This report was written by Elizabeth Ponder and Melinda Moree.

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This report is based on the BIO Ventures for Global Health *Global Health Primer* and associated database. The *Global Health Primer* is available online at www.globalhealthprimer.org.
EXECUTIVE SUMMARY

Understanding the research and development (R&D) pipeline for neglected diseases as well as the spectrum of organizations participating in developing these new drugs and vaccines is essential to evaluate the efficiency and effectiveness of current R&D models and to inform the design of new programs and initiatives to fill gaps in the neglected disease R&D pipeline. However, this type of analysis has been hindered in part because neglected disease pipelines have not been systematically tracked. Millions of lives could be saved through faster and more efficient R&D. It is critical to target our resources and R&D efforts to provide the greatest benefit to the world’s poor.

In 2011, BIO Ventures for Global Health (BVGH) released the new and expanded Global Health Primer, a report and online database of compiled drug and vaccine development pipelines for neglected diseases. Using this unique dataset, we explored for the first time the extent to which different types of organizations are participating in drug and vaccine development for a broad range of neglected diseases. BVGH’s new analysis of product developers participating in drug and vaccine development revealed:

• **Academic/research institution participation is broad and deep but often under recognized.** Academic/research institutions, better known for contributing to our understanding of basic biology of neglected diseases, represent the highest number of unique developers, the greatest breadth of disease focus, the highest number of products with participation, and are involved in every phase of development—for both drugs and vaccines—and have partnered with every developer type profiled.

• **The product development partnership (PDP) model for neglected disease R&D supports 40% of the overall neglected disease pipeline.** Investment in neglected disease R&D has focused to a large extent on the PDP model. However, our analysis found that more than half of drug and vaccine development for neglected diseases is occurring without a PDP partner.

• **Industry participation in product development is similar for products with and without PDP development partners.** The PDP model emphasizes promoting industry partnership to accelerate product development. However, products with and without PDP participation have similar levels of partnership with both biotechnology and large pharmaceutical companies.

• **Biotechnology company participation is higher than anticipated with respect to the number of neglected disease products with at least one biotechnology company developer.** Large pharmaceutical companies invest larger amounts of money in neglected disease R&D than small companies; therefore, the high level of biotechnology company participation was surprising.

• **Biotechnology companies participating in neglected disease R&D represent engagement of less than 3% of the total number of biotechnology companies worldwide.** Despite the large proportion of neglected disease pipeline products with biotechnology company participation, the 104 active companies identified represent a small proportion of the more than 3,800 biotechnology companies worldwide. These data suggest biotech companies are an underutilized resource for neglected disease R&D.

• **Large pharmaceutical companies participating in neglected disease R&D represent engagement of approximately 65% of the total number of large, innovator pharmaceutical companies.** Although pharmaceutical companies are only participating in 17% of neglected
disease products in development, 13 of the 20 large, innovator pharmaceutical companies are engaged.

- **The majority of pharmaceutical company participation is attributable to a minority of companies.** Although the 13 large pharmaceutical companies participating in neglected disease R&D participate in an average of 5.4 products per company, 72% of products in development with a pharmaceutical company partner are being developed by just four companies.

- **Neglected disease product developers primarily represent developed countries.** Although the potential for engagement of emerging market product developers exists, our analysis suggests this potential has not yet been realized.

Based on these findings, BVGH recommends that efforts to fill gaps in neglected disease pipelines be tailored to reflect the needs, obstacles, and opportunities of each of the unique types of public and private organizations that comprise the global health product developers. Our analysis suggests that:

- New industry engagement should focus on engaging the full breadth of innovators in the biotechnology sector and increasing the depth of participation of large pharmaceutical companies.

- Translational research initiatives targeting academic/research institutions should emphasize neglected disease product innovation.

- Engagement of innovators from emerging market countries still affected by neglected diseases should be increased.

This report serves as an in depth analysis of the organizations developing products for neglected diseases and an overview of the neglected disease R&D pipeline (presented in more depth in the online BVGH *Global Health Primer*). The database supporting this analysis will allow us to monitor trends and changes in both developer participation and product pipelines moving forward. In concert with data on U.S. Food & Drug Administration (FDA) approvals and neglected disease R&D funding, we hope our data will inform the evaluation of the efficiency and effectiveness of neglected disease R&D models. We believe the findings of this report are complementary to other reports, and we hope the reported findings stimulate discussion and action in the neglected disease R&D space.
Neglected diseases affect more than 1 billion people worldwide.\(^1\) As the majority of those impacted are poor and living in developing countries, commercial markets that traditionally drive pharmaceutical company investment in new product research and development (R&D) are lacking. Investment in R&D for new products to prevent or treat neglected diseases increased substantially over the last two decades, primarily through public and philanthropic investment. However, a lack of systematic tracking of the organizations participating in product development and the products they support has made it difficult to specifically target groups of product developers to fill gaps in the neglected disease R&D pipeline, evaluate the efficiency and effectiveness of past investments, or inform the design of new programs and initiatives.

Over the last two decades, the R&D landscape for new drugs and vaccines that treat or prevent neglected diseases has evolved. Overall development assistance in the health sector increased substantially during this timeframe, from $5.5 billion in 1990 to $21.8 billion in 2007.\(^2\) The creation of entities such as the Global Alliance for Vaccines and Immunization (GAVI)—founded in 2000—and the Global Fund for AIDS, Tuberculosis and Malaria—founded in 2002—brought billions of dollars of financing to the improvement of health delivery systems and purchasing power to poor countries for lifesaving drugs, vaccines, and diagnostics. In parallel, investment in R&D for neglected diseases increased, largely focused on a new R&D funding vehicle now referred to as product development partnerships (PDPs).\(^3\) The PDPs were created to bring together industry expertise and partners with complementary neglected disease expertise using philanthropic dollars in order to advance product development. Total annual R&D funding for neglected diseases increased from $2.6 billion in 2007 to $3.1 billion in 2010.\(^4\) PDPs are the largest recipients of neglected disease R&D funding. After the United States National Institutes of Health (NIH), PDPs are the largest source of funding granted to others for neglected disease R&D.\(^5\)

 Despite investment in neglected disease R&D, it has been difficult to assess the impact of this investment on neglected disease product approvals and the size of neglected disease pipelines. Multiple factors contribute to the challenge, including variations in definitions of neglected diseases, differences in how products in development are counted, and the lack of

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systematic tracking of the neglected disease R&D pipelines over the last two decades. Between 1975 and 1999, estimates of new product approvals for neglected diseases ranged from 16 to 46.6 Counting methods varied between these studies and have been the subject of ongoing debate.7 Between 2000 and 2009, 26 additional products were approved, but debate over the historical baseline number of U.S. Food & Drug Administration (FDA) approvals has made it difficult to judge whether or not this number represents an increase.8 Unfortunately, comprehensive data on the size of the pipelines that fed these approvals are not available. In order to facilitate neglected disease pipeline tracking over time, BIO Ventures for Global Health (BVGH) built and launched a new online Global Health Primer database in 2011.9 Although BVGH produced snapshot reports on subsets of the neglected disease pipeline in 2007 and 2009,10 the new database facilitates tracking of changes in the neglected disease product development pipeline over time moving forward.

