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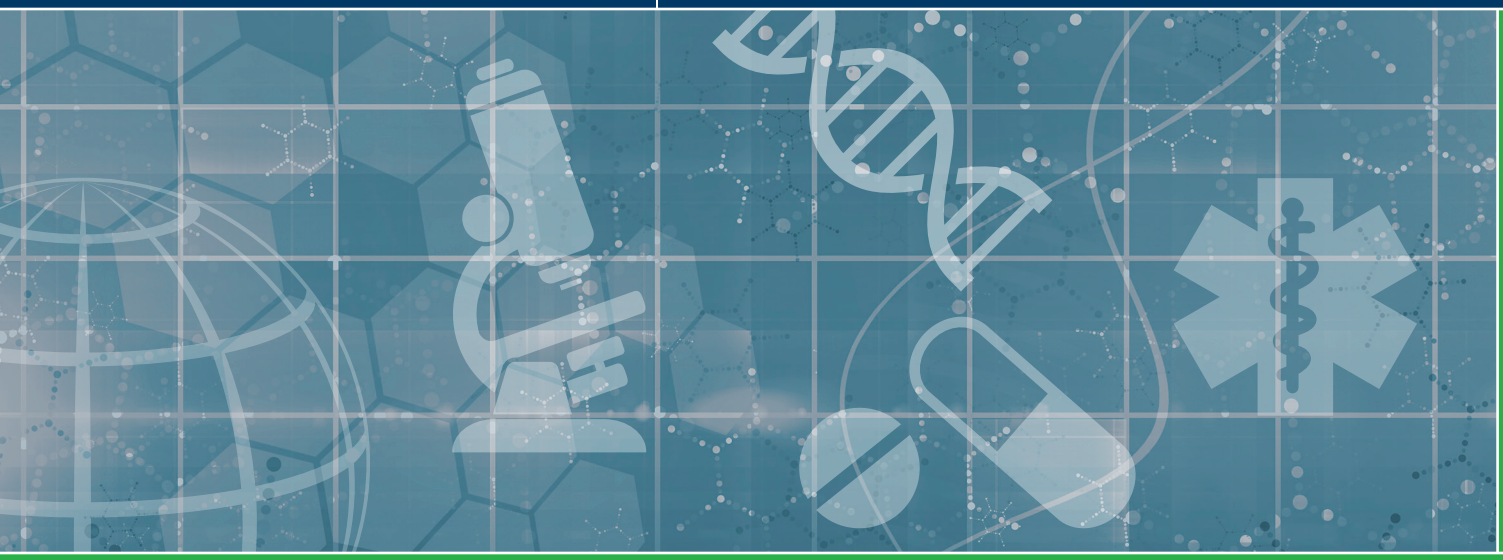

Private Sector Investment in Global Health R&D: Spending Levels, Barriers, and Opportunities

Darrell M. West, John Villasenor, and Jake Schneider

About the Brookings Private Sector Global Health R&D Project

Global health remains one of the world's most pressing challenges. Particularly in developing economies, a complex set of factors impede development, deployment, and affordability of medications, vaccines, and diagnostic tests. While there is no single solution to this challenge, an important part of the overall solution lies in incentivizing investors and pharmaceutical companies to raise their investment in global health R&D.

The Brookings Private Sector Global Health R&D Project seeks to find ways to address this investment shortfall. The project recognizes the need to complement the research on the social returns to global health R&D by examining the potential financial returns to private sector global health R&D investors, and offers policy solutions that can boost those returns. This publication is the second in a series of reports published by the Private Sector Global Health R&D Project. To contact the report authors, please email HealthRD@brookings.edu.

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Private Sector Investment in Global Health R&D: Spending Levels, Barriers, and Opportunities

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Executive Summary

Recent decades have seen considerable progress in fighting illnesses around the world. Through the sustained efforts of many governments, foundations, and businesses, the world is close to eradicating polio. Substantial progress has also been achieved in fighting HIV/AIDS, tuberculosis, and malaria, among other diseases. As one analyst who looked at the gains of recent years concluded, "since 1990, the number of annual child deaths has been cut by more than one half. More than 18.2 million people are now receiving life-saving AIDS treatment. The malaria death rate among children under age 5 is down 69 percent since 2000. Efforts to diagnose and treat tuberculosis, a disease that has plagued humanity for centuries, have saved millions of lives in the same period."[1]

Investments by the public, private, and non-profit sectors have been crucial to the health gains made to date. Advances in vaccines, drug therapies, and diagnostic tools have improved life expectancies and reduced disease incidence.[2] While public sector investment clearly remains important, maximizing the impact of global health R&D will require a sustained effort both on the part of the public and private sectors. That kind of progress, in turn, will only occur if proper incentives are in place to ensure reasonable economic returns.

This is the second in a series of reports in the Brookings Private Sector Global Health R&D Project on ways to strengthen private investment in global health R&D. The first report entitled "Health Governance Capacity: Enhancing Private Sector Investment in Global Health" focused on governing capacity in 18 sub-Saharan African and Asian nations.[3] It rated these countries on 25 indicators of health management, policy, regulation, financing and infrastructure, and health systems. In this analysis, we argued that health governance conditions the climate for private investment by affecting the confidence investors have in countries' ability to take advantage of and benefit from new resources.

In this report, we focus on private sector spending by pharmaceutical firms, venture capital funds, and impact investors in global health R&D. Our analysis combines information from consultations with more than two dozen experts drawn from businesses, venture capital firms, non-profit organizations, public-private partnerships, charitable foundations, and universities (see Appendix for the list), investment data, and case studies of leading examples of venture capital investments and innovative finance. We drew upon data from company financial reports, academic papers, Global Funding for Innovation for Neglected Diseases (G-FINDER) information, University of Washington's Institute for Health Metrics and Evaluation (IHME) "Financing Global Health"

reports, publications by scholars at Duke University, and 10-K and 20-F Securities and Exchange Commission filings. Future papers will examine the rate of return on investments, the financial benefits of global health R&D, and a review of existing research on these topics.

With this analysis, we look at three types of R&D spending:

1. Overall R&D focused on drugs, vaccines, and therapeutics in the developed and developing world,
2. Global health R&D that emphasizes medical treatments in the developing world, and
3. Neglected disease R&D, which focuses on drugs, vaccines, and therapeutics for 35 specific illnesses that primarily impact populations in very poor nations.

As we discuss on pages 7–14, there is an annual total of at least $159.9 billion spent on overall health R&D focused on the developed and developing world. This includes $156.7 billion from pharmaceutical companies and at least $3.2 billion from venture capital. For the second category, there is an annual total of $5.9 billion spent on global health R&D focused on the developing world, with $5.6 billion coming from pharmaceutical firms and $225.8 million from venture capital companies. Neglected diseases attract the least private R&D money with a total of $471 million from pharmaceutical funders and $40 million from impact investors.

There are emerging opportunities for private investment in global health R&D due to advances in the science of drug development, artificial intelligence software, and the growing financial capacity of upper middle income nations.

In recent years, there have been substantial increases in R&D spending by Chinese, Indian, and other non-Western pharmaceutical companies. While still trailing Western firms by a considerable amount, the Chinese pharmaceutical industry raised its overall health spending from $163 million in 2000 to $7.2 billion in 2016. As explained below, Indian companies went from $480 million in 2008 to $1.9 billion in 2016. Since over 35 percent of the global population resides in China or India, working with these companies could yield significant improvements in public health and private sector investment.

Looking to the future, there will likely be a slowdown in public health investment. Governments in a number of countries already have cut their development assistance and future investments will depend heavily on the state of the macro-economy and geo-political considerations. These slowdowns will have serious consequences for private sector investing.

There are many challenges to increasing private investment in global health R&D. These include limited markets, the high cost of drug development, macroeconomic difficulties, geo-political risks, a lack of systematic data about investment returns, and poor health governance that discourages higher investment in the developing world. Yet at the same time, there are emerging opportunities for private investment due to advances in the science of drug development, artificial intelligence software that has the potential to lower costs, the growing financial capacity of upper middle income nations, and spillover benefits from non-health funding that improve the climate for private investment.

We close by making several recommendations for improving private investment in global health R&D. This includes the need to create viable markets, responding to the desire for systematic data, prioritizing funding gaps, strengthening health governance, medical infrastructure and supply chains, expediting regulatory reviews of new drugs and vaccines, encouraging R&D tax incentives, encouraging venture fund investments through redesigned priority review vouchers, implementing a World Health Organization vaccine platform,

providing results-based financing, and pursuing investment opportunities in China and India. Below we explain some of the important steps that need to be undertaken (see the Conclusion section for additional details).

Creating Viable Markets — There are limited drug and vaccine markets for certain diseases. This includes illnesses that afflict small numbers of people, diseases that are prevalent in low income countries where patients often lack the means to pay for drug therapies, illnesses where the science has not advanced sufficiently to make drug development affordable, and diseases where there is a long lead time on drug development. Figuring out ways to build viable markets and create effective incentives should be a high priority.

The Need for Systematic Data — Having data on what works would make a big difference to private investors. Currently, they guess at investment impact and rates of financial return, and this increases the uncertainty and risks surrounding their investment decisions. Among the data that would be helpful to investors would be information on rates of return, drug effectiveness, and the investment climate within particular countries. Data on these topics would enable businesses to assess risk and determine the viability of their own investments. Having greater confidence regarding relevant political or economic conditions would be beneficial for private investment.

Expedite Regulatory Reviews of New Drugs and Vaccines — Expedited reviews would aid pharmaceutical companies and venture funds considering new investments. Right now, many nations have long processes for drug approvals. This raises the costs and increases the uncertainty surrounding clinical trials. In addition, companies that want their products used in developing world public health systems have to go through a rigorous World Health Organization review process. That is time consuming and burdensome for companies, and creates another level to go through. Reducing some of these barriers while still protecting patient safety would encourage private investment.

Improve Tax Incentives for Global Health R&D — Governments should encourage R&D by private firms through tax incentives. China, for example, is encouraging business investment through reduced corporate tax rates. South Africa has implemented an R&D tax incentive that offers accelerated depreciation schedules. These options help private firms focus resources on developing new products, which in the long run should pay off in better treatments.

Utilize Artificial Intelligence Advances in Drug Development — With the costs of drug development running into the millions of dollars, companies should consider new advances in artificial intelligence that have the potential to speed up new drug production. There are data mining and software solutions that scour databases for information that may yield new therapies. There also are advances in genomics and precision medicine that facilitate the targeting of drugs on people whose genetic structure is most conducive to those particular treatments. These are the types of new opportunities that can lower development costs and improve effectiveness.

Pursue Opportunities in China and India — There are considerable opportunities to boost private sector pharmaceutical spending in China and India. Both are in a stronger position than a decade ago to develop drugs and vaccines, often at a much lower cost than in the West. Working with pharmaceutical companies there would yield significant improvements in public health and private sector investment. This would represent a productive way to improve global health R&D.

Defining Global Health R&D

There are extensive resources on public sector global health spending, including publications by scholars at Duke University, researchers at the University of Washington IHME and the G-FINDER analysis of neglected diseases.[4] By contrast, there is relatively little attention given to private sector resources devoted to global health R&D. Therefore, in our analysis, we focus on

private, return-seeking R&D investments in drugs, vaccines, and therapeutics by pharmaceutical companies, venture capital firms, and impact investors.

There are three aspects of R&D in our analysis:

1. Overall health R&D focused on the developed and developing worlds,
2. Global health R&D focused on the developing world, and
3. Neglected disease R&D, which targets very poor nations.

Each defines the R&D universe in different ways. Overall health R&D is the broadest in scope. It looks at spending on drugs, vaccines, and therapeutics in the developed and developing world. Global health R&D refers to investments in drugs, vaccines, and therapeutics that emphasize the developing world. Neglected disease R&D is the narrowest category, focusing on 35 diseases that attract very little attention and primarily impact people in very poor countries. According to the G-FINDER definition, it includes illnesses such as tuberculosis, malaria, diarrhea, dengue, and leprosy, among others.[5]

For all three categories, we compile data on direct R&D spending designed to develop drugs, vaccines, and therapeutics. We do not include money that goes to medical service delivery, health clinics, or public health infrastructure, nor do we look at the provision of in-kind services. Those things clearly are important to healthcare, but we focus on the former categories due to the need to understand the front end investment gap.

Pharmaceutical Company Overall Health R&D Spending

Pharmaceutical firms represent a large investor in overall health R&D. Table 1 shows the overall health R&D spending by firms around the world, regardless of geographical area.[6] Overall in 2016, there was $156.7 billion in R&D spending in the developed and developing worlds. About $93.6 billion came from the top 20 Western firms, while the rest ($63.1 billion) arose from other pharmaceutical companies around the world.[7] We also compiled R&D figures shown on Western pharmaceutical company forms filed with the U.S. Securities and Exchange Commission and the amounts shown on them correspond closely with the numbers listed in this table.

