
Pneumococcal disease				
Syphilis				
TB	Y	Y	Y	
Parasitic Diseases				
Chagas	Y	Y	Y	
Dengue fever				
Filariasis	Y	Y	Y	
Malaria	Y	Y	Y	
Onchocerciasis	Y	Y		
Schistosomiasis	Y			
Sleeping sickness	Y	Y	Y	
Trichomoniasis				
Other Infectious Diseases				
Pneumonia (nosocomial)				
Chronic Diseases				
Diabetes				
Inflammatory Bowel Disease	Y		Y	
Mycetoma	Y	Y		
Neuromyelitis Optica (NMO)				
Psoriasis				
Degenerative Diseases				
ALS				
Alzheimer's	Y	Y		
Cancer	Y	Y		Y
Dementia	Y			
Inherited Diseases				
Batten disease				
Cystic fibrosis	Y			
Total	20	14	8	1

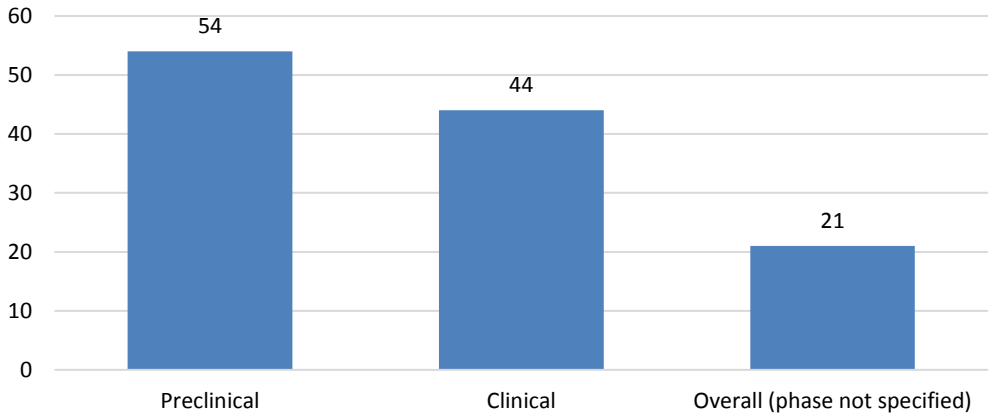
Several sources report that partnerships increase private investment in R&D for neglected diseases. For example, partnerships have been instrumental in developing low-cost vaccines for use in LMICs (Widdus, 2010). Traditionally, vaccines were developed solely by private investment for high-income countries and would later "trickle down to LMICs over a long period of time" (Widdus, 2010). The PPP model develops vaccines for LMICs with cost in mind, facilitating increased availability and coverage of vaccines in LMICs. Olesen et al. (2016)

reports that the cost of all the vaccines in the WHO's Expanded Program on Immunization (EPI) has risen from $0.67 in 2001 to $45.59 in 2014, and that new vaccines that have been licensed within the last decade make up 85% of the total cost of EPI. Olesen et al. (2016) also reports that vaccine development is heavily funded by public and philanthropic sources; industry provides only 20% of TB vaccine R&D worldwide, with the rest coming from the public and philanthropic sectors.

G.4 PPPs by Research Phase

We found a total of 89 sources reporting partnerships between industry and a public or philanthropic organization during any phase of R&D. As shown in Figure G1, we found 54 sources that reported partnerships supporting preclinical research, and 44 sources that reported partnerships supporting clinical research. There were 30 sources that reported partnerships supporting both clinical and preclinical research. Twenty-one sources reported partnerships, but the sources did not indicate the phase of research.

Figure G1: Partnership by phase of research



G.5 PPPs by Research Phase and Funding

Table G2 further breaks down private investment by stage of research and whether or not there was also public and/or philanthropic engagement. The snapshot from our sources suggest that public and philanthropic organizations invest more in preclinical research activities, while private firms invest more R&D overall. We did not find many investment figures on clinical phase research through this review.

Table G2: Investments by private companies with or without public / philanthropic partnership