In this study, we used the Global Health Primer dataset to identify 348 unique organizations participating alone or in partnerships with each other in the development of 374 drugs and vaccines for 23 neglected diseases. Each developer was categorized by organization type to explore trends in participation across subsets of developers. We demonstrate here that neglected disease product development is being carried out by a broad range of organization types and participation varies greatly depending on the product type, disease focus, and type of organization evaluated. Our findings suggest that, while the PDP model for R&D and engaging large pharmaceutical companies in product development has been a key focus areas for global health, other less well recognized developer types—including academic/research institutions and biotechnology companies—are making significant contributions to the landscape. We hope these data will support the evolution and optimization of neglected disease R&D models in the future to better engage the full spectrum of neglected disease product developers. While much progress has been made, much more work is still required to stop the suffering and death of the more than 1 billion people affected by neglected diseases.

RESULTS

OVERVIEW OF THE NEGLLECTED DISEASE RESEARCH & DEVELOPMENT (R&D) PIPELINE

In order to investigate which organizations are participating in product development for neglected diseases, it was necessary to first identify all of the products in development for neglected diseases. Neglected diseases are categorized as a single group due to neglect rather than their biological or medical basis. Therefore, the term “neglected” has been difficult to define and challenging to gain consensus around, even within the global health community. For the purposes of this study, 23 diseases were included, falling into three broad categories as described in the methods section. The full list of diseases and whether drugs and/or vaccines were identified for each disease are listed in Table 1.

More information on how diseases and products were identified and categorized can be found in the methods section along with a table detailing which product types were included for evaluation for each disease (Table 6).

Table 1. Diseases and Products Identified

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DRUGS</th>
<th>VACCINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIG THREE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>9 (Microbicides)</td>
<td>48</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>49</td>
<td>45</td>
</tr>
<tr>
<td>Malaria</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>OTHER NEGLECTED TROPICAL DISEASES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buruli ulcer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Dengue</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>HAT</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Leprosy</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>STH: Hookworm</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>STH: Ascariasis &amp; Trichuriasis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Trachoma</td>
<td>N/A</td>
<td>4</td>
</tr>
<tr>
<td>OTHER IMPORTANT DISEASES OF POVERTY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>4</td>
<td>N/A</td>
</tr>
<tr>
<td>Cholera</td>
<td>N/A</td>
<td>5</td>
</tr>
<tr>
<td>ETEC</td>
<td>N/A</td>
<td>11</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>N/A</td>
<td>4</td>
</tr>
<tr>
<td>Shigellosis</td>
<td>N/A</td>
<td>7</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>N/A</td>
<td>6</td>
</tr>
<tr>
<td>Pneumococcal disease</td>
<td>N/A</td>
<td>13</td>
</tr>
</tbody>
</table>

The neglected diseases included in this study are summarized here. Diseases are divided into three general categories. The numbers of products identified are listed. Those product types not researched for inclusion are designated by not applicable (N/A); STH=Soil Transmitted Helminths
Neglected Disease Pipeline by Disease

Using the criteria described above and outlined in more detail in the methods section, 374 drugs and vaccines currently in development were identified for 23 neglected diseases that disproportionately affect the developing world. Figure 1 summarizes the distribution of these products across the 23 diseases.

As expected, drugs (including microbicides) and vaccines for malaria, tuberculosis, and HIV (the “big three”) represent the largest proportion of the pipeline, totaling 218 out of 374 total products (58%; Figure 1). Fewer products are in development for other neglected diseases, such as those characterized as “neglected tropical diseases” by the World Health Organization, and diarrhea and pneumonia, which are often excluded from neglected disease analyses but have a significant disproportionate effect on the world’s poor.

Neglected Disease Pipeline by Product Type and Phase of Development

Of the 374 products identified, 173 products were drugs (46% of all products) and 201 products were vaccines (54% of all products) (Figure 2). The distribution of drugs and vaccines across the phases of development differ by product type. The drug development pipeline is shaped much as would be expected and desired, given the likelihood of attrition across the development phases, with the majority of products in the early stages and tapering off at the later stages of clinical development. In contrast, there are relatively even numbers of vaccines in pre-clinical through phase II clinical development, dropping off only at phase III. Differences in the vaccine and drug pipelines will be discussed in more detail in subsequent sections.

Figure 1 Overall Research and Development (R&D) Pipeline by Disease

The disease name and total number of products covered in this study are summarized in the Mekko plot here. The area of each rectangle in the Mekko plot is proportional to the number of products for that disease. Restrictions on drugs or vaccines evaluated for each disease are summarized in Table 6. The total number of products in each of the three disease categories is listed at the top of the column.

Figure 2 Distribution of Drugs and Vaccines by Phase of Development

The total number of drugs (including HIV microbicides) and vaccines were summed for each phase of development.
OVERVIEW OF NEGLECTED DISEASE PRODUCT DEVELOPERS

The 374 drugs and vaccines included in this study are in development by 348 organizations spanning both the private and public sectors as summarized in Figure 3. Definitions of organization types used to categorize developers are provided in the methods section and will be discussed in more detail in subsequent sections. Academic/research institutions and biotechnology companies represent the largest number of unique organizations (Figure 3).

Partnering Among Neglected Disease Product Developers

While 348 unique organizations were identified, it is generally understood that product development for neglected diseases rarely occurs within a single organization. Therefore, we determined how many developers were associated with each neglected disease product identified in this study by calculating the average number of unique developers associated with each product. Of the 374 products in development, 39% were found to be in development by a single organization with no partners (data not shown). The average number of developers was 2.2 unique developers per product. The average number of partners varied little for drugs as compared to vaccines (2.1–2.3) or phase of development (1.9–2.7) (data not shown). These averages only reflect the number of partners associated with products in this study at the time of analysis and do not account for developers who may have participated in development at earlier stages but are no longer involved.

![Figure 3](image1.png)

**Figure 3** Unique Developers by Type Participating in Neglected Disease Product Development

**Figure 4** Unique Developers by Country or Region of Headquarters Participating in Neglected Disease Product Development

*Organizations identified as participating in the development of the 374 products included in this study were categorized by organization type. Here, the proportion of the total 348 unique organizations identified is presented by organization type.*

*Organizations identified as participating in the development of the 374 products included in this study were categorized by country or region of headquarters. Here, the proportion of the total 348 unique developers identified is presented by country or region.*
Neglected Disease Product Developers by Country

Neglected diseases disproportionately affect the developing world, but drug and vaccine research and development outside of neglected diseases traditionally occur in the developed world. Therefore, the country or region of each of the 348 unique developer’s headquarters was evaluated as a surrogate measurement of the participation of developed versus developing country organizations in product development. The number of unique organizations participating in product development for neglected diseases is summarized by country of headquarters in Figure 4. European organizations participating in neglected disease drug development are further broken down by country in Figure 5.

The majority of developers participating in neglected disease product development were based in the United States, Europe, and other developed countries (246 out of 348 unique developers, or 71% of all developers identified; Figure 4). While there were some developers from Brazil, India, China, Russia, and South Africa—known to be innovative, emerging market countries, these made up a small minority of organizations identified in this study.

European country governments and the European Commission account for nine of the top 12 public sector funders of neglected disease R&D. Therefore, we looked at the distribution of developers across European countries in more detail (Figure 5). The United Kingdom had the largest number of developers participating in neglected disease product development followed by the Netherlands, Switzerland, Germany, and France.

Figure 5 Unique Developers in Europe by Country Participating in Neglected Disease Product Development

Organizations identified as participating in the development of products for neglected diseases headquartered in Europe were counted based on country of headquarters. Here, the proportion of the total 115 unique developers identified as being headquartered in Europe are presented by country.