TABLE 1 **Total Pharmaceuctical Overall Health R&D Spending, 2016**

Company	R&D Spending (billion US$)
Roche	$8.7
Novartis	7.9
Pfizer	7.0
Johnson & Johnson	7.8
Merck	6.8
Sanofi	5.7
AstraZeneca	5.6
GlaxoSmithKline	2.8
Eli Lilly	4.7
Bristol-Myers Squibb	4.4
Amgen	4.9
AbbVie	4.2
Boehringer Ingelheim	3.2
Gilead Sciences	3.9
Takeda	3.8
Bayer	3.1
Celgene	2.9
Novo Nordisk	2.2
Biogen	2.0
Regeneron Pharmaceuticals	2.1
Other Firms Around the World Including China, India, and Elsewhere	63.1
Total	**$156.7**

Source: Evaluate Group, "EvaluatePharma World Preview," June 2017, p. 20.

Overall Health R&D Spending by Pharmaceutical Firms in China and India

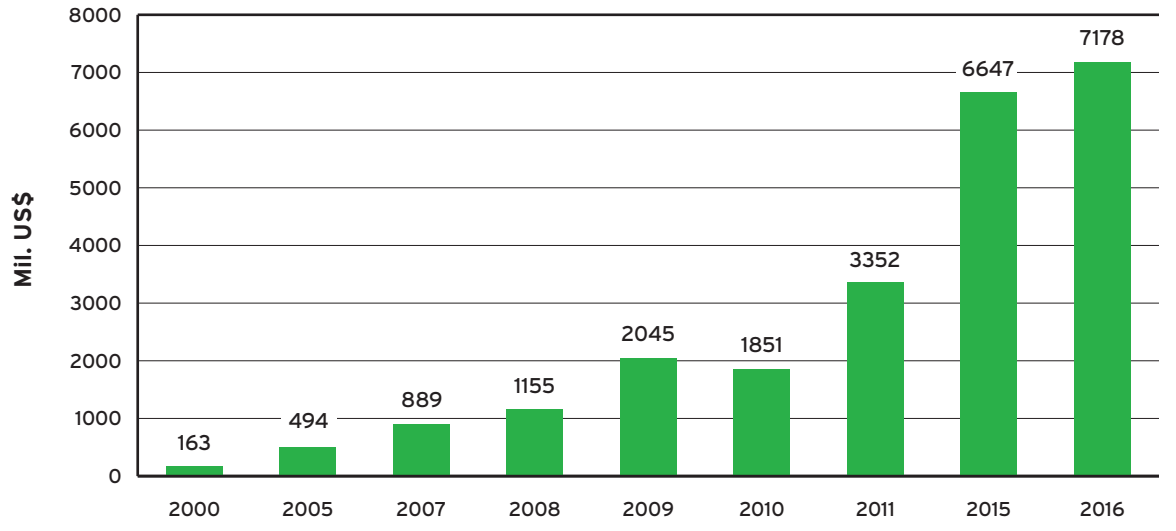
There is growing investment from local pharmaceutical firms operating in China and India. Both countries have enormous populations and therefore represent attractive investment opportunities. As each nation has gained income and expertise, it has increased the capacity of its local firms to assess market risk and design medical products for its local markets. Each nation has rising incomes and an aging population, so the market for pharmaceutical products has risen substantially.[8] It is estimated by the World Bank that 9.5 percent of the population in China is 65 years or older. And in India, that number is 5.6 percent.[9]

Much of the Chinese pharmaceutical manufacturing market consists of small, low-cost producers that sell their products locally. There are around 5,000 drug manufacturers there and most of them are not large. The biggest 100 firms control only one-third of the total sales market. About 64 percent of pharmaceutical sales in China is generic drugs, and patented drugs comprise around 22 percent of pharmaceutical sales there.[10]

However, the quality of the drug manufacturing there has improved and Chinese firms are starting to export to other countries. As a sign of this progress, the U.S. Food and Drug Administration (FDA) has opened a field office in Beijing that inspects drugs destined for other markets. Western drug companies also have invested considerable sums in Chinese companies and with Chinese academics in order to develop new treatments.[11]

Figure 1 shows Chinese pharmaceutical R&D spending by local firms from 2000 to 2016 as documented by *Health Research Policy Systems*. The figure demonstrates that expenditures rose from $163 million in 2000 to $7.2 billion in 2016. The vast majority of this funding came from the private sector. In general, about 90 percent of the financing was private in nature, including money from Chinese corporations, venture capital, and private equity.[12]

FIGURE 1 | **Chinese Pharmaceutical R&D Spending, 2000–2016**



Source: Lan Qiu, Zi-Ya Chen, Deng-Yu Lu, Hao Hu, and Yi-Tao, Wang, "Public Funding and Private Investment for R&D: A Survey in China's Pharmaceutical Industry," Health Research Policy Systems, 2014. The 2015 number comes from the Statistics Portal, "Internal Research and Development Spending in China in 2015 by Industry," 2016. The 2016 number is an estimate extrapolated from the ratio of 2015 R&D on medicine to 2015 total R&D from the Statistics Portal, "Internal R&D Spending in China from 2006 to 2016," 2017. Currency conversion calculated using exchange rates from Haver Analytics.

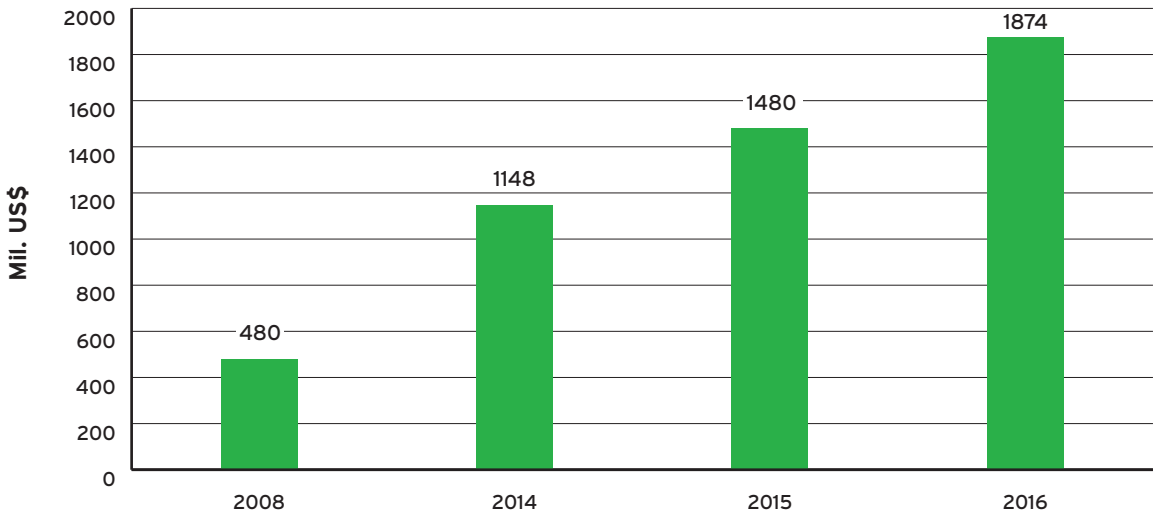
In India, pharmaceutical companies also have grown substantially. The sector currently generates around $32 billion in revenues. It is rising around 15 percent a year and is expected to reach $55 billion by 2020. The country is the world's largest provider of generic drugs and covers 20 percent of generic global exports.[13] Most of their products are designed for the Indian market, albeit with some sales to foreign countries.

There is considerable interest in improving drug manufacturing quality so that Indian products are competitive in the marketplace. This is one of the reasons why firms are increasing their R&D investments. They see opportunities elsewhere, especially with countries that are involved with multilateral aid or philanthropic efforts to export drugs and vaccines. As disease tracking systems have been introduced, a number of places have prioritized healthcare and trying to determine where their products can achieve impact.

Figure 2 shows the R&D spending by Indian pharmaceutical companies over the past decade, based on data provided by IBEF.[14] Expenditures went from $480 million in 2008 to $1.9 billion in 2016. Among the leading domestic firms are Sun Pharmaceutical Industries, Dr. Reddy's Laboratories, and Lupin Limited. In the last decade, these companies benefited from a U.S. patent cliff, whereby patents on several Western medications ended. That created opportunities for Indian businesses to develop generic drugs and domestic firms sharply raised their R&D spending. Indian researchers estimate that it takes around $5 million to develop a complex generic and between $1 million and $2 million to develop a simple one.[15] Those costs are far below what the comparable development figures are in the United States or Europe.

With the substantial growth of private spending in China and India, there clearly are major opportunities to boost drug development through private investments there. Firms operating in those areas can develop drugs at lower costs than in the West. In our Conclusion section, we return to this theme about investment opportunities in China and India.

FIGURE 2 | **Indian Pharmaceutical R&D Spending, 2008–2016**



Source: IBEF, "Indian Pharmaceutical Industry," March 2017.

The Computation of Global Health R&D Spending by Pharmaceutical Companies

Companies include a variety of expenditures in their overall R&D spending. According to their 10-K public filings with the U.S. Securities and Exchange Commission, not all the money goes to drug and vaccine development. For example, Johnson and Johnson says that "these expenditures relate to the processes of discovering, testing and developing new products, upfront payments and milestones, improving existing products, as well as ensuring product efficacy and regulatory compliance prior to launch."[16] Of the $9.1 billion devoted to R&D in 2016, the company noted that $7.0 billion was devoted to pharmaceutical products, $1.6 billion was spent on medical devices, and $580 million was outlayed on consumer products.

Novartis spent $2.6 billion on research and exploratory development and $5.1 billion on confirmatory development in 2016.[17] Merck increased its R&D expenditures from $6.7 billion in 2015 to $10.1 billion in 2016, indicating:

> [T]he increase was driven primarily by higher acquired in-process research and development (IPR&D) impairment charges, increased clinical development spending, higher restructuring and licensing costs, partially offset by a reduction in expenses associated with a decrease in the estimated fair value measurement of liabilities for contingent consideration, as well as by the favorable effects of foreign exchange.[18]

Gilead Sciences spent $5.1 billion on R&D in 2016. Of this, $3.2 billion was on clinical studies and outside services, $1.1 billion on personnel and infrastructure expenses, $325 million on facilities and IT, and $432 million on IPR&D impairment charges.[19]

To break down the amount of overall health R&D devoted to global health R&D, we relied upon data computations shown in Table 2. The first line lists overall health R&D spending as described in previous sections for Western, Chinese, Indian, and other non-Western pharmaceutical companies.

We then developed estimates of the percent of these monies devoted to patented drugs and vaccines. Not every Western company itemized its spending on drugs and vaccines, but of the ones who did, their R&D expenditures devoted to drugs and vaccines averaged 13.5 percent of overall health R&D. That number is similar to the 14 percent figure developed by Marco Schaferhoff and colleagues for "global public goods," including global health R&D and pandemic preparation.[20] In the case of Chinese firms, the percentage devoted to patented drugs is 22 percent, based on published sources.[21] From those numbers, we extrapolated a lower figure of 5 percent for India and other non-Western companies.[22]

We used a 10 percent figure for Western pharmaceutical companies in terms of the percentage of their health R&D devoted to patented drugs and vaccines targeted on the developing world.[23] For China, India, and other places outside the developed world, we assigned 100 percent of their R&D expenditures to the developing world because their drugs and vaccines are sold either locally in their own nations or regionally in the developing world. In 2016, we estimate that Western and non-Western pharmaceutical companies contributed $5.6 billion in global health R&D targeting the developing world for drug and vaccine development.

In 2016, we estimate that Western and non-Western pharmaceutical companies contributed $5.6 billion in global health R&D targeting the developing world for drug and vaccine development.

TABLE 2 | **Estimated Global Health R&D Spending by Pharmaceutical Companies, 2016**

	Western Pharma	Chinese Pharma	Indian Pharma	Other Non-Western Pharma	Total
Overall Health R&D Spending	$93.6 billion	$7.2 billion	$1.9 billion	$54.0 billion	$156.7 billion
% of Overall R&D Spent on Patented Drugs/Vaccines	13.5%	22%	5%	5%	–
Amount R&D Spent on Patented Drugs/Vaccines	$12.6 billion	$1.6 billion	$95 million	$2.7 billion	$17.0 billion
% of R&D Drug Expenditures Devoted to Developing World	10%	100%	100%	100%	–
Amount R&D on Patented Drugs/Vaccines Devoted to Developing World	$1.3 billion	$1.6 billion	$95 million	$2.7 billion	$5.6 billion

Source: Authors' calculations.

Our number of $5.6 billion is higher than that reported in the 2016 G-FINDER analysis. Its authors find about $3 billion in global health product development for 35 neglected diseases, mainly from Western sources.[24] But it is important to note that we find significant investment in global health R&D in the developing world by Chinese, Indian, and other non-Western companies. Pharmaceutical firms in countries such as Brazil, China, India, Mexico, Russia, South Africa, Turkey, and Vietnam have increased their global health R&D in recent years. Experts expect these and other emerging markets to comprise "nearly a third of the global pharmaceutical market by 2016," and domestic firms are investing in R&D to provide products for this market.[25]

Venture Capital Firms

Information on venture capital investments is hard to find since much of the data regarding investments and returns are proprietary in nature. Venture capital firms are not required publicly to disclose their investments or returns. The estimates that we provide in this section should be taken as rough numbers, not precise figures, given the difficulty of compiling information in this area.

We compiled information from company websites, expert consultations, and Crunchbase. Table 3 provides a list of leading venture capital firms with $1 billion or more in assets under management (AUM) investing in drugs, vaccines, and therapeutics. This chart lists the approximate assets under management, amount invested during the previous year, amount invested in overall health R&D, and amount invested in global health R&D.