Type of Partnership	Median dollars invested (2016 USD millions)	Range (2016 USD millions)	Description of Minimum Amount	Description of Maximum Amount	Number of sources
Pre-Clinical					
Amount invested by Private Sector in Public/Philanthropic Partnership	$23.3	$8.3-$113	Contribution by one private company over five years to fund range of projects	Contribution from 10 private sector companies over five years for the Accelerating Medicines Partnership	7
Amount invested by Private Sector without Public/Philanthropic Partnership	$645	$645	Average cost of preclinical R&D per new drug (out-of-pocket + capitalized costs)	N/A	1
Amount invested by Private Sector with Unspecified Partnership Status	$11,172	$11,172	Total PhRMA member preclinical R&D spending in single year	N/A	1
Clinical					
Amount invested by Private Sector in Public/Philanthropic Partnership	N/A	N/A	N/A	N/A	0
Amount invested by Private Sector without Public/Philanthropic Partnership	$956	$891-$1,019	Amount spent from 2012-2014 by Gilead for sofosbuvir (hepatitis C drug) clinical trials	Average cost of clinical R&D per new drug (out-of-pocket + capitalized costs)	2
Amount invested by Private Sector with Unspecified Partnership Status	$160	$27.9-$21,846	Initial payment by private company for exclusive rights for HPV therapy	Total PhRMA member Phase I-Phase III R&D spending in single year	11
Overall*					
Amount invested by Private Sector in Public/Philanthropic Partnership	$126	$1.01-$24,909	Amount of private sector contributions and pledges to TBVI between 2010-2012	Industry R&D expenditures in 1996	17
Amount invested by Private Sector without Public/Philanthropic Partnership	$837	$10.1-$1,664	Amount AstraZeneca spent to purchase an exclusive for a small molecule immunology candidate	Average cost of R&D per new drug (out-of-pocket + capitalized costs)	2
Amount invested by Private Sector with Unspecified Partnership Status	$365	$6.1 -$53,948	Total spent for diagnostic kit/product technology	Total overall PhRMA member Preclinical – Phase III R&D spending in single year	61

** Overall refers investments in pre-clinical and/or clinical, where the source does not distinguish between research phases. This section includes all sources that invested in both pre-clinical and clinical, but excludes sources that only invested in either pre-clinical or clinical research phases.*

Table G3 presents information from our database of 285 sources on health R&D investments made through partnerships worldwide (not specific to LMICs) by sector: private, public or philanthropic. We define private to denote investments made by private for-profit organizations or private sector investments into any kind of partnership (temporary agreements, organized PDPs, PPPs, etc.). Public refers to public sector investment contributions by governments and multilateral agencies. Philanthropic refers to investment contributions by private or humanitarian foundations. This selective set of partnership investments is not comprehensive, but rather reflects what our published and grey literature search revealed. The investments occur across multiple years, starting in 2000 and in some cases extending to 2021. The length of investments varies from one to ten years, with a wide range of investment values. Although we aren't able to aggregate these into total investment costs, a cursory review of the frequency and amounts in Table G5 suggests that private sector investments in partnerships are more frequent and of higher investment levels compared to public and philanthropic partners for worldwide R&D investments.

Nine different companies are represented as investing in these partnerships. GSK invests in four partnerships, while Merck, AstraZeneca, Tolerx, Takeda, Serum Institute of India, Novartis, Emergent Biosolutions, and Sanofi all invest in one partnership.

Table G3: Selected investments for any type of partnership worldwide (USD 2016 millions)

Disease	Source	Investment period	Value of Private Investment	Value of Public Investment	Value of Philanthropic Investment
Infectious Diseases					
Bacterial Diseases					
Bacterial infections	Kostyanev et al., 2015	2013-2021	393	355	
	Merck & Co, 2016a	2009-2016	23		
	Outterson et al., 2016	2016-2020		350	
	WHO, 2015b	2013-2017		205	
Meningitis	Widdus, 2010	2000-2010			86
TB (vaccine)	Li & Garnsey, 2014	2009			8
	TBVI, 2016	2010-2017	1	57	6
TB (drug)	Ardal, C., 2012	2008-2017		37	
Parasitic Diseases					
Malaria (vaccine)	Holmes, 2013	2013			3
	PATH, 2011	2001-2011	324		216
Viral Diseases					
Hepatitis C	Merck & Co, 2015b	2015-2017	9		
Respiratory Syncytial Virus	Sanofi, 2017b	2017	133		
Multiple Infectious Diseases					
Infectious diseases	CEPI, 2017	2017-2021		256	200
MDR TB, dengue	Normile, 2003	2003-2013	190		
Neglected Tropical Diseases	GSK, N.D.	2010-2013	14	1	
Vaccines for dengue, yellow fever, malaria	Neto & Jayaraman, 2009	2009-2015	72		72
Chronic, Degenerative, & Inherited Diseases					
Alzheimer's disease	AstraZeneca, 2015a	2014	51		
Cancer	AstraZeneca, 2013	2013	72		
	AstraZeneca, 2015b	2015	10		
	AstraZeneca, 2015c	2015	355		
	AstraZeneca, 2015e	2015	456		
	Merck & Co, 2014	2014	102		
	Merck & Co, 2016c	2016	200		
	Merck KGaA, 2012	2012	27		
	Novartis, 2015	2015	203		
	Printz, 2011	2010			2
	Sanofi, 2015c	2015	61		
	Sanofi, 2015e	2015	648		
	Merck & Co, 2016b	2016	20		