11 Moran M et al. (2011) Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, Policy Cures, Australia
DEVELOPER PARTICIPATION BY ORGANIZATION TYPE

For the purposes of this report, we chose to focus on four developer categories: academic/research institutions, product development partnerships (PDPs), biotechnology companies, and large pharmaceutical companies. Table 2 provides an overview of the level of participation of each organization type as measured by the percentage of products in development with at least one associated developer of that type.

When we calculated how many products in development had at least one academic/research institution, PDP, or biotechnology company participating in development, similar proportions of products in development for neglected diseases were identified for each organization type, whether analyzed in the aggregate (40–43%) or segregated by drugs and vaccines (39–40% for drugs and 39–46% for vaccines) (Table 2). Using this same approach, large pharmaceutical companies were participating in 17% of products in development with lower participation in vaccines as compared to drugs (10% versus 32%, respectively). The participation of each organization type in neglected disease product development is examined in more detail in the subsequent sections.

The current analysis is not designed to quantify or provide qualitative assessment of the nature of developer participation in neglected disease product development, such as the extent to which each organization contributes money, employee time, physical reagents, know-how, etc. This is particularly true in the case of products with multiple development partners. Here, and for the remainder of this analysis, all participation in product development in the context of a partnership is assumed equal. While this is an oversimplification, it provides a mechanism to understand the level of participation of different organization types in terms of number of products as a proportion of all products in development.

Table 2. Level of Participation of Developers by Organization

<table>
<thead>
<tr>
<th>DEVELOPER TYPE</th>
<th>TOTAL PRODUCTS (% OF ALL PRODUCTS)</th>
<th>DRUGS (% OF ALL DRUGS)</th>
<th>VACCINES (% OF ALL VACCINES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic/Research Institution</td>
<td>162 (43%)</td>
<td>69 (40%)</td>
<td>93 (46%)</td>
</tr>
<tr>
<td>PDP</td>
<td>149 (40%)</td>
<td>70 (41%)</td>
<td>79 (39%)</td>
</tr>
<tr>
<td>Biotech</td>
<td>153 (41%)</td>
<td>68 (39%)</td>
<td>85 (42%)</td>
</tr>
<tr>
<td>Big Pharma</td>
<td>65 (17%)</td>
<td>44 (25%)</td>
<td>21 (10%)</td>
</tr>
</tbody>
</table>

*Note: the percentages will not total to 100% as several developers may be involved with the R&D of a unique drug or vaccine.
Academic/Research Institutions

Academic/Research institutions made up the largest number of organizations participating in neglected disease product development (129 out of 348 total unique organizations; Figure 3). They participated in the development of the greatest number of products (162 of 374 products, 43%; Table 2) and the greatest range of diseases with products in development (20 of the 23 neglected diseases included in this study; Figure 6) of any individual developer type.

Academic/research institutions are participating in the development of a greater number of vaccines than drugs (Figure 7 and Figure 8), but their participation across drugs, vaccines, and phases of development was largely reflective of the overall pipeline (Figure 2) and relatively consistent across drugs, vaccines, and phases of development, ranging from participation in 21-54% of products in a given phase (Figure 7 and Figure 8). In general, academic/research institutions are participating in more discovery and preclinical phase products with lesser participation as product development moves into the clinical phases of testing (Figure 7 and Figure 8).

As most products in development for neglected diseases are being developed by partnerships of multiple organizations, we next wanted to assess the extent to which academic/research institutions partner with other organizations. While we could not assess the nature of partnerships using the current dataset, we could determine the average number of partners participating in the development of drugs or vaccines with at least one academic/research institution developer. The number and proportion of all products with at least one academic/research institution developer with zero, one, two, or three/greater than three partners is summarized in Figure 9 by product type and Figure 10 by phase of development.

On average, products in development for neglected diseases with at least one academic/research institution developer have more partners per product than the neglected disease pipeline
as a whole—2.9 total developers per product as compared to 2.2 for the composite pipeline (Figure 9; Figure 10). Also, the number of products in development with an academic/research institution developer with no additional partners was 19% (30 total products; Figure 9) which is less than the 39% of the neglected disease pipeline as a whole (146 total products). While there is essentially no difference in the average number or distribution of developer numbers by drug or vaccine (Figure 9), the number of partners per product is higher for products in late stage clinical development than early stage products (Figure 10).

The number of partners associated with products in development with at least one academic/research institution developer raised the question as to what types of organizations academic/research institutions are collaborating or partnering with. For each of the 132 products in development that have at least one academic/research institutions and at least one additional partner, we asked what organization types any additional partners represented. For example, if a product in development by an academic/research institution was also partnered with a PDP and a pharmaceutical company, that product is counted as a collaboration between an academic research institution and a PDP.

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**Figure 7** Academic/Research Institution Participation in Drug Development by Phase

**Figure 8** Academic/Research Institution Participation in Vaccine Development by Phase

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The total number of drugs with at least one academic/research institution developer was summed for each phase of development in the bar graph (left Y-axis). The percentage of drugs in the given phase of development with at least one academic developer relative to the total number of drugs at the indicated phase was calculated and presented as a line (right Y-axis).

The total number of vaccines with at least one academic/research institution developer was summed for each phase of development in the bar graph (left Y-axis). The percentage of vaccines in the given phase of development with at least one academic developer relative to the total number of vaccines at the indicated phase was calculated and presented as a line (right Y-axis).
Figure 9  Academic/Research Institution Collaborations by Number of Partners and Product Type

For all products with at least one academic/research institution developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products with the given number of partners for all products, drugs, or vaccines and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one academic/research institution partner. The average number of partners per product across all products, drugs, or vaccines with at least one academic/research institution partner is given below the graph.

Figure 10  Academic/Research Institution Collaboration by Phase of Product Development

For all products with at least one academic/research institution developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products with the given number of partners for all products for each phase of development and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one academic/research institution partner at the given phase. The average number of partners per product at each phase with at least one academic/research institution partner is given below the graph.
(one of the 47 products counted in the bar labeled “PDP”) and a collaboration between an academic/research institution and a pharmaceutical company (one of 18 products counted in the bar labeled “Big Pharma”) in Figure 11. The results of this analysis are presented in Figure 11.

Academic/research institutions participated in collaborations with all other organization types for neglected disease product development, including other academic/research institutions, PDPs, biotechnology companies, large pharmaceutical companies, and other organization types not included in this analysis. At least half of all projects had at least one PDP partner, irrespective of product type (Figure 11). This was not surprising as partnerships are necessary to drive early stage discoveries in academia toward product development.

**Figure 11 Who is Partnering with Academic/Research Institutions?**

<table>
<thead>
<tr>
<th># of Products (% of All Products)</th>
<th>Other Academic</th>
<th>PDP</th>
<th>Biotech</th>
<th>Big Pharma</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Projects</td>
<td>5 (6%)</td>
<td>30 (38%)</td>
<td>37 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Projects</td>
<td>13 (19%)</td>
<td>17 (24%)</td>
<td>38 (54%)</td>
<td>13 (19%)</td>
<td></td>
</tr>
<tr>
<td>Total Projects</td>
<td>18 (12%)</td>
<td>47 (32%)</td>
<td>79 (53%)</td>
<td>50 (34%)</td>
<td></td>
</tr>
</tbody>
</table>

For each of the 132 products in development that have at least one academic/research institution developer and at least one additional partner, it was determined whether the additional partner(s) included at least one of the following developer types: other academic/research institution, PDP, biotechnology company, large pharmaceutical company, or some other type of organization. The number of products and the proportion of all products, drugs, or vaccines with an academic/research institution developer and at least one of the indicated organization types as a partner are given at the end of each bar.
Product Development Partnerships (PDPs)

Although there are a relatively small number of PDPs (26 unique organizations identified in this study), 40% of products in development have at least one PDP developer (149 products; Table 2). Given the emphasis on the PDP model for new funding for neglected disease research and development (R&D) in the last 10 years, it is interesting to note that more than half of the products identified here are being developed outside of this R&D model.