Overall, these firms have $69.7 billion in total assets under management. Of this, $8.9 billion was invested in the year running from May 1, 2016 to May 1, 2017 and around $3.2 billion of that amount was invested in overall health R&D and $225.8 million was invested in global health R&D.[26]

TABLE 3 | Leading Venture Capital Firms Investing in Health R&D (in millions)

Venture Firm	Total Assets Under Management	Total Investments During the Previous Year	Total Investments in Drugs, Vaccines, and Therapeutics During Previous Year	Total Investments in Global Health Drugs, Vaccines, and Therapeutics During Previous Year
OrbiMed Advisors	$13,000	$418.2	$337.7	$30.4
Deerfield	7,000	272.8	155.3	0
Polaris Partners	4,300	445.2	158.2	25.7
Lightspeed Venture	4,000	986.9	10.6	10.6
Canaan Partners	3,500	398.3	150.6	0
Venrock	3,250	520.4	122.7	0
MPM Capital	3,190	158.9	158.9	0
Frazier Healthcare	3,000	105.7	105.7	20.0
Domain Associates	2,700	123.5	35.5	0
Kleiner Perkins Caufield	2,680	1,778.4	34.4	0
Sofinnova Partners	2,200	68.5	68.5	0
Lundbeckfonden	2,080	73.8	37.2	15.2
ARCH Venture Partners	2,000	1,336.7	333.5	14.0
SV Health Investors	2,000	287.2	102.4	15.2
Versant Ventures	1,900	463.3	321.8	0
Third Rock Ventures	1,900	366.9	366.9	0
Atlas Venture	1,810	135.4	121.8	0
Aisling Capital	1,800	138.7	69.7	0
Vivo Capital	1,800	121.5	104.0	0
Clarus Ventures	1,700	115.0	104.5	25.0
Flagship Pioneering	1,680	171.4	25.6	10.6
Sectoral Asset	1,285	45.0	45.0	0
Longitude Capital	1,200	84.5	62.0	22.0
Abingworth	1,100	35.5	35.5	22.0
New Leaf Venture Partners	1,030	74.7	59.7	0
5AM Ventures	1,000	198.3	128.6	15.2
Total	**$69,740**	**$8,924.5**	**$3,256.0**	**$225.8**

Source: Company websites, Crunchbase, and authors' calculations.
Note: The previous year was defined as investments made between May 1, 2016 and May 1, 2017. Some individual investments had multiple investors so we estimated each firm's contribution in order to avoid double-counting.

A Summary of Private Health R&D Spending

Table 4 summarizes the private sector spending on overall health, global health, and neglected disease R&D. As discussed above, there is a total of $159.9 billion spent on overall health R&D focused on the developed and developing world. This includes $156.7 billion from pharmaceutical companies and $3.2 billion from venture capital.

Neglected diseases that primarily afflict impoverished nations attract the least private R&D money, totaling $511 million.

Second, there is a total of $5.9 billion spent on global health R&D focused on the developing world, with $5.6 billion coming from pharmaceutical firms and $225.8 million from venture capital companies.

Third, 35 neglected diseases that primarily afflict impoverished nations attract the least private R&D money. According to G-FINDER data, neglected disease R&D spending from pharmaceutical funders totals $471 million, while $40 million comes from impact investors, based on Tideline analysis.[27]

Venture Capital Case Studies

To see how venture capital firms make investments and assess risks, we conducted interviews with several company executives. One example of a major investor is Clarus Ventures, a life sciences capital fund started in 2005 that manages $1.7 billion across three funds. According to Clarus partner Scott Requadt, the firm focuses on therapeutics and chooses investments where it "can fund a credible team and get therapeutics with an attractive exit for investors." Global health R&D investments generally are risky so it looks for returns where investors can earn "3X or 4X their money over a 3 to 5 year period."[28]

Clarus relies upon different kinds of investments: risk-sharing partnerships, pre-commercial royalties, and traditional investments in public and private companies. For risk-sharing partnerships, it works with other organizations on therapeutic products. For example, it has teamed up with PATH in the past on a late-stage clinical trial of a hookworm treatment. This $25 million deal involves a priority review voucher (PRV) that provides for an expedited FDA review. That cuts four to six months off the typical process and is of great value for drug development. When the product is approved, it can be sold to a large pharmaceutical company for a significant sum, and Clarus splits the financial proceeds with PATH.

TABLE 4 **A Summary of Private Sector Spending on Overall Health, Global Health, and Neglected Disease R&D, 2016**

	Pharmaceutical	Venture Capital/ Impact Investors	Total
Overall Health R&D	$156.7 billion	$3.2 billion	$159.9 billion
Global Health R&D	5.6 billion	225.8 million	5.9 billion
35 Neglected Diseases R&D	471 million	40 million	511 million

Source: Authors' calculations.
Note: The amounts in this table are computed primarily based on calendar year data, except for the venture capital data for the categories "Overall Health R&D" and "Global Health R&D," which use data from May 1, 2016 to May 1, 2017. For venture capital, we assume that spending rates are equivalent for the four months immediately preceding that time window, thereby enabling a combination with 2016 calendar year data.

Pre-commercial royalties involve the acquisition of drugs that are not yet approved. Clarus will invest if there is a credible player doing the drug development and commercialization and there is a good likelihood of the product gaining FDA approval. Generally, these acquisitions come from academic medical centers or inventors who don't want to wait two to three years for product royalties.

Another venture fund firm is Canaan Partners. It focuses much of its recent investing in biopharmaceutical products and is particularly interested in antibiotics for infectious diseases. The company has funded four of the last 10 new antibiotics approved in the last decade. It works with businesses interested in improving disease treatments, devising new medical devices, or strengthening clinical care.

In judging possible investments, it looks for companies where there is likely to be a buyer for its medical products. According to partner Julie Papanek, the exit strategy is important and "a majority are building something pharma wants to buy."[29] In cases where pharmaceutical companies are not interested in purchasing a firm or licensing its assets, it generally means there are few prospects for its products. Her firm has a threshold that investments can return at least 10 percent of the total value of the fund.

Many venture capital firms do not invest substantial resources in global health R&D targeting the developing world. As Elizabeth Bailey, Meg Wirth, and David Zapol wrote, "Venture capitalists look for: large and growing markets in excess of $1 billion; momentum to help get a product though development; and a proven management team. Unfortunately, these basic criteria are often not met in the context of global health businesses."[30]

A study of the venture firm Bioventures in South Africa found modest rates of return in global health R&D. Of its eight investments totaling $12 million, returns ranged from 0X (meaning a zero percent return on investment) to 7X (seven times return on investment), which averages (using the arithmetic mean) to a 2.1X rate of return. Its founders discovered:

> Providing hands-on support to early-stage health ventures poses problems due to the fund's relatively small size, overhead and management expenses were tightly constrained. Bioventures sometimes wasn't able to make follow-on investments, being forced instead to give up equity to raise follow-on investment capital.[31]

As of yet, many venture capital firms haven't invested substantial resources in global health R&D targeting the developing world.

Amie Batson, Filip Meheus, and Steve Brooke of PATH emphasize the concerns private investors have regarding the profitability of new vaccines. They note:

> When considering investments, firms evaluate the probability of a market return. Unfortunately, the developing country vaccine market is small (in revenue terms) and often demand can be more difficult to estimate, particularly given that the decision to finance a vaccine may be made by global donors while the decision to introduce a vaccine is made by national governments. [There has been] inaccurate forecasting in the past. Low-income developing countries expect low prices. Demand (the actual decisions to pay for and introduce the vaccine) has sometimes been confused with need. It is almost always lower than need.[32]

Innovative Financing Models

Some of the most interesting private sector developments in recent years have come from innovative financing models. These are examples where governments, businesses, and foundations found creative ways to leverage resources or provide financial guarantees that reduce investment risks.[33]

One example is Arsanis, a Massachusetts biotech firm that has raised $90.5 million in equity funding and $4 million in debt financing. It aims "to develop treatments for bacterial and viral infections" and "to finance a mid-stage clinical trial for its lead drug program." The company has a new drug called ASN100, which combats staphylococcus aureus pneumonia, which arises from staph infections. It is in a phase 2 clinical trial for this treatment, and the firm has raised money from the Bill & Melinda Gates Foundation, GV (Google Ventures), OrbiMed, Alexandria Venture Investments, Polaris Venture Partners, SV Health Investors, NeoMed, EMBL Ventures, and the Anna Maria and Stephen Kellen Foundation.[34]

Vir Biotechnology is another new company that has raised $150 million of a planned $500 million goal. It is focused on "new solutions for scourges like HIV and tuberculosis." It has the support of the Bill & Melinda Gates Foundation and ARCH Venture Partners, among other investors. One of its projects focuses on "an HIV vaccine that uses cytomegalovirus ... [that] has shown promise in primates." Emilio Emini, the director of the Gates HIV program, noted the foundation's interest in generating greater industry efforts in fighting germs. "It's a new company with a focus on infectious disease and inherently that is very interesting and important," he said. The firm has a novel strategy of purchasing experimental drugs developed at big pharmaceutical businesses, but that are de-emphasized when the firms focus on other illnesses. That gives companies such as Vir the opportunity to build on existing research and develop new drugs.[35]

To support these and other ventures, the Bill & Melinda Gates Foundation has launched a $1.5 billion fund designed "to make investments in technologies being developed in the private sector. The goal of the fund isn't to generate a financial return but to back ideas with equity, loans and other financing that advance the foundation's charitable mission," according to Andrew Farnum, the organization's director of program-related investments.[36] To date, the foundation has made around 50 investments in different companies since 2009. Sometimes, the foundation takes an equity stake in companies to support promising ideas. It also has undertaken around a dozen direct equity investments and provided "volume guarantees" to encourage drug companies to push drug development.[37]

Public-private partnerships and blended finance represent a major area of investment growth. It is difficult to attract venture capital and high net-worth individuals who want a large financial return. As noted by Karlee Silver of Grand Challenges Canada (GCC), "When you put returns first, it is going to limit the interventions and products that you back." From her perspective, "the ability to do blended finance will be the most effective in the long run."[38]

For that reason, many organizations that work on "blended finance" solutions deploy money from governmental and philanthropic sources to catalyze private investment by creating a risk-return profile that is acceptable for the private sector. The common catch-phrase often used here is "billions to trillions," which encapsulates the notion that targeted public money can attract additional investment from non-public sources.

Many organizations that work on "blended finance" solutions deploy money from governmental and philanthropic sources to catalyze private investment.

PATH is a non-profit funded by foundations, companies, individuals, USAID, and the Department for International Development in the United Kingdom that focuses on "vaccines, drugs, devices, and system and service innovations." It works with governments, corporations, foundations and entrepreneurs to bring needed change to healthcare. According to its chief strategy officer, Amie Batson, its partnerships "help to de-risk the development possibilities process for industry."[39] The organization was launched in 1977 with support from the Ford Foundation and now has $288.6 million in annual revenues. Fifty-five percent of its funding comes from foundations, 26 percent from the U.S. government, 14 percent from other governments and non-governmental organizations, and the remainder is provided by individuals and corporations.[40] Among other items, it uses product development partnerships and public-private partnerships to bring vaccines to the marketplace. For example, it has done this with a meningococcal vaccine, rotavirus vaccine, malaria vaccine, Japanese encephalitis treatments, and the like.

There also are some new entrants to the area of blended financing. GCC combines government money with resources from private firms and multilateral organizations. They support initiatives in renewable energy, infrastructure, agriculture, education, and healthcare. Their aim is to support sustainable development through innovative products and services in the developing world.

According to Karlee Silver of that group, her organization does early-stage financing. Their seed grants range between $100,000 to $250,000, and they have awarded 600 over the past seven years. For a small set of this financing (around 7 to 10 percent), GCC offers second stage funding designed to transition to scale. That helps the targeted companies attract other capital and implement their health remedies.[41]

Convergence Finance is an example of a public-private partnership funded by the Canadian government, Ford Foundation, and Citi Foundation. It provides design funding grants up to $750,000, an investment network for matching investors and donors to investments in emerging markets, and training, conferences, and workshops on blended finance. For example, it has worked with Emily Gustafsson-Wright of the Brookings Institution on workshops dealing with development impact bonds. Its grants have supported projects on low-cost eye surgery and efforts to reduce maternal and infant mortality in the developing world. Its platform helps to connect companies that are seeking funding with donors willing to provide support.[42]

> "Can we fund direct development of products for the developing world and be profitable?"
>
> **– Curt Labelle, Global Health Investment Fund**

The Case of the Global Health Investment Fund

The Global Health Investment Fund (GHIF) is a social impact investment fund designed to provide financing to advance the development of drugs, vaccines, diagnostics, and other interventions against diseases that disproportionately harm low- and middle-income countries. According to Managing Partner Curt LaBelle, "It is a novel model—can we fund direct development of products for the developing world and be profitable?"[43] GHIF focuses on diseases such as "malaria, pre-eclampsia, cholera, HIV, and river blindness" and "maternal and infant health issues that cause significant morbidity and mortality in resource-limited settings."[44]

GHIF was conceived by a group of investors, including the Bill & Melinda Gates Foundation, in 2011 as part of a project that is currently led by now-partner Glenn Rockman. The fund closed in late 2013. Today GHIF is a fully independent investment firm located in New York

City. With a $108 million fund at the time of publication, the firm has eight investments and is in the process of finalizing its ninth investment. The fund aims to generate financial returns *and* social impact through investments in companies developing innovative healthcare products for low-income populations. The fund benefits from "downside protection" from the Bill & Melinda Gates Foundation that provides a partial backstop against losses, a unique feature that attracted a diverse group of investors to commit capital to the fund. Investors include the Children's Investment Fund Foundation, Grand Challenges Canada, GlaxoSmithKline, J.P. Morgan, AXA, KfW Development Bank, Merck, and the Pfizer Foundation.[45]

GHIF is not a typical private equity fund, as it enjoys significant flexibility in how it can structure its investments to maximize both social and financial returns. Focusing on late-stage (Phase III) pharmaceutical and device investments, GHIF could be characterized as a "growth" capital firm that utilizes innovative equity, debt, and project financing structures to support promising global health products. Rockman says:

> We are not afraid of complex or innovative financial structures. We like the safety and security of debt instruments but also try to include ways to participate in the upside potential of our investments by using warrants [that allow investors to buy an underlying stock at a certain price] and conversion features [that enable people to exchange one asset type for another].[46]

This flexibility allows the firm to deploy capital to support a broad universe of products ranging from traditional biotechnology startups to large pharmaceutical companies.