Disease	Source	Investment period	Value of Private Investment	Value of Public Investment	Value of Philanthropic Investment
Cystic fibrosis	Willyard, 2016	2000-2012			152
Diabetes	Sanofi, 2015d	2015	304		
Non-communicable diseases	GSK, 2014b	2014	35		
Psoriasis	AstraZeneca, 2015d	2015	101		
Alzheimer's, cancer, rare diseases	AstraZeneca, 2015j	2011		10	
Alzheimer's, diabetes, arthritis, lupus	NIH, 2014b	2014-2018	113	125	
Cancer, rare diseases	AstraZeneca, 2015f	Not reported		412	
Multiple Diseases					
Basic research	AstraZeneca, 2014c	2014-2018	8	4	
Cancer, bacterial infections	Sanofi, 2016b	2016-2020	750		
General R&D	AstraZeneca, 2016e	2016-2021	14	14	
	Merck & Co, 2015a	2015	440		
	Merck & Co, 2015c	2015-2019	253		
	Sanofi, 2016a	2016-2020	50		
Inflammation	AstraZeneca, 2014e	2014		1	
	Merck & Co, 2016d	2016	20		

Table G4 presents a subset of sources from Table G5 (above) for partnership investments targeted to global health R&D low and middle-income countries (LMIC). These partnerships focus on diseases that disproportionately burden LMICs or are partnerships that explicitly state that their R&D is focused on the needs of LMICs. The list of investments is considerably shorter than for health R&D worldwide. When focusing on global health R&D in LMIC, the frequency and value of investments made by the public and philanthropic sectors are higher than private sector activities. These partnerships invest primarily on infectious diseases as follows: four focus on bacterial infections, four on tuberculosis, three on malaria and one for meningitis. The remaining partnerships focus on multiple diseases.

Table G4: Selected investments for any type of partnerships for global health R&D (2016 USD millions)

Disease	Source	Investment period	Value of Private Investment	Value of Public Investment	Value of Philanthropic Investment
Infectious Diseases					
Bacterial Diseases					
Meningitis	Widdus, 2010	2000-2010			86
TB (vaccine)	Li & Garnsey, 2014	2009			8
	TBVI, 2016	2010-2017	1	56	6
TB (drug)	Ardal, C., 2012	2008-2017		37	
Parasitic Diseases					
Malaria (vaccine)	Holmes, 2013	2013			3
	PATH, 2011	2001-2011	324		216
Multiple Infectious Diseases					
Infectious diseases	CEPI, 2017	2017-2021		256	200
MDR TB, dengue	Normile, 2003	2003-2013	190		
Neglected Tropical Diseases	GSK, N.D.	2010-2013	14	1	
Vaccines for dengue, yellow fever, malaria	Neto & Jayaraman, 2009	2009-2015	72		72
Chronic, Degenerative, & Inherited Diseases					
Non-communicable diseases	GSK, 2014b	2014	35		

Tables G5 and G6 focus on another subset from Table G3, providing the investment amounts reported by 18 PPP/PDP partnerships for various diseases by sector for worldwide and global health, respectively. Based on data from our 285 sources, generally speaking, when partnerships are involved, the public and philanthropic sectors invest more frequently investments and higher values compared to the private sector alone. This holds true for partnerships that benefit worldwide health R&D (Table G5) or for more targeted global health R&D in LMICs (Table G6). It is interesting to note that public private and philanthropic partnerships have been used as a strategy for not only infectious diseases in low and middle income countries, but also chronic and degenerative diseases found in high income countries.

Table G5: Selected investments for PPP and PDP partnerships worldwide (2016 USD millions)

Disease	Name of PPP/PDP	Investment period	Value of Private Investment	Value of Public Investment	Value of Philanthropic Investment
Infectious Diseases					
Bacterial Diseases					
Bacterial infections	1. Antimicrobial Resistance Action Plan	2009-2016	23		
	2. Biomedical Advanced Research and Development Authority (BARDA)- Broad Spectrum Antimicrobials program (BSA)	2014-2018		205	
	3. CARB-X	2016-2020		350	
	4. New Drugs for Bad Bugs	2013-2021	393	355	
Meningitis	5. Meningitis Vaccine Project	2000-2010			86
TB (vaccine)	6. Oxford Emergent Tuberculosis Consortium (OETC)	2009			8
	7. Tuberculosis Vaccine Initiative (TVI)	2010-2017	1	56	6
TB (drug)	8. The Council for Scientific and Industrial Research Team India Consortium's Open Source Drug Discovery project (CSIR OSDD)	2008-2017		37	
Parasitic Diseases					
Malaria (vaccine)	9. Clinical Trial Partnership Committee	2001-2011	324		216
	10. Medicines for Malaria Venture (MMV)	2013			3
Multiple Infectious Diseases					
Infectious diseases	11. Coalition for Epidemic Preparedness Innovations (CEPI)	2017-2021		256	200
	12. Global Health Innovative Technology Fund (GHIT)	2013-2017	34	34	34
MDR TB, dengue	13. Novartis Institute for Tropical Diseases (NITD)	2003-2013	190		
Chronic and Degenerative Diseases					
Alzheimer's, diabetes, arthritis, lupus	14. Accelerating Medicines Partnership (AMP)	2014-2018	113	125	
Non-communicable diseases	15. Africa 'Open Lab'	2014	35		