PDPs have products in development for 16 of the 23 diseases included in this study (Figure 12). Well over half (61%) of the products with PDP participation are in development for HIV (microbicides and vaccines only), malaria, and tuberculosis.

PDPs are participating in the development of a greater number of vaccines than drugs (Figure 13 and Figure 14), and their participation across drugs, vaccines, and phases of development is largely reflective of the overall pipeline (Figure 2) and relatively consistent across drugs, vaccines, and phases of development, ranging from participation in 22-57% of products in a given phase (Figure 13 and Figure 14).

Surprisingly, PDPs are only involved in 10 of the 23 total products in phase III, representing participation in 43% of products at this phase (Figure 13 and Figure 14). If we break participation in phase III products down by products type, PDPs are participating in 57% of drugs in phase III development (Figure 13) but only 22% of vaccines in phase III development (Figure 14). Because of the expense of phase III clinical trials and the emphasis on public-private sharing of financial risk fostered by the PDP model, we would have expected nearly all the phase III trials to involve a PDP.

As the PDP model is designed for foster partnership, particularly between the public and private sectors, we next wanted to assess the extent to which PDPs partnered with other organizations on the products identified in this study. While we could not assess the nature of these partnerships, we could determine the average number of partners participating in the

---


Figure 12 Product Development Partnership (PDP) Pipeline by Disease

The disease name and total number of products with at least one PDP developer covered in this study are summarized in the Mekko plot here. The area of each rectangle in the Mekko plot is proportional to the number of products for that disease. Restrictions on drugs or vaccines evaluated for each disease are summarized in Table 1. The total number of products in each of the three disease categories is listed at the top of the column.
development of drugs or vaccines with at least one PDP developer. The number and proportion of all products with at least one PDP developer with zero, one, two, or three/greater than three partners is summarized in Figure 15 by product type and Figure 16 by phase of development.

On average, products in development for neglected diseases with at least one PDP developer have more partners per product than the neglected disease pipeline as a whole—3.1 total developers per product as compared to 2.2 for the composite pipeline (Figure 15; Figure 16). Also, PDPs have virtually no products in development with no additional development partners (Figure 15) as compared to 39% of the neglected disease pipeline as a whole. There is little variation in the number of collaborators participating in products with at least one PDP developer by drugs, vaccines, or by phase, although the average number of partners increases slightly in the late clinical stages of development (Figure 16).

PDPs, both by design and in the data presented here, use partnering as part of their core model for neglected disease R&D. Therefore, for those products with at least one PDP developer, we asked which types of organizations PDPs were collaborating with. For each of the 142 products in development that have

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**Figure 13** Product Development Partnership (PDP) Participation in Drug Development by Phase

**DRUGS IN DEVELOPMENT**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Products</th>
<th>Percentage of All Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>13</td>
<td>26%</td>
</tr>
<tr>
<td>Pre-Clinical</td>
<td>6</td>
<td>38%</td>
</tr>
<tr>
<td>Phase I</td>
<td>8</td>
<td>44%</td>
</tr>
<tr>
<td>Phase II</td>
<td>8</td>
<td>47%</td>
</tr>
<tr>
<td>Phase III</td>
<td>35</td>
<td>57%</td>
</tr>
</tbody>
</table>

*The total number of drugs with at least one PDP developer was summed for each phase of development in the bar graph (left Y-axis). The percentage of drugs in the given phase of development with at least one PDP relative to the total number of drugs at the indicated phase was calculated and presented as a line (right Y-axis).*

**Figure 14** Product Development Partnership (PDP) Participation in Vaccine Development by Phase

**VACCINES IN DEVELOPMENT**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Products</th>
<th>Percentage of All Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>15</td>
<td>26%</td>
</tr>
<tr>
<td>Pre-Clinical</td>
<td>18</td>
<td>22%</td>
</tr>
<tr>
<td>Phase I</td>
<td>22</td>
<td>22%</td>
</tr>
<tr>
<td>Phase II</td>
<td>22</td>
<td>22%</td>
</tr>
<tr>
<td>Phase III</td>
<td>2</td>
<td>22%</td>
</tr>
</tbody>
</table>

*The total number of vaccines with at least one PDP developer was summed for each phase of development in the bar graph (left Y-axis). The percentage of vaccines in the given phase of development with at least one PDP relative to the total number of vaccines at the indicated phase was calculated and presented as a line (right Y-axis).*
For all products with at least one PDP developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products with the given number of partners for all products, drugs, or vaccines and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one PDP partner. The average number of developers per product across all products, drugs, or vaccines with at least one PDP partner is given below the graph.

For all products with at least one PDP developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products with the given number of partners for all products for each phase of development and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one PDP partner at the given phase. The average number of developers per product at each phase with at least one PDP partner is given below the graph.
at least one PDP and at least one additional partner, we determined what organization types any additional partners represented. The results are presented in Figure 17.

PDPs partnered with the full range of organization types examined in this study, including other PDPs, academic/research institutions, biotechnology companies, pharmaceutical companies, and others. PDPs collaborated to the greatest extent with academic/research institutions for both drugs and vaccines. Collaboration with biotechnology and pharmaceutical companies differed for drugs as compared to vaccines. Biotechnology companies were collaborating with PDPs on 46% of PDP vaccine projects but only 21% of PDP drug products (Figure 17). In contrast, pharmaceutical companies were collaborating with PDPs on 36% of PDP drug projects and only 6% of PDP vaccine projects (Figure 17).

Figure 17 Who is Partnering with Product Development Partnerships (PDPs)?

For each of the 142 products in development that have at least one PDP developer and at least one additional partner, it was determined whether the additional partner(s) included at least one of the following developer types: other PDP, academic/research institution, biotechnology company, large pharmaceutical company, or some other type of organization. The number of products and the proportion of all products, drugs, or vaccines with a PDP developer and at least one of the indicated organization types as a partner.
Biotechnology Companies

Biotechnology companies make up the second largest number of organizations participating in neglected disease product development (104 out of 348 total unique organizations; Figure 3). These companies participated in the development of 153 of 374 products (41%; Table 2) and 16 of the 23 neglected diseases included in this study (Figure 18). Unlike the academic/research institutions and PDPs already profiled, the neglected tropical disease with the largest number of products in development with at least one biotechnology company partner was dengue, with 16 products (Figure 18).

Biotechnology companies participated in the development of a greater number of vaccines than drugs and their pattern of participation varies greatly by product type (Figure 19 and Figure 20).

Participation in drug development was greatest in the discovery and pre-clinical phases with 29 and 30 products, representing participation in 39 and 60% of all drugs at those phases (Figure 19), respectively. In the pre-clinical stage in particular, biotechnology company participation was higher than any other developer type (Figure 19). The high level of participation in pre-clinical stage projects is interesting, as this is generally considered the “valley of death” in neglected disease product development. Biotechnology company participation is substantially lower for products in the later clinical stages of drug development (Figure 19).

In contrast, biotechnology company participation in vaccine development is high across products in discovery through phase II of development, ranging from participation in 39-51% of all vaccines at these phases of development (Figure 19 and Figure 20). The high level of biotechnology company participation through phase II is surprising as phase II efficacy trials are expensive.