According to GHIF, the fund's first eight investments will save over 300,000 lives and improve over 11 million lives per year by 2025. Table 5 below breaks out these statistics by the particular investment using company data.

Table 5 | Lives Saved and Improved by GHIF Therapeutics, per annum by 2025

Medical Product	Lives Saved	Lives Improved
Access Bio	2,025	989,146
Atomo Diagnostics	66,697	844,266
Becton Dickinson / DiabetOmics (BD)	12,706	261,383
EuBiologics	8,130	694,858
Genedrive	1,755	7,963
Moxidectin (MGDH)	–	620,044
Tribendimidine / PATH	–	6,209,178
Serum Institute of India	209,190	1,404,750
Total	**300,503**	**11,031,588**

Source: Global Health Investment Fund (GHIF).
Note: GHIF notes that these statistics "represent preliminary impact modeling efforts by the Global Healthcare Innovation Academy; subject to refinement and change as the GHIF portfolio matures and assumptions evolve.

Of course, the question remains as to whether the model can provide attractive financial returns in addition to impact. According to LaBelle and Rockman, the answer is "yes." Although detailed performance data are not made public, the two principals say that their fund targets returns "commensurate with the public market."[47] Although typical private equity and venture capital firms aim to provide returns in excess of equity market indices, GHIF provides a unique advantage to investors: in the case of a loss-generating fund, the "downside protection" significantly reduces losses to investors relative to traditional funds. The fund has yet to call on this guarantee and doesn't anticipate doing so for the current portfolio, but believes downside protection that leverages the balance sheets of forward-thinking foundations like the Bill & Melinda Gates Foundation could continue to play an important role in driving more capital to impact funds like GHIF, especially in the case of unproven business models.

For the past three years, the Global Health Investment Fund has served as an example of direct investment in difficult-to-finance pharmaceuticals and devices for the developing world. With the near completion of its first fund, GHIF is on track to show that this model can be both socially impactful and financially sustainable. "We think this is a model that should be repeated and will generate positive outcomes," stated LaBelle and Rockman.[48]

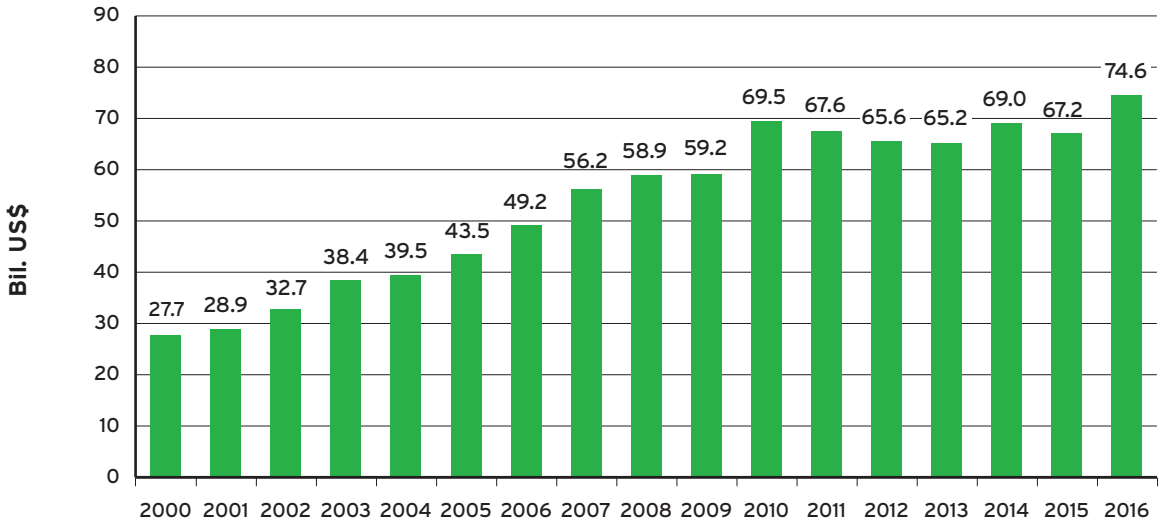
A Flattening of Growth in Overall Private Sector Health R&D

To examine private spending trends in recent decades, we collected data from company filings of 10-K and 20-F annual reports with the U.S. Securities and Exchange Commission, or in the case of non-U.S. firms not listed on U.S. exchanges, we used the company's annual reports filed with their investors.[49] Figure 3 lists the overall pharmaceutical R&D spending by the top 10 Western firms between 1990 and 2016. It shows that overall R&D spending increased from $27.4 billion in 2000 to $74.6 billion in 2016.

The average annual growth rate was 9.8 percent between 2000 and 2010. Since that period, though, R&D spending has plateaued and in some years actually decreased from the preceding year, with an average annual growth rate during this period of 1.2 percent annually. For example, spending declined from $69.5 billion in 2010 to $67.6 billion in 2011, $69.0 billion in 2014, and $67.2 billion in 2015, before rebounding to its highest level of $74.6 billion in 2016.

Overall expenditures are relevant for global health R&D because the flattening of overall health R&D compresses

FIGURE 3 | **Pharmaceutical R&D Spending by Top 10 Firms, 2000–2016**



Source: These data come from company filings of 10-K and 20-F annual reports with the U.S. Securities and Exchange Commission, or in the case of non-U.S. firms not listed on U.S. exchanges, we used the company's annual reports filed with their investors.

the money devoted to drugs and vaccines. When companies' growth is under duress, as it was during the Great Recession, it limits R&D money targeted on the developing world. Diseases that are most prevalent there are not likely to get adequate funding, and this harms drug development investment in those illnesses.

According to the annual survey by the Pharmaceutical Research and Manufacturing Association, 80 percent of its member's 2015 R&D spending was undertaken by companies based in the United States, while 20 percent included expenditures outside the United States conducted by American companies.[50] In addition, 21.2 percent of the R&D spending was devoted to pre-clinical functions, 8.9 percent were for phase I trials, 10.7 percent went for phase II trials, 28.7 percent were devoted to phase III trials, 5.1 percent went for approvals, 16.6 percent went for phase IV trials, and 8.9 percent was uncategorized as to function.[51]

One possible explanation for the slowdown of recent years is the reduction in life sciences employment in recent years owing to the post-2008 recession. According to *R&D Magazine*:

> Life sciences R&D employment has fallen over the past several years as federal funding for the National Institutes of Health (NIH) R&D efforts has stagnated in current dollars and steadily fallen in real dollars since 2002. A study by the NIH found that between 500 to 1,000 NIH researchers (principal investigators or PIs) dropped out of the industry in just one year alone due to concerns/issues in obtaining NIH grants.[52]

While overall health R&D spending among the top 10 Western firms increased substantially in the 2000s, it has plateaued since 2010.

Chris Clubb of Convergence Finance, a blended finance firm, noted:

> One of the reasons behind the concentration of large players in the pharma sector is that their balance sheets are effectively a place to 'blend' finance. Their portfolio of mature products selling into large developed markets allows them to raise money at a relatively low cost to fund R&D. The impact of overt blending, i.e., public funding for private entities pursuing highly speculative R&D, is to mimic this effect, but to do so in a way that gets many, smaller, and potentially indigenous firms engaged.

Barriers to Private Investment

In looking at private sector investment, there are multiple barriers that constrain R&D spending. They include limited markets, the costs of drug development, the possibility of difficult macroeconomic conditions, geo-political risks, the lack of systematic data on what works, and health governance problems that discourage possible investments. In general, according to Dean Segell of Convergence Finance, "it is hard for commercial private investors like insurance companies and pension funds with limited risk appetite and fiduciary responsibilities to their shareholders to invest in global health R&D. Returns are a long way off."[53]

Limited Markets for Certain Diseases

There are limited drug and vaccine markets for certain diseases. This includes illnesses that afflict small numbers of people, diseases that are prevalent in low income countries where patients often lack the means to pay for drug therapies, illnesses where the science has not advanced sufficiently to make drug development affordable, and diseases where there is a long lead time on drug development.

Chris McCahan of the International Finance Corporation (IFC) says that his organization has around $50 billion in outstanding loans and equity investments in emerging markets. Of that, $1.6 billion or around 3 to 4 percent is in the healthcare sector. The IFC has a dual mandate of profitability and positive social outcomes. In general, he says that IFC doesn't directly invest in health R&D because it is not an area of expertise and its strategy is to invest in "less risky" companies and projects that have gone through regulatory approvals and have some commercial traction.[54]

In order to respond to these uncertainties, pharmaceutical firms often invest in developing dual-market drugs that, as a by-product, also creates investment in global health-relevant drugs. For example, there may be drugs designed for one sickness that are applicable to other illnesses. That increases the market for those treatments, and therefore reduces financial risk.[55]

Some non-profit organizations provide purchase volume guarantees that provide support for company drug development if drugs and vaccines do not generate sufficient sales to cover research costs. The Bill & Melinda Gates Foundation and the Clinton Global Health Initiative, for example, have undertaken these types of agreements with drug manufacturers, and seen considerable success.[56] They have leveraged their resources to encourage pharmaceutical firms to support low-cost drugs and vaccines for the developing world.

The Cost of Drug Development

For pharmaceutical companies, the process of drug and vaccine development is very costly. According to GlaxoSmithKline, it can take a dozen years to develop a single drug. Its researchers start with as many as 5,000 to 10,000 possible molecular drug candidates (or biologics) and then work through drug discovery, pre-clinical testing, clinical trials, and licensing approvals to produce a single drug or vaccine.[57]

Not surprisingly, given the long development cycle, it takes a large amount of money to develop particular therapies. In their review of drug development costs, for example, Waye, Jacobs, and Schryvers conclude that expenses vary between $800 million and $1.8 billion for a major drug.[58] Effective drugs also are expensive because of the detailed clinical and regulatory rules that must be followed.

Costs also are high for vaccine development. These treatments must go through rigorous clinical and regulatory approvals, but also must be registered and licensed, and therefore deemed safe for the public in general. Researchers say it takes between $200 million and $500 million to develop a single vaccine.[59] And there often are many failures along the way. As a sign of the high vaccine costs, the Coalition for Epidemic Preparedness Innovations plans to raise $1 billion to fund vaccine development for viral diseases.[60] While $1 billion is a lot of money, it is only enough to fund development of a modest number (e.g., between half a dozen and a dozen) of vaccines.

It is difficult for public sources to fund drug development. Robert Hecht of Results for Development analyzed this situation and found a mismatch with R&D processes:

> Drug and vaccine development is lengthy and uncertain, and R&D organizations therefore require stable long-term financing. Instead, grants from public sources tend to be short term (less than five years, often shorter) and unpredictable during a time of great change. This makes it difficult for grant recipients to plan and commit to long-term R&D investments.[61]

Many developing countries do not invest much in the basic science that is crucial for drug development.

Hecht also highlighted the risks and uncertainty surrounding drug development. He observed:

> [E]xisting financing mechanisms and other policies aimed at stimulating private-sector involvement do not provide sufficient incentive

to overcome the scientific and commercial risks that companies face in considering whether to invest in R&D for a drug or vaccine aimed primarily at low-income countries. It is difficult for companies to forecast demand or project prices in these markets because of lack of information and uncertainty about subsidies from the donor organizations that support drug and vaccine purchase by the poorest countries. At the same time, the opportunity cost of capital to the firms is high, given the large returns they can obtain from alternative investments in the development of new products for affluent-country markets.[62]

Politics affects the environment in which business leaders make decisions, and unsettling events in one area can have major ramifications for health investments elsewhere.

Macroeconomic Difficulties

Aside from developments costs, there are complex and evolving monetary risks facing private investors. In developed economies, the past few years have seen a period of low inflation and near-zero interest rates. Capital has been unusually cheap as the world struggles to recover from the Great Recession of 2008–09. Yet in looking ahead, there is a possibility that interest rates may rise, inflation could increase, or the dollar will change in value. If any of those things happen, it would put pressure on financial resources and the currencies of other countries, impacting both the costs of drug development and the dollar size of the target markets.