Disease	Name of PPP/PDP	Investment period	Value of Private Investment	Value of Public Investment	Value of Philanthropic Investment
Cancer	16. Cancer Vaccine Acceleration Fund (CVAF)	2010			2.2
General R&D	17. Apollo Therapeutics Fund	2016-2021	14	14	

Table G6: Selected investments for PPP and PDP partnerships for global health R&D (US$2016 millions)

Disease	Name of PPP/PDP	Investment period	Value of Private Investment	Value of Public Investment	Value of Philanthropic Investment
Infectious Diseases					
Bacterial Diseases					
Meningitis	1. Meningitis Vaccine Project	2000-2010			86
TB (vaccine)	2. Oxford Emergent Tuberculosis Consortium (OETC)	2009			8
	3. TBVAC2020	2010-2017	1	56	6
TB (drug)	4. The Council for Scientific and Industrial Research Team India Consortium's Open Source Drug Discovery project (CSIR OSDD)	2008-2017		37	
Parasitic Diseases					
Malaria (vaccine)	5. Clinical Trial Partnership Committee	2001-2011	324		216
	6. Medicines for Malaria Venture (MMV)	2013			3
Multiple Infectious Diseases					
Infectious diseases	7. Coalition for Epidemic Preparedness Innovations (CEPI)	2017-2021		256	200
	8. Global Health Innovative Technology Fund (GHIT)	2013-2017	34	34	34
MDR TB, dengue	9. Novartis Institute for Tropical Diseases (NITD)	2003-2013	190		
Chronic and Degenerative Diseases					
Non-communicable diseases	10. Africa 'Open Lab'	2014	34		

Lastly, as a validation to explore targeted partnerships for global health R&D in LMIC, we identify investments from all types of partnerships (Table G2) that are classified as neglected diseases, as defined by the 2016 G-Finder report (Chapman, 2016).[11] Table G6 shows unique investments over multiple years in funding amounts

[11] The 2016 G-finder report defines neglected diseases as HIV/AIDS, TB, malaria, diarrhoeal diseases (rotavirus, cholera, *Shigella*, *E. coli*, giardia, others), kinetoplastids (Leishmaniasis, sleeping sickness, Chagas disease, others), dengue, bacterial pneumonia, meningitis, helminth infections (schistosomiasis, filariasis, onchocerciasis, hookworm, tapeworm, intestinal roundworms, whipworm, other), typhoid, salmonella, hepatitis C, leprosy, meningitis, trachoma, rheumatic fever, Buruli ulcer, leptospirosis, Ebola, and Marburg.

for neglected diseases. GlaxoSmithKline was mentioned in five of these sources, while Takeda, Emergent Biosolutions, Merck, Novartiss, and the Serum Institute of India were all each mentioned in one source as the private firm providing funding for the partnership. As with the PPPs and PDPs shown in tables G4 and G5, public and philanthropic organizations have contributed more frequently and at higher investment levels compared to private sector investments

Table G7: Overall funding for all partnerships targeting neglected diseases (as defined by G-Finder) (2016 USD millions)

Source	Disease	Private	Public/Philanthropic
Årdal & Røttingen, 2012	Schistosomiasis/TB		37
CEPI, 2017	Infectious diseases		456
GSK, N.D.	NTD	14	1
Holmes, 2013	Malaria		3
Li & Garnsey, 2014	TB		8
Merck & Co, 2015b	Hepatitis C	9	
Normile, 2003	MDR TB, dengue	190	
PATH, 2011	Malaria	324	216
TBVI, 2016	TB	1	62
Widdus, 2010	Meningitis		86

Also of note are the number of sources, peer-reviewed and otherwise, which point to partnerships as a useful model for inducing R&D investments for diseases that would otherwise go ignored (Johnson & Johnson, 2014c; DNDi, 2009a, 2009b; Brooke et al., 2007; Bond, 2001; Wheeler & Berkley, 2001; see also survey articles including Pammolli, Magazzini, & Riccaboni, 2011 and Webber & Kremer, 2001). Nwaka & Ridley (2003) conclude that "A consolidated public-private and philanthropic approach that stimulates R&D for [neglected] diseases can compensate for market failure by reducing the costs and risks involved for both public- and private- sector partners" (p. 919).