As biotechnology company participation differed substantially across drugs, vaccines, and phases of development, we wanted to understand if the extent of collaborations of biotechnology companies differed across these parameters. While we could not assess the nature of these partnerships, we could determine the
average number of partners participating in the development of drugs or vaccines with at least one biotechnology company developer. The number and proportion of all products with at least one biotechnology company developer with zero, one, two, or three/greater than three partners is summarized in Figure 21 by product type and Figure 22 by phase of development.

On average, products in development for neglected diseases with at least one biotechnology company developer had the same number of developers per product as the neglected disease pipeline as a whole, 2.3 total developers per product as compared to 2.2 for the composite pipeline (Figure 21; Figure 22).

Interestingly, the average number of developers per product differed by drugs and vaccines. Biotechnology companies had fewer partners per products for drugs, with an average of 2.0 developers per product (Figure 21), likely reflecting the large number of discovery and pre-clinical stage projects with biotechnology company partners where these companies are known to excel. In Figure 22, the distribution of products with different numbers of partners supports this theory, where nearly half of all discovery and pre-clinical stage products have no additional partners as compared to products in phase I or II of development where less than one quarter of products have no additional partners.
For all products with at least one biotech developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products with the given number of partners for all products, drugs, or vaccines and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one biotech partner. The average number of developers per product across all products, drugs, or vaccines with at least one biotech partner is given below the graph.
In contrast, vaccines in development with at least one biotechnology company partner averaged 2.6 developers per product (Figure 21). This may reflect the high level of participation of biotechnology companies in vaccines as advanced as phase II of development, again reflected in the decreased proportion of products with zero or only one additional partner in phases I and II of development as compared to the discovery and preclinical stages (Figure 22). Late stage clinical trials are extremely expensive and not generally considered the strength of small companies, therefore it is logical that increased partnering would be necessary for biotechnology companies to participate in the development of products at these phases of development.

For those products with at least one biotechnology company developer, we determined which types of organizations with which biotechnology companies were partnering or collaborating. For each of the 90 products in development that had at least one biotechnology company developer and at least one additional partner, we determined the organization types any additional partners represented. The results are presented in Figure 23.

Biotechnology companies are partnering to the greatest extent with academic/research institutions and PDPs. Of projects with at least one biotechnology company developer, 33 and 35% of projects also have at least one academic/research institution or PDP partner, respectively (Figure 23). Interestingly, biotechnology companies are collaborating with other biotechnology companies, particularly on their vaccine projects, but they partner very infrequently with large pharmaceutical companies.
Large Pharmaceutical Companies

There are a relatively small number of multi-national, pharmaceutical companies, referred to as large pharmaceutical companies or “big pharma.” In this study, 13 of these companies were identified as participating in neglected disease product development, accounting for 13 of the 348 total unique organizations included (Figure 3). They participate in the development of 65 of 374 products (17%; Table 2) and 14 of the 23 neglected diseases included in this study (Figure 24).

As with the other developer types profiled in this study, the largest proportion of products with at least one pharmaceutical company developer were drugs and vaccines for the “big three,” HIV, tuberculosis, and malaria—representing 38 of 65 products (Figure 24). For academic/research institutions, PDPs, and biotechnology companies, malaria products accounted for the largest component of products for these three diseases (Figure 6; Figure 12; Figure 18). In contrast, large pharmaceutical companies products in development for tuberculosis made up the largest proportion of all big three products, 21 out of 38 total products (Figure 24). As observed for biotechnology companies, dengue products accounted for the largest proportion of “other neglected disease” products with pharmaceutical company participation (Figure 24).

In contrast to the other developer types profiled in this study, large pharmaceutical companies are participating in the development of more drugs than vaccines. Large pharmaceutical companies are participating in the development of 55 drugs and 21 vaccines (Figure 25 and Figure 26), accounting for participation in 32 and 10% of all drugs and vaccines in development for neglected diseases, respectively (Table 2).

The largest number of large pharmaceutical industry projects, in terms of absolute project numbers, were discovery stage drug projects, with 23 projects accounting for 31% participation in drug projects at this phase overall (Figure 25). Participation at this phase is likely the result of companies sharing compound libraries for early stage screening projects for a variety of neglected diseases. Despite the high number of discovery stage drug products with larger pharmaceutical company participation, pharmaceutical participation was lowest in the pre-clinical stage (4 projects, 8% participation in all drug projects
at this phase) raising the question as to who is participating in the follow-up to early stage drug screening projects. Large pharmaceutical company participation was 50, 33, and 21% in the development of drugs in phases I, II, and III, respectively (Figure 25). As pharmaceutical companies have extensive expertise in clinical development, it is logical that they participate in a sizeable portion of projects in these phases of development.

In contrast, participation of large pharmaceutical companies in vaccine development was relatively low across the early phases of development (5-7% in discovery through phase I) (Figure 26). Pharmaceutical company participation was substantially higher for phase II and III vaccines, with participation in 19 and 33% of vaccines in development at those stages, respectively.

We next wanted to understand the extent to which products in development with at least one pharmaceutical industry partner also had additional collaborators. The number and proportion of all products with at least one large pharmaceutical company developer with zero, one, two, or three/greater than three partners is summarized in Figure 27 and Figure 28.

As large pharmaceutical companies have considerable capital relative to other organization types evaluated here, we hypothesized large pharmaceutical companies would partner to a lesser extent than other developer types. Products in development with at least one large pharmaceutical company developer had a similar number of developers per product as the neglected disease pipeline as a whole, with an average of 2.3 developers

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**Figure 25 Large Pharmaceutical Company Participation in Drug Development by Phase**

**Figure 26 Large Pharmaceutical Company Participation in Vaccine Development by Phase**

*The total number of drugs with at least one large pharmaceutical company developer was summed for each phase of development in the bar graph (left Y-axis). The percentage of drugs in the given phase of development with at least one large pharmaceutical company relative to the total number of drugs at the indicated phase was calculated and presented as a line (right Y-axis).*

*The total number of vaccines with at least one large pharmaceutical company developer was summed for each phase of development in the bar graph (left Y-axis). The percentage of vaccines in the given phase of development with at least one large pharmaceutical company relative to the total number of vaccines at the indicated phase was calculated and presented as a line (right Y-axis).*
For all products with at least one large pharmaceutical company developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products with the given number of partners for all products, drugs, or vaccines and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one pharmaceutical company partner. The average number of developers per product across all products, drugs, or vaccines with at least one pharmaceutical company partner is given below the graph.

For all products with at least one large pharmaceutical company developer, the number of additional developers associated with that product was counted. Each bar graph segment is number of products for each phase of development and the proportion of all products (%) with that number of partners. The total at the top of the column is the total number of products with at least one pharmaceutical company partner at the given phase. The average number of developers per product at each phase with at least one pharmaceutical company partner is given below the graph.
per product as compared to 2.2 developers per products for the composite pipeline (Figure 27 and Figure 28). However, pharmaceutical companies had the smallest proportion of products with three or more partners when considering all products or the drug or vaccine products alone (9-10% ; Figure 27) when compared to products with three or more partners with at least one academic/research institution, PDP or biotechnology company (Figure 9; Figure 15; Figure 21). As a percentage of their overall pipeline, 25% of all products with at least one large pharmaceutical company developer had no additional partners (Figure 27) although this number as well as the number of partners per project, varied widely by phase of development (Figure 28).