Along with other financial considerations, rate hikes can alter the opportunity costs for possible investors and affect their ability to raise capital. Either of these scenarios would have damaging ramifications for the rate of return on their investments. Concern over higher rates and the costs of raising capital could lead them to alter their portfolio decisions and become less likely to invest in global health R&D.

Recession also poses a risk to global health investments. If a recession happened in a leading economy, it would reduce the ability of private investors to put money into health R&D or the capacity of the public sector to undertake additional investments. And if it happened in a developing nation, it could affect that country's capacity to deliver healthcare or maintain infrastructure that is conducive for foreign direct investment.

Geo-Political Risks

Beyond macroeconomic-specific conditions, there are substantial broader risks associated with changing geo-politics in the developed world. Large forces of transformation in Europe and the United States associated with populism, nationalism, globalization, and technology innovation are buffeting societies in many places.[63] Leaders (and potential future leaders) have emerged in a number of Western countries who are advocating altering existing alliances and global engagements, often in ways that would potentially alter (and in some cases, decrease) the incentives for investment in global health R&D.

Each of those developments has the potential to alter investment calculations and affect the delivery of medical products and services. Politics affects the environment in which business leaders make decisions, and unsettling events in one area can have major ramifications for health investments elsewhere.

There also are investment risks in developing nations in places such as Brazil, China, and India where there are emerging pharmaceutical companies. According to Chris Clubb of Convergence Finance, "private investment is driven by risk-return with country risk the overwhelming risk determinant in emerging markets." Western investors use Standard & Poor's, Moodys, and Fitch ratings as the baseline of country risk. Largely, institutional investors require investment grade risk

of BBB- or better, and all investors require a risk-return mix that competes with other assets. "More than 85% of sovereigns in emerging markets are below investment grade, with private sector borrowers even higher risk. Therefore, there are hardly any companies and projects that meet the main institutional risk standard," he noted.[64] Historically, this approach has made it more difficult to take advantage of new R&D opportunities in China, India, Brazil, and elsewhere, though as discussed elsewhere in this report, there is increasing evidence that the investment opportunities have been improving in recent years.

A Lack of Systematic Data

Private investors don't have reliable data on investment returns, infrastructure costs, or the effects of system change on healthcare. That raises the risks and uncertainties associated with investment decisions. In this situation, it is hard to know where to put money and what efforts will produce the greatest results. Traditional venture firms often aim for annualized returns in the range of 20 to 30 percent, according to Andrew Farnum of the Bill & Melinda Gates Foundation. In the global health area, he pointed out, it is difficult to reach those kinds of returns unless they are dual market drugs or platforms with wide applicability.[65]

Investors want evidence that justifies global health investments. These include information on risk-return issues, what interventions are working, and what is called "counterfactuals" or "additionality," i.e., what would have happened without a financial intervention. Results-based financing through development impact bonds or other vehicles requires clear answers to these questions. Private sector sources such as banks, insurance companies, or commercial companies have an opportunity cost of diverting funds that might otherwise go to mainstream investments and require a premium to invest in emerging markets above what they would earn from developed market investments in order to justify their investment risks.[66]

This is particularly relevant in regard to product development partnerships (PDPs). According to participants at a recent workshop of investors convened by impact investing consulting firm Tideline and the Bill & Melinda Gates Foundation, there are capacity problems, funding difficulties, and a desire for better transparency in this area.[67] Investors decry the lack of clear rules of the road on global health R&D investments. Right now, they see a lack of clarity and a lack of metrics on global health. Investment professionals don't know what works or how to gauge their rate of return. Of the 103 innovative financing proposals involving private investors studied by PolicyCures, "only one targeted new no/low-profit R&D model (the PDPs) and very few intended to target developing country markets."[68]

What is needed is to align incentives with market opportunities and create "win-win situations" for private investors. The goal is to create situations where the treatment platform has value itself. For example, Farnum noted that a tuberculosis drug may not make much money on its own, but a firm that develops a proven platform for drug treatments can sell that to a pharmaceutical company or use it to generate new financing for other projects.[69]

Without systematic data in global health R&D, it is hard to know where private investors should put their money and what efforts will produce the greatest results.

In addition, there are alternative methods of estimating benefits from global health investments. They include "full income" approaches that estimate the dollar value of living a longer life. In general, these models demonstrate even greater benefits than contributions to gross domestic product or economic growth because of the value placed on each year of additional living.[70]

Health Governance Challenges

Poor health governance is a problem in many places around the world. As we noted in our first report in the Brookings Private Sector Global Health R&D Project, governance is a foundational consideration that affects public perceptions, the investment climate, and business decisions regarding health R&D.[71] If some investors do not believe that their resources will improve the situation or reach intended beneficiaries, it will be very difficult to persuade them to put money into new initiatives. They need confidence that governments and civil society in target countries can benefit from new investments and put their money to effective use.

Opportunities for Private Investment

While there are investment challenges in global health R&D, there also are several opportunities with the potential to encourage private investment. This includes advances in the science of drug discovery, new developments in artificial intelligence, the growth of upper middle income countries with improved financial capacity, and spillover benefits from non-health investments that improve the private investment climate.

Advances in the Science of Drug Discovery

Recent advancements in genomics offer the potential to improve private sector development of new drugs.[72] Research has demonstrated that many patients are not able to benefit from particular drug therapies. For example, Iressa and Tarceva are drugs for treatment of non-small cell lung cancer, but they are effective only in tumors that express the epidermal growth factor receptor gene. Other medications are ineffective for 70 percent of Alzheimer's sufferers, 50 percent for those with arthritis, 43 percent who are diabetic, 40 percent who suffer from asthma, and 38 percent who take SSRI antidepressants.[73] Since people metabolize medicine in so many different ways depending on their particular genes, the resulting enzymes, and their current health status, it is vital to have an understanding of genomic information to reduce adverse events and determine optimal therapies.

According to Amy Bell of Tideline, "there are new ways to deliver treatments and cures that we don't have the means to fully fund right now."[74] Previously, it was difficult to personalize medical treatments, but care-givers now can run genetic tests that determine how effective a drug is likely to be for that individual. These tools give drug developers a better handle on the efficacy of their medications and the possible markets for their products. They have the potential to lower treatment costs and therefore stimulate greater investment. By harnessing the power of these new discoveries, it is possible to bring quality healthcare to various parts of the world.

New Developments in Artificial Intelligence

It costs millions of dollars to develop new pharmaceutical products. This delays the production of new treatments and their application to new markets. But with the advent of supercomputers and artificial intelligence, it is possible to speed up drug creation and reduce development costs. Atomwise, for example, is a firm that uses supercomputers to map molecular structures and search for medications that can be repurposed for other diseases. In its quest for treatments for the Ebola virus, it was able to cut processing time from months to days. Company chief operating officer Alexander Levy argues that "if we can fight back deadly viruses months or years faster that represents tens of thousands of lives."[75]

While there are investment challenges in global health R&D, there also are several opportunities to encourage private expenditures, including advances in drug discovery and artificial intelligence.

How the Growth of Upper Middle Income Nations Creates Opportunities

The World Bank segments the globe into four categories: high income, upper middle income, lower middle income, and low income nations.[76] Places such as Argentina, Brazil, China, Colombia, Malaysia, Mexico, South Africa, Thailand, and Turkey fall within the upper middle income range, and they have greater capacity to invest in healthcare than in the past. As noted earlier in the paper, pharmaceutical firms in these countries are investing more resources in R&D. With their low drug development costs, they represent major opportunities for medical R&D focused on the developing world.

Some of these nations have adopted favorable incentives for domestic drug companies and these firms are well-positioned to fund R&D initiatives at a reduced cost. They are stronger economically than was the case a couple of decades ago, and they have more business entities capable of supporting healthcare R&D. This creates new opportunities to make progress on drug development.

Spillover Benefits From Non-Health Investments Have Strengthened Developing Nations

The health sector benefits from investments taking place in non-health areas. For example, spending on general infrastructure has spillover benefits across a variety of sectors. Infrastructure investment is a force multiplier that creates benefits in a number of different areas. Better roads, having more health clinics, and possessing better delivery systems benefits all parts of the health ecosystem from drug development to commercializing products. Infrastructure improvements enable faster transportation and communications, and helps businesses develop and market new products.

Research by Cesar Calderon and Luis Serven finds major benefits of infrastructure investment.[77] It boosts overall economic growth, improves the income distribution, and strengthens business development in many different sectors. Basic improvements in transportation and communications make it possible for firms to form and prosper, especially in the developing world.

The same is true for investment in education. Improving human capital pays off in a variety of areas. Researchers have found using a full income approach that "every dollar invested in female schooling in low- and middle-income countries would return $5 in terms of the value of under-5 mortality reduction alone."[78] Education spending gives businesses the ability to recruit high skilled workers and develop their businesses. This is true in healthcare as well as many other sectors. Having higher skills is good for business development because it improves the workforce and builds stronger companies.

How Investment Opportunities Vary by Market Size and Rate of Return

Businesses generally do not think about R&D opportunities in a monolithic form, but focus on targeted opportunities that offer the best chance of earning a reasonable rate of return. In our expert consultations, it was clear that investment opportunities depend on two basic conditions that affect perceptions of risk and uncertainty: the size of the market and the possible return on investment. The related tradeoffs are helpful to visualize in the manner shown in Table 6.

TABLE 6 | **A Matrix of Private R&D Investment Opportunities**

Return on Investment	Small Market	Large Market
Low	Little Opportunity and Incentives Won't Improve Investment	Moderate Opportunity and Incentives Could Help
High	Moderate Opportunity and Incentives Could Help	Large Opportunity and No Need for Investment Incentives

Source: Authors' calculations.

In situations where there are large markets and a high rate of return, there are considerable opportunities for businesses to invest in R&D. These represent situations where companies naturally will invest because they perceive reasonable opportunities to make money. There isn't much need for government incentives because the market conditions are favorable for business. Risk and uncertainty are relatively low in this scenario.

Conversely, there is little opportunity when the market is small and the return on investment is low. These kinds of market conditions are best filled by public investment. Governments should invest directly in these areas and provide coverage for activities that are not likely to be supported by the private sector. There is little need to create incentives for business investment because those incentives are not likely to improve perceptions of risk or alter the climate concerning the rate of return.

A number of governments and multilateral aid organizations have reduced their spending on global health R&D over the past decade, in turn discouraging private investing.

Following within those scenarios are the moderate opportunities where there are low returns but a large market, and situations where there are high returns but a small market. It is in these situations where private investment could be spurred through policies or regulatory actions that improve the investment climate or where there are actions by governments or charitable organizations that help businesses reduce risk and uncertainty surrounding their spending.

A key notion for private companies is the "hurdle rate," i.e., the level at which companies can earn a profit.[79] This is the discount rate at which the net present value is zero. It is the minimum return over time that justifies the investment given the firm's cost of capital and the other investing alternatives available to the firm. Investors are highly attuned to this rate because it dictates when and where they invest, and how they assess risk and opportunity.

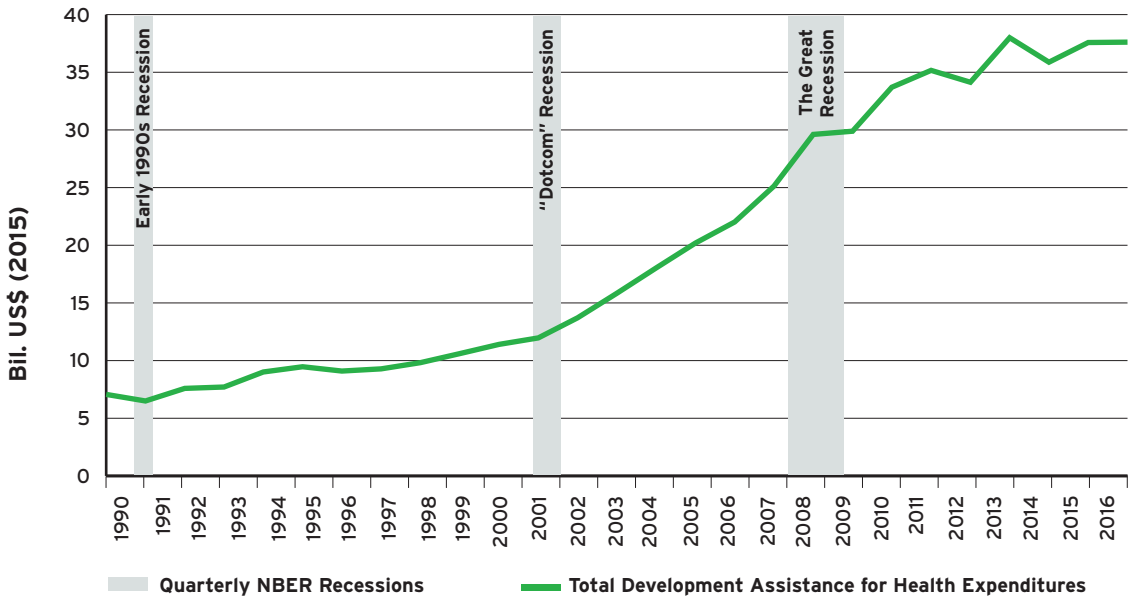
It is important to distinguish these types of business situations because there likely are differing remedies for each of the matrix boxes based on the risk profile of each condition. Governments and charities have the potential to help in certain situations but not in other ones. It matters greatly for global health R&D what the size of the market is and what the possible rates of return are.