For those products with at least one large pharmaceutical company developer, we next wanted to determine the types of organizations with which large pharmaceutical companies are

![Figure 29 Who is Partnering with Large Pharmaceutical Companies?](image)

For each of the 49 products in development that have at least one pharmaceutical company developer and at least one additional partner, it was determined whether the additional partner(s) included at least one of the following developer types: other pharmaceutical company, academic/research institution, biotechnology company, PDP, or some other type of organization. The number of products and the proportion of all products, drugs, or vaccines with a pharmaceutical company developer and at least one of the indicated organization types as a partner.
collaborating. For each of the 49 products in development that had at least one large pharmaceutical company developer and at least one additional partner, we determined which organization types any additional partners represented. The results are presented in Figure 29.

Large pharmaceutical companies are partnering to the greatest extent with PDPs and academic/research institutions. Of projects with at least one large pharmaceutical company developer, 46 and 28% of projects had at least one PDP or academic/research institution partner, respectively (Figure 29). For drug development projects, 57% of all projects with at least one large pharmaceutical industry partner had at least one PDP partner.

**Other Developers**

There are 69 developers not profiled in more detail here, primarily consisting of government agencies, other non-profits, and other industry, primarily biopharmaceutical industry players excluded from the definition of biotechnology and large pharmaceutical companies used in this study (e.g. CROs, generics manufacturers, etc).

**COMPARISON OF DRUG & VACCINE PIPELINES**

Our study showed that as of September 2011, the composite neglected disease pipeline contained 374 products for 23 diseases. While a lack of systematic analyses of the pipeline over the last two decades makes it difficult to put this number into historical perspective, most in the global health field acknowledge that there were few products in development for neglected diseases prior to the year 2000 and very few in advanced development. Indicators of neglected disease R&D activity have been reported in terms of FDA approvals for neglected disease products (1975-2009)\(^\text{13}\) and self-reported R&D contributions (2007-2010),\(^\text{14}\) but to date it has not been possible to link FDA approvals or R&D dollars to specific products or historical pipelines.

Examining the drug and vaccine pipelines separately revealed that neglected disease R&D for these product types differed. Of the 374 products identified, 173 products were drugs (46% of all products) and 201 products were vaccines (54% of all products) (Figure 2). The higher number of vaccines identified may reflect the longer list of diseases for which vaccines were evaluated in this study or may reflect the greater emphasis on prevention in poor countries. However, there were differences in the distribution of products across the phases of development for each of these product types.

Drugs in development for neglected diseases are distributed as would be expected for a standard R&D pipeline, with the largest number of products in the early stages and decreasing across the stages of development. Unfortunately, the total number of drugs in clinical development (phases I-III) is more reflective of a pipeline for a single disease rather than the composite pipeline for 15 distinct diseases. The industry-wide success rate for a therapeutic product in the clinical stages of development is about 11%, suggesting that only 1 in 9 products that enter human clinical trials are approved.\(^\text{15}\) Applying this estimate to the 48 drugs in clinical development for neglected diseases as identified in this study, we would expect a total of 5 products to come to market across the 15 diseases. Fortunately, there are 125 drugs in discovery or pre-clinical development which should serve to refill the drug pipeline as products progress or drop out. What we have not evaluated here is the quality of the drugs included in the pipeline. Products in development include a range of levels of scientific novelty, including entirely novel molecules with novel mechanisms of action, analogs of existing drugs, repurposing of drugs approved for other indications, and combinations or pediatric formulations of existing products. Deeper analysis of the drug pipeline with respect to the degree of novelty of new products is warranted, especially given how quickly drug resistance can develop.

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The vaccines in the pipeline for neglected diseases were distributed quite differently across the phases of development, with the majority of products in pre-clinical through phase II development (Figure 2). Unlike drugs for neglected diseases, there are very few existing vaccines that can simply be reformulated or repurposed as low risk projects in the pipeline. While there are follow-on vaccines in development for pneumococcal disease and several of the diarrheal diseases, many of the neglected diseases have never had an effective vaccine approved. In these cases, novel vaccines face a tremendous proof-of-concept hurdle in phase II. The large number of vaccines in pre-clinical through phase II development may represent a bottleneck in the pipeline for novel vaccines for which vaccination in humans has never been proven effective. Alternatively, these differences may represent differences in vaccine development. Vaccines, unlike drugs, aim to enter human trials as early as possible as there are fewer pre-clinical safety studies that are available to predict failure in clinical trials. There are also many efforts to create combination vaccines using “prime-boost” strategies. Multiple vaccines need to progress through efficacy trials to provide options for pursuing combinations in phase III. In any case, projections suggest that as many as six new neglected disease vaccines will be approved between 2011 and 2018.17

Drugs and vaccines differ on many levels, from their biological basis to their cost of development. It was not surprising, therefore, to find variations in neglected disease pipelines when segregated by product type. Beyond differences in product distribution across the phases of development, the extent of developer participation varied for drugs and vaccines. These differences will be discussed in more detail in subsequent sections. Overall, the differences in pipeline distribution and developer participation suggest that different strategies may be needed to promote drug as compared to vaccine development for neglected diseases.

16 BVGH (2011) The Vaccine Landscape for Neglected Diseases: A Perspective from the Global Health Primer, BIO Ventures for Global Health, San Francisco, CA, USA.

Figure 30  Country Neglected Disease R&D Activity Relative to Overall R&D Activity

Plotted here are country contributions to neglected disease R&D (2010 G-FINDER data; Y-Axis)\(^\text{18}\), overall country participation in life sciences R&D as a proportion of GDP (R&D Magazine data; X-Axis)\(^\text{19}\), and number of neglected disease product developers per country represented by the size of the circles. Countries designated as Emerging Economies by IMF\(^\text{20}\) are designated in pink.


NEGLECTED DISEASE VERSUS OVERALL R&D ACTIVITY BY COUNTRY

Neglected diseases disproportionately affect the developing world, but the majority of the organizations found to be participating in neglected disease product development in our study were based in the developed world (Figure 4). This was not unexpected, as the majority of traditional biotechnology and pharmaceutical industry product innovators are based in the developed world. In order to understand the relationship between overall R&D participation of countries relative to their participation in neglected disease R&D, we plotted overall R&D expenditures relative to gross domestic product (GDP), neglected disease R&D spending, and number of neglected disease product developers by country. Only those countries for which all three data types could be obtained were included. These data are summarized in Figure 30.

Combining these datasets demonstrate that neither funding for neglected disease R&D nor R&D spending as a proportion of GDP correlates with the number of developers participating in neglected disease R&D (Figure 30).

Interestingly, Argentina, Brazil, Mexico, India, and South Africa have developers for neglected diseases and public R&D contributions despite relatively low R&D spending as a proportion of GDP. The United States, the United Kingdom, and France stand out among the developed countries as contributing significant money to neglected disease R&D. Perhaps most intriguing are those countries that spend a high percentage of their GDP on R&D, but who contribute relatively little money to neglected disease R&D and have relatively few neglected disease product developers (lower right-hand corner; Figure 30). More research is warranted to understand the relationship between overall R&D spending and contributions of individual countries to neglected disease R&D.

IMPACT OF TRANSLATIONAL RESEARCH

Academic/research institutions represented the highest number of unique developers, the greatest breadth of disease focus, the highest number of products with participation, and are involved in every phase of development—for both drugs and vaccines—and have partnered with every developer type profiled (Figure 4; Table 2; Figure 6 through Figure 11). The high level of participation in neglected disease product development by academic/research institutions in this study may reflect increased participation of academic/research organizations in product development more broadly.

A survey of all new drugs and biologics approved between 1998 and 2007 determined that 24.1% of products originated from universities. University discoveries were attributed to 31 and 48% of approvals for scientifically novel and orphan products, respectively, highlighting the even higher level of participation when only innovative products are considered. A recent survey of 78 US academic drug discovery centers reported 71% of centers have a therapeutic focus area on infectious diseases and 30% have a therapeutic focus area on diseases of least developed countries. These data suggest that neglected disease product development is likely to benefit directly from translational and product development work in academia.


PRODUCT DEVELOPMENT OUTSIDE OF THE PRODUCT DEVELOPMENT PARTNERSHIP (PDP) MODEL

Much of the money invested in neglected disease R&D over the last two decades has been either invested in or distributed through the PDP model which was originally conceptualized by the Rockefeller Foundation through the creation of the International AIDS Vaccine Initiative. Between 1996 and 2007, 16 new PDPs were established with significant support from the Bill & Melinda Gates Foundation, and PDPs continue to be the largest recipients of external neglected disease R&D funding. After the United States National Institutes of Health (NIH), PDPs are the largest source of funding granted to others for neglected diseases R&D.

In the current analysis, we identified 26 PDPs participating in the development of 40% of drugs and vaccines for neglected diseases (Table 2). Products with at least one PDP developer had a higher than average number of collaborators and included partnerships with academic/research institutions, biotechnology companies, large pharmaceutical companies, and other PDPs, as well as other organization types not profiled in detail here (Figure 15; Figure 17). These data are in line with the original mission of PDPs to promote industry partnerships with neglected disease experts. In fact, 46% of all products with a large pharmaceutical company developer also involved a PDP partner (Figure 29).

Although our current study cannot assess the nature of collaborations between PDPs and their partners, PDPs generally act through financing product development. The high degree of partnering with PDPs for all of the developer types analyzed here suggests that changes in PDP funding have the potential to impact a wide range of products and developer types. This is highly concerning as R&D funding received by PDPs decreased from a high of US$580 million in 2008 to US$483 million in 2010. Funding decreased by US$50.0 million (-8.6%) in 2009 and an additional US$46.8 million (-8.9%) in 2010, retreating nearly to the 2007 level of US$469 million. Funding cuts to PDPs raise the question of how the other 60% of the neglected disease pipeline not partnered with PDPs is financed and functioning. While we cannot answer this question fully with the current dataset, we can look at the segment of the overall neglected disease pipeline with no PDP involvement along the same parameters used to describe developer types above. There were 225 total products (103 drugs and 122 vaccines) in development without a PDP partner, including drugs and vaccines for 20 of the 23 disease analyzed here (Figure 31 and Figure 32).

The pipeline of neglected disease products with no PDP involvement closely mirrored the overall neglected disease pipeline (Figure 2), suggesting that PDP involvement is not supporting any one targeted segment of the pipeline but rather is additive across phases and product types with the non-PDP involved pipeline.

We then analyzed who was participating in the development of products with no PDP developers. The results are summarized in Figure 33.

Of the products with no PDP developer, 45% had at least one biotechnology company partner, 37% had at least one academic/research institution partner, and 16% had at least one large pharmaceutical company partner (“Total Projects with No PDP”, Figure 33). These data largely reflected overall participation of these organizations in product development (“Total Projects”, Figure 33). We compared the level of participation of academic/research institutions, biotechnology companies, and pharmaceutical companies across the total pipeline, those products with at least one PDP developer, and those products with no PDP developers. We found that academic/research


institution and large pharmaceutical industry participation increased with PDP involvement whereas participation from biotechnology companies decreased relative to products with no PDP involvement (Figure 33).

There is a general conception in the global health community that products being developed in partnership with PDPs are of higher quality due to the greater breadth of expertise of the staff at these organizations and the level of partnership with industry. It is not possible to assess the relative quality or probability of success of products with or without PDP partners included in this study at this date; however, we can look at the percentage of products with or without a PDP development partner that are also engaging industry. Although participation of large pharmaceutical companies is slightly higher in the pipeline of products with at least one PDP developer, biotechnology company engagement is actually higher for those products that have no PDP developer (34 versus 45% participation, respectively; Figure 33). Additional assessment of industry and PDP partnerships is warranted to understand if partnering with a PDP actually increases the probability of success of a product. With the Global Health Primer database BVGH has developed, we will be able to track and answer these questions over time.

Figure 31 Neglected Disease Drug Pipeline with No PDP Involvement by Phase

The number of drugs in development with at least one PDP developer was subtracted from the total number of drugs in development. The remaining drugs were summed for each phase of development in the bar graph (left Y-axis). The percentage of drugs in the given phase of development with no PDP developers relative to the total number of drugs at the indicated phase was calculated and presented as a line (right Y-axis).

Figure 32 Neglected Disease Vaccine Pipeline with No PDP Involvement by Phase

The number of vaccines in development with at least one PDP developer was subtracted from the total number of vaccines in development. The remaining vaccines were summed for each phase of development in the bar graph (left Y-axis). The percentage of vaccines in the given phase of development with no PDP developers relative to the total number of vaccines at the indicated phase was calculated and presented as a line (right Y-axis).
Figure 33  Level of Participation of Other Developer Types in All Projects, Projects with PDP developers, and Projects with no PDP Developer

% of Products

- Total Projects (874)
  - Academic/Research Institution: 43%
  - Other Biotech: 41%
  - Big Pharma: 17%

- Total Projects with PDP (149)
  - Academic/Research Institution: 53%
  - Other Biotech: 34%
  - Big Pharma: 20%

- Total Projects with no PDP (225)
  - Academic/Research Institution: 37%
  - Other Biotech: 45%
  - Big Pharma: 16%
COMPARISON OF BIOTECHNOLOGY AND PHARMACEUTICAL COMPANY PARTICIPATION

Although biotechnology and pharmaceutical companies both represent the private sector, their participation in product development for neglected diseases, in terms of absolute numbers of products, differed in our analysis. Along with changes in neglected disease R&D, the last two decades have brought changes to the biopharmaceutical industry more broadly. Large pharmaceutical companies have merged, and the consolidation has left a very small number of large firms. In contrast, the biotechnology sector has expanded substantially, bringing new innovations into development and the marketplace. Therefore, in order to understand better the extent to which the biotechnology sector and pharmaceutical sectors differ in their participation in neglected disease R&D, we wanted to look at the level of participation of these organization types relative to the number of organizations that exist in these sectors as a whole.

Our analysis identified 104 biotechnology companies participating in the development of 153 products, representing participation in 41% of the neglected disease R&D pipeline (Figure 3; Table 2). However, this likely represents a very small level of participation across the biotechnology sector as a whole. Ernst & Young estimated that there were 1,726 U.S., 1,834 European, and 293 Canadian biotechnology companies in 2010. Using the sum of the Ernst & Young numbers as the denominator, our analysis suggests that just under 3% of global biotechnology companies participate in neglected disease product development.

In contrast, we identified only 13 pharmaceutical developers participating in the development of 65 products, representing participation in 17% of the neglected disease R&D pipeline (Figure 3; Table 2). Unlike the biotechnology sector, which is rapidly growing, the large pharmaceutical industry now consists of only about 20 large companies. Therefore, the 13 companies identified in this study represent approximately 65% participation across the large innovator pharmaceutical companies.