How a Slowdown in Public Sector Spending Affects Private Investment

The U.S. and foreign governments are major funders of health, and slowdowns there affect the environment for private R&D investing. Over the past decade, there have been significant slowdowns in the rate of overall development assistance by public sector agencies and multilateral organizations, and some actual declines.[80] Figure 4 shows development assistance for health (DAH) between 1990 and 2016.[81] The trend line of a spending slowdown in recent years is clear. Between 2000 and 2010, spending growth averaged 11.4 percent a year, compared to only 1.9 percent between 2010 and 2016. The Great Recession clearly was a major drag on government assistance and multilateral aid.

A number of governments and multilateral aid organizations have reduced their spending. According to IHME data on DAH, the Inter-American Development Bank went from $801 million in 2015 to $689 million in 2016. Canada dropped from $321 million in 2015 to $295 million in 2016. Italy implemented a dramatic reduction from $265 million to $93 million over the past year.

FIGURE 4 | **Development Assistance for Health, 1990–2016**



Source: Institute for Health Metrics and Evaluation (IHME) and authors' calculations.
Note: As stated by the IHME in "Financing Global Health 2016," the 2015 and 2016 data are preliminary estimates.

Australia dropped from $244 million in 2015 to $155 million in 2016. Sweden went from $139 million to $112 million in the last year. The Netherlands dropped from $136 million to $102 million over the past year. France decreased its DAH funding by 3 percent in the last year.[82]

The U.S.-based President's Emergency Plan for AIDS Relief (PEPFAR) is a component of the Global Health Initiative) and it stopped its rapid growth in 2008. It provided treatment to 11.5 million people in 2016.[83] In addition, NIH funding is down $300 million annually since 2010. In terms of its Global Health Initiative, HIV/AIDS funding has declined $800 million annually from 2010 to 2013. There also has been a $1 billion drop in non-U.S. aid for HIV/AIDS in Europe.[84]

In spring 2017, President Donald Trump's administration proposed cutting foreign assistance by 37 percent, including plans to make significant cuts in medical research supported by the National Institutes of Health (NIH). In the draft budget released in April 2017, NIH spending was reduced by $5.8 billion or 18 percent of its total expenditures. The budget also called for the complete elimination of the Fogarty International Center, which focuses on HIV/AIDS, dengue, Ebola, and other global health issues.[85]

Although these reductions were not approved by Congress, the Trump administration has not given up on its plans for very large budget reductions. As characterized by the *Washington Post*, in its 2018 budget request released in May 2017, the president seeks "massive cuts in spending on scientific research, medical research, disease prevention programs and health insurance for children of the working poor." For example:

> The National Cancer Institute would be hit with a $1 billion cut compared to its 2017 budget. The National Heart, Lung and Blood Institute would see a $575 million cut, and the National

> Institute of Allergy and Infectious Diseases would see a reduction of $838 million. The administration would cut the overall National Institutes of Health budget from $31.8 billion to $26 billion.

It furthermore "seeks an $82 million cut at the center that works on vaccine-preventable and respiratory diseases, such as influenza and measles. It proposes a cut of $186 million from programs at CDC's center on HIV/AIDS, viral hepatitis, sexually transmitted infections and tuberculosis prevention."[86]

This slowdown in DAH has important ramifications for private sector R&D investment. As noted above, some public money supports medical research that undergirds global health R&D development. Without support for basic research, it will be harder for pharmaceutical companies and other firms to discover new drug compounds and bring them to market. In addition, there are potential risks for public-private partnerships funded by USAID. According to the Global Health Technologies Coalition, "In 2015, USAID provided nearly US$80 million in funding to support global health R&D. Cuts to USAID funding could stall promising innovations under development and halt efforts to roll out new technologies in USAID programs."[87]

The slowdown in public and private funding concerns health experts. For example, Joseph Dieleman of the University of Washington believes strong growth similar to what is sometimes called the "golden age" of DAH funding from 2000 to 2010 is unlikely: "[There] will likely be moderate growth, although it may be less than [during] the 1990s, and returning to 11% growth seen in the first decade of the 2000s is especially unlikely."[88] If realized, that trend will have enormous consequences for drug discovery and commercialization.

With the recent slowdown in public and private investments, health experts don't expect to see another golden age of DAH funding soon—something that would have enormous consequences for drug discovery and commercialization.

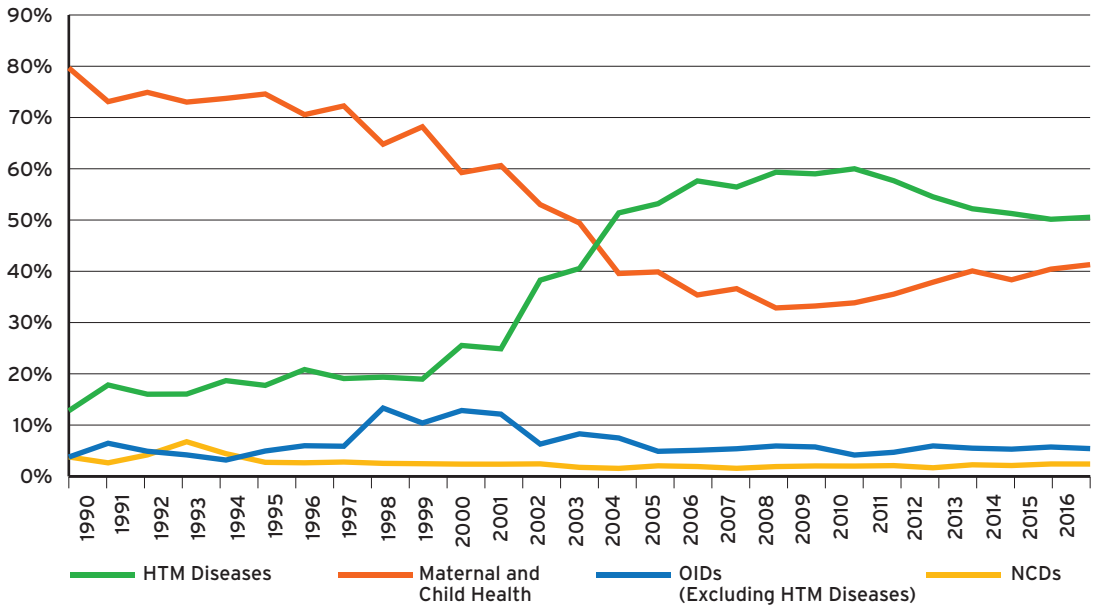
The Question of Disease Priorities

Both public and private financing has slowed since the great recession, but the types of illnesses funded have dramatically changed as well, especially when looking at development assistance for health. In general, there is some misalignment or mismatch between DAH disease investment and the fatalities associated with those illnesses.

During the so-called golden age of DAH funding, the HTM diseases (HIV/AIDS, tuberculosis, and malaria) and especially malaria had the largest year-over-year funding growth. Figure 5 breaks down the DAH spending by disease type between 1990 and 2016. It shows that money for HTM diseases increased after 2000 before plateauing and falling since 2010. Money for maternal and child health dropped from 1990 to 2008 and rose thereafter. At the same time, funding for other infectious and non-communicable diseases (NCDs) remained relatively low and constant over the last three decades.

People familiar with the global health landscape are aware of the numerous challenges that make R&D funding of pharmaceuticals, vaccines, and diagnostics for the developing world one of the most intractable problems in international development. Although disease incidence—and therefore need—is often quite high in these regions, poor populations in those places generally don't have the money to pay for the drugs. This diminishes the incentive for companies to invest in these therapies. As researchers Alice Albright, Michael

FIGURE 5 **Percent of Total DAH Expenditures Devoted to HIV/AIDS, Tuberculosis, and Malaria (HTM Diseases) Maternal/Childhood, Other Infectious and Non-Communicable Diseases, 1990–2016**



Source: Institute for Health Metrics and Evaluation (IHME) and authors' calculations.
Note: The DAH expenditures were computed as total DAH spending minus HSS/SWAPs, other, and unallocated monies. All years sum to 100 percent except for 2014 and 2015, which add up to 97 percent and 99 percent, respectively.

Kremer, and Ruth Levine of the Center for Global Development's Advanced Market Commitment Working Group note: "Just 10% of the world's research and development on health is targeted on diseases affecting 90% of the world's people."[89]

Table 7 lists the mortality rates for several diseases and disability-adjusted life years (DALYs) by disease for the bottom four socio-demographic index quintiles, and the percentage of the DAH investment money that flows into each illness. It shows that 50.2 percent of funding is put into HTM diseases, yet only 7.5 percent of the deaths and 8.6 percent of the DALY losses occur from those illnesses. Similarly, 40.4 percent of the funding goes to maternal and childhood diseases, yet only 6.1 percent of people die from them and 11.2 percent of the DALY losses occur there.[90]

Conversely, 73.6 percent of deaths and 62.7 percent of the DALY losses occur from non-communicable illnesses such as heart disease, cancer, or mental health problems, but only 2.4 percent of global health investment flows into those areas. Andrin Oswald of the Bill & Melinda Gates Foundation observes that "NCDs have been underfunded over the past 10 years; however, I would have thought that diseases of the aging populations (diabetes and obesity) would have had more investment … however, they are for sure flattening out since the 1990s."[91]

The only area where this is a discernible alignment between death rates and investment level is with other infectious diseases not including HTMs. Researching those, 12.8 percent of people die from those illnesses and 17.5 percent of the DALY losses occur there, while these diseases receive 5.7 percent of the funding.

TABLE 7 | Mortality Rate, DALYs, and DAH Investment Level by Disease, 2015

Disease	DAH Investment Level for Each Disease	Mortality Rate By Disease	DALY Losses By Disease
HIV/AIDS, Tuberculosis, and Malaria (HTM Diseases)	50.2%	7.5%	8.6%
Maternal and Childhood Diseases	40.4	6.1	11.2
Other Infectious Diseases (OIDs) or Other Communicable Diseases	5.7	12.8	17.5
Non-Communicable Diseases (Heart, Cancer, Mental Health)	2.4	73.6	62.7
Total	**98.7%**	**100.0%**	**100.0%**

Source: Institute for Health Metrics and Evaluation (IHME) and authors' calculations.
Note: Mortality Rate uses "Other Communicable Diseases," while Investment Level (DAH) uses Other Infectious Diseases (OIDs excluding HTM). The Total subtracts out Injuries and NTDs for Mortality Rate, and HSS/SWAPs, Other, and Unallocated for Development Assistance for Health (DAH). The year of 2015 was utilized because the Global Burden of Disease (GBD) mortality data for 2016 had not been released as of the report publication. In this analysis, we compare DAH spending on the bottom four socio-demographic index countries as defined by the IHME.

It is a complex topic to think about the best ways to make allocation decisions. The kinds of numbers we observed could indicate that previous death rates were much higher, as was the case with HIV/AIDS, but major DAH investment brought needed treatment to patients and thereby drove down mortality. Indeed, it seems clear that improved funding for HIV/AIDS helped to produce positive health results.

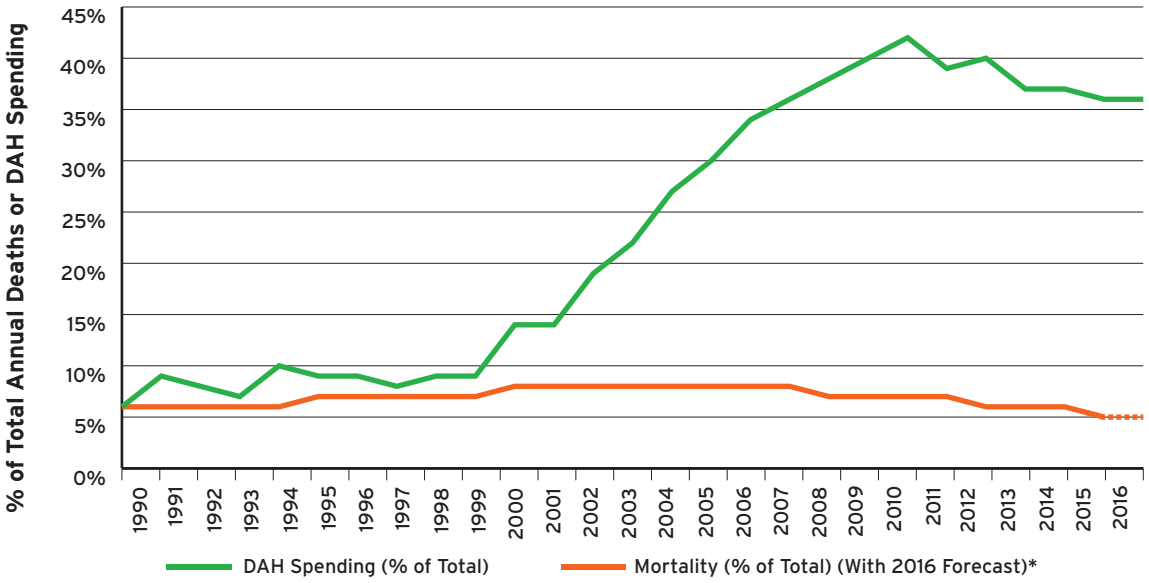
Illnesses such as HIV/AIDS pose broad societal consequences because of the huge impact on many socioeconomic classes and geographic areas. It is not just a disease of the poor, but one that afflicts many different individuals and therefore has a broad economic and social impact on society. Its patients often die young and subsequently rob their communities of more life years than tends to be the case with non-communicable diseases, that are more likely to afflict older people.

There also could be differences between DAH investment (which mainly comes from governments, multilateral organizations, and foundations) versus private sector investment coming from pharmaceutical companies or venture capital firms. It is nearly impossible to test the alignment of private investment and mortality or DALYs due to the lack of data on pharmaceutical spending by particular diseases. Most companies do not provide detailed information regarding their global health R&D expenditures by specific illnesses so researchers cannot assess alignment or misalignment.

In looking overtime at DAH investment, it appears that the misalignment has widened. Figure 6 shows data from 1990 to 2016. It demonstrates that the misalignment of spending on HTM diseases started out relatively small in the 1990s but has widened significantly since then. In 1999, for example, about 9 percent of DAH funding was devoted to HTM and around 7 percent of people died from those illnesses. By 2016, however, those diseases garnered 36 percent of the funding, but 5 percent of the fatalities.

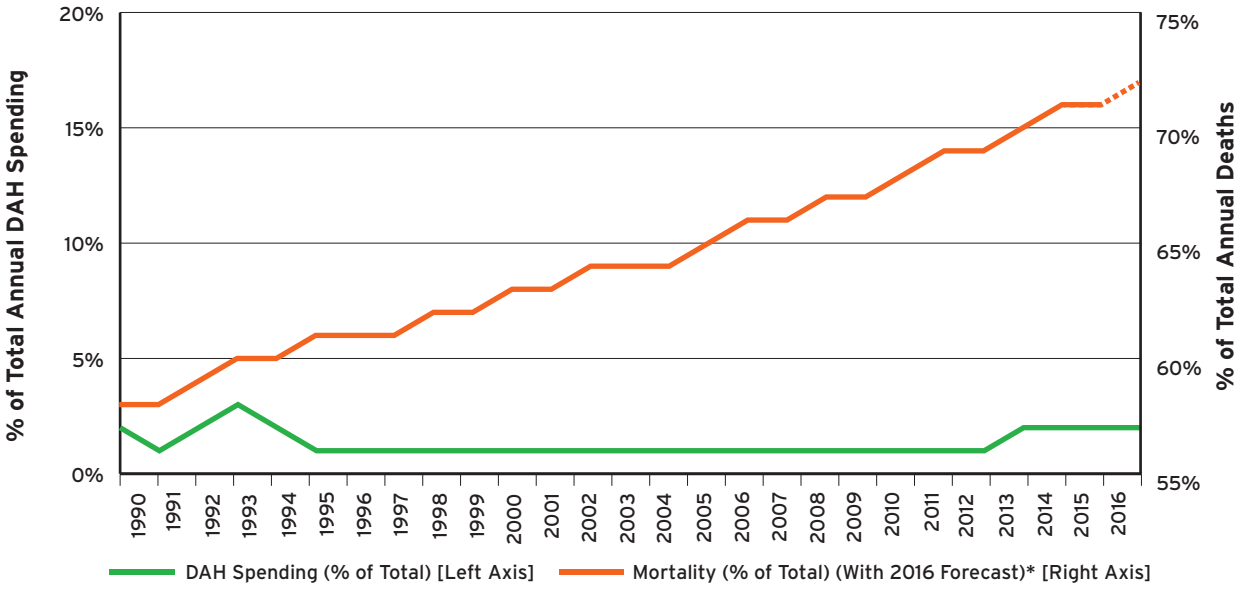
Figure 7 shows the numbers for non-communicable diseases, and the pattern is reversed. These illnesses represent 2 percent of the funding, but around 72 percent of the deaths.

FIGURE 6 **Percent of DAH Spent on HIV/AIDS, Tuberculosis, and Malaria (HTM Diseases) Versus Percent of Mortality from Those Illnesses, 1990–2016**



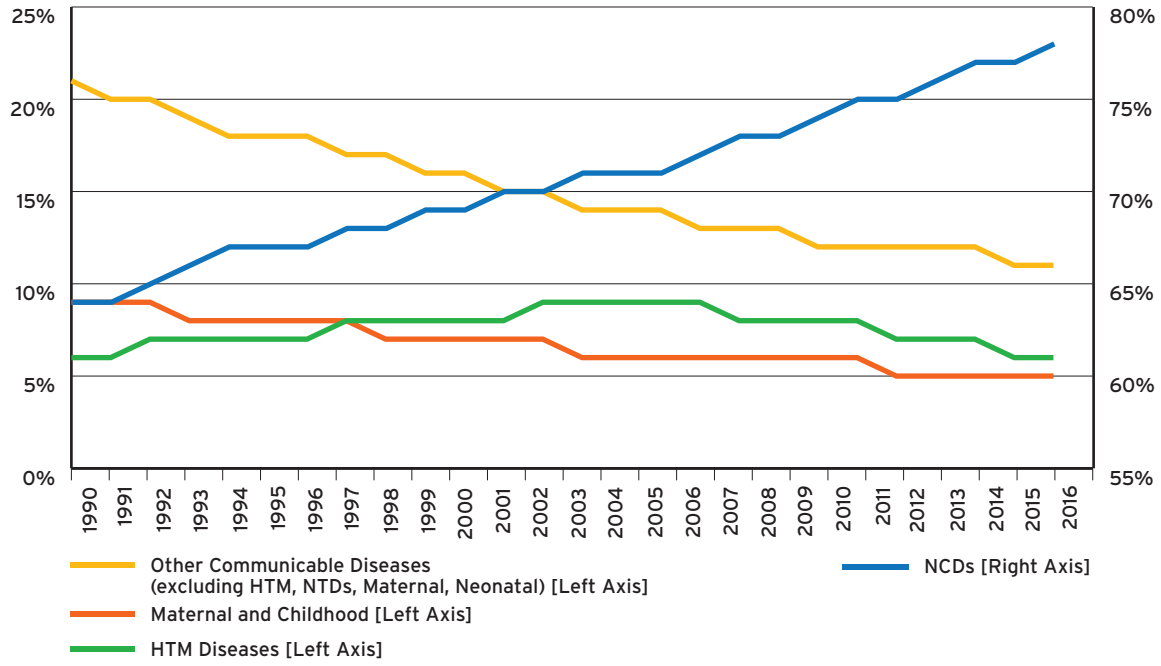
Source: Institute for Health Metrics and Evaluation (IHME) and authors' calculations.
Note: The 2016 mortality data were extrapolated using linear regression.

FIGURE 7 **Percent of DAH Spent on Non-Communicable Diseases (NCDs) Versus Percent of Mortality from Those Illnesses, 1990–2016**



Source: Institute for Health Metrics and Evaluation (IHME) and authors' calculations.
Note: 2016 mortality data extrapolated using linear regression.

FIGURE 8 **HIV/AIDs, Tuberculosis, and Malaria (HTM Diseases), Maternal and Childhood, Other Infectious, and Non-Communicable Diseases as Percent of Total Mortality, 1990–2016**



Source: Institute for Health Metrics and Evaluation (IHME) and authors' calculations.
Note: Total Mortality is calculated as Total Annual Mortality minus Injuries and NTDs.

If one looks at all four disease categories between 1990 and 2016 as a percentage of mortality in Figure 8, it is clear that deaths due to non-communicable diseases has risen during this time period, while fatalities from all the other illnesses has dropped.

In thinking about funding issues, Dieleman of the University of Washington argues that "there is always a space to do this better; there are space for improvement and very few would disagree with this. The question is how to do aid allocation better? That is the crux of this issue, more controversial, and certainly more challenging." Some trends in spending depend on short-term considerations and *not necessarily* on systematic data or best practices or empirical research.[92]

Some of the individuals with whom we spoke bemoaned the lack of evidence-based information as a basis for making aid investment decisions. Amie Batson, the chief strategy officer at PATH, notes that "[there] is a need to ensure good data is available to the right decision makers to inform investments and priorities."[93] From her standpoint, most of the current health funding focuses on communicable diseases, such as HIV/AIDS, tuberculosis, and malaria. There is relatively little money supporting non-communicable diseases in the developing world.

Nick Chapman of Policy Cures argues that disease funding decisions should reflect a variety of criteria such as the current state of the R&D pipeline, scientific issues, the gap between current spending levels and projected investment needs, health technology gaps, and risk-adjusted probabilities of success.[94]

Recommendations for Improving Private Investment in Global Health R&D

In order to encourage greater private sector investments, there are a number of steps that would break the current cycle of poverty and disease in the developing world. They include improving markets, the need for systematic data on what works, strengthening governance, and reducing investor uncertainty. These steps are most relevant for developing countries that are growing economically and therefore in the strongest position to undertake reforms, build investor confidence, and help products and services reach their intended beneficiaries.

In a recent speech at the London School of Economics, World Bank President Jim Yong Kim argued that "our top priority should be to systematically de-risk both projects and countries to enable private sector financing, while at the same time ensuring that these investments benefit poor countries and poor people."[95] He cited the importance of crowding-in private capital and encouraging upstream regulatory and policy reforms that make projects commercially viable.

Having drugs and vaccines targeted on the developing world is crucial in order to move ahead. According to the World Health Organization Global Vaccine Action Plan, a measles vaccine would save 10.6 million lives over the next 10 years, a hepatitis B vaccine would save up to 6 million people, a haemophilus influenza type b vaccine would save up to 1.7 million lives, a pneumococcus vaccine would save up to 1.8 million lives, a rotavirus vaccine would save 900,000 lives, and a human papillomavirus vaccine would save 500,000 lives if there were widespread coverage.[96] Right now, based on analysis from the Access to Medicine Index, around 2 billion people globally have no access to drugs and vaccines, so there is a glaring need for progress in this area.[97]

1) Creating Markets

There are several reasons why private individuals and commercial firms are less likely to direct their resources to support global health R&D and therefore why it is hard to create a viable market. First, there are serious risks involved, given the complexities of the science of developing drugs and vaccines. It generally takes millions or more to develop and bring these kinds of new products to the market. Second, there are challenges in terms of convincing major firms to manufacture and distribute drugs and vaccines in the developing world. The market for such products is unclear in many places, and it is hard to predict the possible profitability of new materials. Third, poor governance structures in many parts of the developing world discourage impact investors. As we point out in an earlier paper, health governance suffers from difficulties in terms of management, policies, regulation, infrastructure, and health systems.[98] Although there are variations from country-to-country on these dimensions, the situation in many places does not encourage investors that even good products will reach their intended beneficiaries and generate the hoped for health outcomes. Figuring out ways to build viable markets and create effective incentives needs to be a high priority.[99]

2) Compiling Systematic Data

Having data on what works and what it would cost to move medical products into production would make a big difference to private investors. Currently, both public and private donors have too much uncertainty regarding investment impact and rates of financial return, and this increases the risks surrounding their investment decisions. In our interviews, several investors cited a need for better transparency on what works. They feel that the lack of current data holds investment back and makes it difficult for donors to have confidence about allocating their financial resources. Against this backdrop, it would be beneficial to the market if pharmaceutical companies were more transparent about their return-on-investments and the results of their risk-adjusted capital investments.

Among the data that would be helpful to investors would be information on investments, rates of return, drug effectiveness, and the investment climate within particular countries. Data on these topics would enable businesses to assess risk and determine the viability of their own investments. Uncertainty surrounding risk or rate of return reduces their confidence and makes it difficult for them to allocate scarce money. Having greater confidence regarding political or economic conditions would be beneficial for private investment.

The Netherlands-based Health Insurance Fund is an example of an investment vehicle that places a high priority on program evaluation. After it was launched by the Ministry of Foreign Affairs and supported the PharmAccess Group, it sought to evaluate the initiative's impact and effectiveness. It undertook a variety of strategies such as examining participation in health insurance, conducting follow-up surveys, and monitoring progress toward achieving key objectives. Having that kind of systematic data helped give the Fund confidence in what it was doing.[100]

Groups often resort to societal considerations rather than making decisions based on clear evidence of need or impact. Having a more systematic means of making these decisions would improve the climate for private investment.

3) Prioritizing Funding Gaps in Disease Treatment

There are R&D funding gaps that need to be addressed. The most important aspect of this is determining what are the most important principles that characterize a "gap." For example, there is little doubt that there are misalignments between funding levels and disease incidence. But in addressing these divergences, should assessments be based on population need, disease incidence rates, patient mortality, return on investment, or some other societal criteria?

In its assessment of global health R&D, the Access to Medicine Index ranks pharmaceutical companies on the performance in targeting priority R&D gaps and linking their activities to public health goals as specified in the 2030 Agenda for Sustainable Development. According to index researchers, top companies "lead in product development, with relatively large pipelines that demonstrably address the needs of people in low- and middle-income countries (i.e., by targeting high-burden diseases and taking specific steps to make products suitable for people in a country in scope)." In addition, these firms "target high-priority product gaps with over half of their pipeline projects (the gaps, as identified by G-FINDER, show where there is a clear product need, yet no commercial incentive)."[101]

In the absence of systematic data, it is hard for private investors to assess need or effectiveness. People often resort to societal considerations such as diseases that afflict popular groups rather than making decisions based on clear evidence of need or impact. Having a more systematic means of making these decisions would improve the climate for private investment.

Seth Berkley, the chief executive officer of Gavi, the Vaccine Alliance, argues that there needs to be greater attention paid to yellow fever. He says it is a "greater potential threat" than Ebola and that half of those suffering severe cases end up dying. Brazil currently has 715 confirmed cases and 820 suspected outbreaks. It kills around 30,000 people each year, and therefore deserves greater attention from the investment community.[102] This is an area where we need to scale up existing vaccines and get them to the people most at risk.

4) Improving Health Governance, Medical Infrastructure, and Supply Chains

Improving health governance would be beneficial for private investment. In our earlier paper on this

topic, we argued that anything that builds investor confidence would be positive for private investment.[103] Investors currently have doubts about the ability of some developing nations to absorb new resources or take advantage of new funding. They think that medical supply chains are not mature and there are no guarantees that drugs and products that make it to local warehouses will reach intended beneficiaries.

Improvements in supply chains and local infrastructure would help business leaders believe that needed medical products will get out of the warehouse and make it to hospitals, doctors, nurses, and medical clinics. That would encourage them to invest new resources and allocate money for global health R&D. An example where this is being tried is in East Africa, where some companies are using low-cost drones to deal with high land transport costs for drug distribution and get medical products to beneficiaries.

Improving transparency in government and strengthening the management capacity of health systems in the developing world would aid private investment. If governments were more open about their medical service delivery or the way they handle budgets, it would advance progress in many countries. Improved integrity in government would improve political stability and reduce corruption. In those ways, these steps would promote a better climate for private investment.

5) Expediting Regulatory Reviews of New Drugs/Vaccines

Expedited and safe regulatory reviews of new drugs and vaccines would aid pharmaceutical companies considering new investments. Right now, many nations around the world have very long processes for drug approvals. This raises the costs and increases the uncertainty surrounding clinical trials. It is hard for firms to know how long it will take to gain approvals and how the regulatory process will affect their rate of return. The FDA has implemented a new "fast track" review process that has yielded positive results. It has speeded up approvals and helped companies push their products to market.

In addition, companies that want their products used in developing world public health systems have to go through a rigorous World Health Organization review process. That is time consuming and burdensome for companies, and creates another level of hurdles for them to go through. Reducing some of these barriers while still protecting patient safety potentially could boost private investment. For example, a number of countries in Africa are pursuing regulatory harmonization that would streamline government processes and make it less burdensome to obtain approvals.

> Improving health governance in the developing world, such as efforts to strengthen transparency and the management capacity of health systems, would promote a better climate for private investment.

6) Encouraging Venture Fund Investments Through Redesigned Priority Review Vouchers

To help manage these risks, advocates have developed priority review vouchers (PRVs) designed to expedite FDA approvals by up to six months and help drug developers sell their products to pharmaceutical companies. Yet the results of PRVs to date have been mixed at best. Only 11 PRVs have been approved in the last five years.[104] Critics complain that there is no access guarantee for poor people in the developing world. The inability to afford relevant treatments nullifies the possible benefits of this program.

In its recent reauthorization of the 21st Century Cures Act, Congress extended the vouchers beyond the neglected tropical diseases, where they are needed, to pediatrics emergency drugs and bio-terrorism agents.

Scott Requadt pointed out that "there is no need for vouchers in the pediatrics area because venture firms are eager to fund those products, there are reasonable prices, and large trials are not needed for FDA approvals."[105] From his standpoint, adding more categories of drugs eligible for PRVs is counter-productive because it floods the marketplace and therefore drives down the value of PRVs for neglected tropical diseases. That reduces the overall investment incentives for PRVs.

In order to encourage greater venture capital investment, it would be helpful to redesign PRVs in two ways. First, the focus of PRVs should remain on neglected diseases because that is where the greatest need for new drugs is. Adding more categories of drugs to the PRV list is counter-productive from a venture capital standpoint because it reduces the resale value of vouchers. Second, PRVs right now apply only to drugs that already are going through the FDA approval process. Venture capital investors think there would be greater investment if drugs earlier in the development stage were eligible for PRVs. Providing financial incentives earlier in the cycle would reduce investment risks and help firms cope with the uncertainty of drug development.

Having targeted tax incentives can be an effective way to stimulate greater private sector investment.

7) Providing Tax Incentives for Global Health R&D

Governments can encourage R&D by private firms through properly targeted tax incentives. China, for example, is encouraging business investment through reduced corporate tax rates. Firms that qualify as high and new-technology enterprises, which include the life sciences, are taxed at 15, not the usual 25 percent rate.[106] Businesses must certify that at least 10 percent of their workforce are devoted to R&D in order to be eligible for this reduction, and they must spend at least five percent of their revenue on R&D.[107]

South Africa has implemented an R&D tax incentive that "allows for tax deductions of 150 percent for R&D expenses and an accelerated depreciation for spending on related machinery and equipment."[108] That helps private firms focus resources on developing new products, which in the long run should pay off in better public health. However, some businesses say the process is not very transparent and there are lengthy administrative delays in getting approvals.

Companies that have capital spending devoted to improving products, processes, or software qualify for a tax credit. Having targeted tax incentives can be an effective way to stimulate greater private sector investment. It encourages companies to spend money because they can write-off the expenditure and recoup some of their R&D costs.

8) Implementing WHO Vaccine Platform

In its Research and Development Blueprint, the World Health Organization proposes an action plan to prevent epidemics. It seeks to "ensure that targeted R&D can strengthen the emergency responses by bringing medical technologies to patients during epidemics."[109] The Blueprint says it is important to improve coordination, accelerate R&D, and develop new norms and standards to frame collaborations and exchanges and to provide evidence that can inform regulatory review and policy development.

In order to improve R&D development, the agency proposes the creation of a "vaccine platform." This tool would take advantage of the experience with the Ebola disease in West Africa. In that epidemic, there was a need for "effective interventions in a timely manner for control of severe emerging infectious diseases." In these situations, "early decisions need to be made during an outbreak, and in advance of

outbreaks investments should be made into systems and technologies that enable rapid response vaccine development and production." A vaccine platform allows researchers and investors to chart the onset of possible epidemics, the size of the affected populations, the investment required for vaccine development, the novel antigens needed to be produced at large scale, and rapid clinical trials that demonstrate drug effectiveness. That information then facilitates the development, production, and distribution of effective vaccines on an emergency basis.[110]

The Coalition for Epidemic Preparedness Innovation has attracted significant public sector support. It is attempting to answer the WHO Vaccine Platform recommendation from the Blueprint process. However, it has not attracted much private sector support, and that has limited its overall impact.

This type of platform should be implemented in order to address future outbreaks. Rather than wait until an epidemic unfolds, it would be useful to plan in advance for possible scenarios and anticipate needs and market possibilities. That would help investors and pharmaceutical companies scale up their activities when an epidemic actually took place. Among the factors that need to be incorporated in the platform include information on the target population, schedule, onset of immunity, safety, efficacy, stability, adaptability, scaling up of production facilities, distribution of vaccines, and clinical administration.[111]

9) Utilizing Artificial Intelligence Advances in Drug Development

With the costs of drug development running into the millions of dollars, companies should consider new advances in artificial intelligence that have the potential to speed up new drug production. Berg Health, for example, represents a biopharmaceutical business that "mines data to find out why some people survive diseases and thus improve current treatment or create new therapies. They combine AI with the patients' own biological data to map out the differences between healthy and disease-friendly environments and help in the discovery and development of drugs, diagnostics and healthcare applications."[112] This type of advance creates opportunities for businesses to lower costs and increase their profitability.

Countries like China and South Africa are encouraging global health R&D by providing targeted tax incentives for business, a model that could be expanded to other nations to stimulate private sector investment.

10) Results-Based Financing

Some funders have moved toward a model termed "results-based financing," a form of financing in which grants or loans are made contingent upon the achievement of outputs or outcomes. A relatively new form of results-based financing is the impact bond. As described by Emily Gustafsson-Wright of the Brookings Institution:

> In this model, an investor provides upfront risk capital to an non-governmental organization (although public providers can also receive funding through this mechanism) and an outcome funder agrees to pay back the investor their principal plus interest if a set of agreed upon outcomes are achieved. In the case of a social impact bond, the outcome funder is a government entity (national or subnational level) and in the case of a development impact bond, the outcome funder is a third party such as a multi- or bilateral institution or a foundation.[113]

For example, a Ministry of Health may agree to pay for the improvement of particular maternal health indicators, while an NGO provider is given the upfront funds and flexibility to figure out the best way to achieve those outcomes.

Working with Chinese and Indian pharmaceutical companies would yield significant improvements in public health and private sector investment around the globe.

The nascent nature of this model (it has only been implementation since 2010) means that there is still much to be learned about designing and implementing impact bonds. To date, many of the transactions have been quite time and resource intensive. Considerable negotiations are required early in investment discussions regarding organization goals and performance metrics. In each transaction there can be multiple investors and stakeholders, so gaining agreement can be challenging. But having clear performance goals and accountability standards is attractive to certain investors because it reduces their risks and ties their investment directly to performance. There is hope that as experience accumulates and some processes are standardized, that transaction costs will be reduced.

According to Gustafsson-Wright, there are "81 impact bonds globally across seven sectors including social welfare, employment, education, criminal justice, health, environment, and agriculture." Of these, only three are in developing countries. Nevertheless, there are approximately 30 in design phase in low and middle-income countries the majority of which are in the health sector.[114] Based on trends so far, Gustafsson-Wright believes:

> [Impact bonds are] well-suited to 'middle-phase' financing, and intensive learning. And while they may not be the silver bullet to addressing the intractable challenges faced in developing countries in the health or other sectors, impact bonds may provide an approach that breeds systemic change with improved collaboration across stakeholders, an increased focus on outcome achievement and enhanced sustainability.[115]

11) Opportunities in China and India

There are considerable opportunities to boost private sector pharmaceutical spending in China and India. As noted earlier in this paper, each country is experiencing income growth and improvements in domestic R&D expenditures related to public health. Both are in a stronger position than a decade ago to develop drugs and vaccines, often at a fraction of the cost in the West.

Leaders in both places are eager to improve medical treatment in their countries because of the clear need to do so and the fact that each nation faces an aging society. China is expected to have around 24 percent of its population be 65 years or older by 2050. Senior citizens will number about 350 million people, up from 140 million today.[116] That is more than the entire population of the United States.

Working with Chinese and Indian pharmaceutical companies would yield significant improvements in public health and private sector investment. Businesses in each place there are investing more and more in R&D, and with their drug development costs being much smaller than in the United States, the potential payoffs would be substantial. Developing partnerships, engaging in blended finance agreements, providing tax incentives, and encouraging venture capital investments in the East would be productive ways to improve global health R&D.

Of course, there remain challenges in terms of doing business there. This includes barriers in setting up new

businesses, a lack of transparency about government regulations, large out-of-pocket expenses that people incur with drugs, and the need to have local partners. But with the size of the markets in these countries and improved research capabilities, it is important to recognize the resulting investment opportunities.

Conclusion

There has been significant progress in fighting illness and death around the world. The world is close to eradicating polio and making improvements with other diseases. Investments by public, private, and non-profit sectors have contributed to these important gains. Advances in vaccines, drug therapies, and medical therapeutics have improved life expectancies and reduced disease incidence.

However, both public and private health financing are at a difficult point. There has been a slowing in the rate of growth of investment in global health R&D by the public sector and some multilateral organizations, and this creates serious risks in terms of health outcomes. At the same time, since the Great Recession, there has been a slowdown in private sector funding. Many pharmaceutical firms have slowed their health spending over the past decade, and other sources have not increased their investment to offset the slowdown.

In order not to lose the health gains of recent decades, private companies, pharmaceutical firms, and charitable foundations should increase their investments in global health R&D. With advances in science and technology, growing opportunities in upper middle income nations, and spillover benefits from non-health investments, there is a chance to make meaningful inroads in fighting disease and bringing greater wellness and prosperity to developing nations.

Appendix

List of Expert Consultations

Amie Batson	PATH
Amy Bell	Tideline
Thomas Bollyky	Council on Foreign Relations
Dr. Michael Borowitz	The Global Fund
Nick Chapman	Policy Cures
Chris Clubb	Convergence Finance
Joseph Dieleman	Institute for Health Metrics and Evaluation, U. of Washington
Andrew Farnum	Gates Foundation
Greg Ferrante	Gates Foundation
Amanda Glassman	Center for Global Development
Karen Kajmo	Health Care Private Equity Association
Curt LaBelle and Glenn Rockman	Global Health Investment Fund
Chris McCahan	International Finance Corporation
Jaime Bay Nishi and Courtney Carson	Global Health Technologies Coalition
Andrin Oswald	Gates Foundation
Julie Papanek	Canaan Partners
Dan Peters	Gates Foundation
Scott Requadt	Clarus
Dean Segell	Convergence Finance
Karlee Silver	Grand Challenges Canada
Sharon Van Pelt and Global Health Team	Chemonics
Claire Wingfield	PATH
Gavin Yamey	Duke University

Endnotes

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