Although there are fewer pharmaceutical companies, the large size and market share of these companies relative to biotechnology companies would suggest that large pharmaceutical companies should be able to participate in a larger number of products per company. Therefore, we calculated the average number of products per organization in development for neglected diseases for both biotechnology and pharmaceutical companies identified in this study.

Biotechnology companies participating in neglected disease R&D on average are participating in the development of 1.6

<table>
<thead>
<tr>
<th>LARGE PHARMACEUTICAL COMPANIES</th>
<th># OF PRODUCTS IN DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>15</td>
</tr>
<tr>
<td>Novartis AG</td>
<td>13</td>
</tr>
<tr>
<td>Sanofi</td>
<td>12</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>7</td>
</tr>
<tr>
<td>---Average # Products Per Company---</td>
<td>-------5.4-------</td>
</tr>
<tr>
<td>Merck &amp; Co., Inc.</td>
<td>5</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>5</td>
</tr>
<tr>
<td>Johnson &amp; Johnson*</td>
<td>3</td>
</tr>
<tr>
<td>Bayer AG</td>
<td>2</td>
</tr>
<tr>
<td>Eisai Inc.</td>
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<tr>
<td>Eli Lilly &amp; Co.</td>
<td>2</td>
</tr>
<tr>
<td>Roche</td>
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</tr>
<tr>
<td>Otsuka Pharmaceutical Co., Ltd.</td>
<td>1</td>
</tr>
<tr>
<td>Takeda Pharmaceutical Company LTD</td>
<td>1</td>
</tr>
</tbody>
</table>

*Due to our definition of biotechnology companies, Crucell is counted as a biotechnology company as it was purchased less than 3 years ago by Johnson & Johnson. Crucell has 4 products in development which would bring the Johnson & Johnson total to 7 products.

products per organization (range of 1–8 products per company; data not shown). As expected, large pharmaceutical companies are participating in the development of a larger average number of products on a per company basis (5.4 products per company; Table 3). However, the range of products per company varied greatly, as highlighted in Table 3. Just four companies, GlaxoSmithKline, Novartis, Sanofi, and AstraZeneca account for 47 of the 65 products (72% of all products). These data suggest that while a few large pharmaceutical companies are participating in a large number of products, other large companies are participating in a number of products more similar to that of the much smaller biotechnology companies.

Outside of the neglected diseases space, large pharmaceutical companies are increasingly sourcing their products from biotechnology companies. These partnerships usually involve the translation of a discovery into an early stage product within the biotechnology company and the transfer of later stage product development to the large pharmaceutical companies through staged partnerships. Biotechnology companies are thought of as key early stage product innovators, focusing on discovery and early stage development of innovative products. Technology from biotechnology companies is often licensed by larger multinational pharmaceutical companies, or biotech companies are purchased to actually bring products to market. Therefore, the relative participation of biotechnology and pharmaceutical companies may reflect a bias generated by the relatively large number of products in early stage development as compared to late-stage development for neglected diseases in this study. This led us to examine whether differences in biotechnology and pharmaceutical company participation reflect difference in phase of development expertise. Results of this analysis are presented in Figure 34 and Figure 35.

We hypothesized that neglected disease products have a higher level of biotechnology company participation in the early stages of development with a shifting focus towards pharmaceutical company participation in the later stages of development. If examining just the drug development pipeline, biotechnology company participation was highest in the early stages as hypothesized (Figure 34). Pharmaceutical company participation, however, did not increase steadily across the phases. In contrast, biotechnology company participation was higher than large pharmaceutical industry participation at every phase of development from discovery through phase II in the vaccine development pipeline (Figure 35). Pharmaceutical company participation increased across the phases of development, as would be hypothesized, but only exceeded biotechnology company participation in phase III.

One element of biotechnology company participation that stood out was the level of participation of biotechnology companies in the pre-clinical stage of drug development. This phase is often referred to as the “valley of death” in neglected disease and global health product development. Moving promising compounds from hits in a high throughput screen through lead optimization, animal efficacy, safety and toxicity studies, and formulations towards an investigation new drug (IND) filing with the FDA is a significant financial investment with a high risk of failure. Our data suggest that biotechnology companies may be playing a significant role in this challenging stage of neglected disease drug development.

The difference in product participation between the biotechnology and large pharmaceutical companies identified in this study may also reflect real differences in funding. A key limitation of our analysis is that we do not know the specific role or depth of each developer’s participation; however, other studies have explored the neglected disease R&D funding given and received by companies.

Industry as a whole was the second largest funder of neglected disease R&D in 2010, but pharmaceutical company contributions were nearly seven times higher than contributions from


small biotech/pharmaceutical companies.\textsuperscript{32} Pharmaceutical companies contributed $442 million in 2010, increasing from US$185 million in 2007.\textsuperscript{33} In contrast, small biotech/pharmaceutical companies contributed only US$46 million in 2007 increasing to US$61 million in 2010.\textsuperscript{34} Unfortunately, data on pharmaceutical company and biotechnology company contributions have only been reported in the aggregate, making it difficult to correlate dollars directly with pipeline products.

We hypothesized that R&D spending on a per company basis was higher for a pharmaceutical company than a biotechnology company, reflecting the increased access of pharmaceutical companies to revenue from existing product sales relative to small companies. We cannot directly compare R&D spending in 2010 as reported by Policy Cures to the number of companies or products identified in our study in 2011 due to differences in company type, disease, and product scope definitions between

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure34}
\caption{Biotechnology and Pharmaceutical Company Participation in Drug Development by Phase}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure35}
\caption{Biotechnology and Pharmaceutical Company Participation in Vaccine Development by Phase}
\end{figure}

\textsuperscript{32} Moran M et al. (2011) Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, Policy Cures, Australia
\textsuperscript{33} Moran M et al. (2011) Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, Policy Cures, Australia
\textsuperscript{34} Moran M et al. (2011) Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, Policy Cures, Australia
our two studies. However, as a rough estimate of the difference in per organization and per product money spent by pharmaceutical as compared to biotechnology companies, we divided the R&D investment dollars reported by Policy Cures by the number of organizations with active products identified here. We then divided dollars per organization by the average number of products per organization to estimate the R&D investment per product. The results of these calculations are summarized in Table 4.

Large multinational pharmaceutical companies contributed significantly more funding to neglected disease R&D in total and on a per organization or per product basis as compared to small pharmaceutical or biotechnology companies as calculated here (Table 4). While very approximate, these data suggest that large pharmaceutical company financial participation is an order of magnitude higher than that of biotechnology company financial participation on both a per organization and a per product basis.

As biotechnology companies contributed less money to neglected disease R&D both in the aggregate and as estimated on a per organization or per product basis, we hypothesized PDP funding of pharmaceutical versus biotechnology products would compensate for the observed difference. PDPs often state that biotech companies are expensive to work with as they require more cash investment than partnerships with large pharmaceutical companies. Previous analysis of traceable PDP expenditures determined that nearly half (48.2%) of external PDP R&D funding went to private sector organizations in the developed world. Of this funding, small biotech/pharmaceutical companies received 18% ($26.2 million) while large pharmaceutical companies received 9.3% ($13.5 million), in line with PDP reports that biotechnology companies require more cash investment. This difference in PDP expenditures is not surprising given that biotechnology companies operate off of investment whereas pharmaceutical companies operate off of revenue.

Based on the increased financial participation of pharmaceutical companies relative to biotechnology companies, we would hypothesize that biotechnology companies would be more reliant on partnerships, particularly with PDPs, than pharmaceutical companies. However, this was not the case. A larger percentage of projects with at least one biotechnology company had no additional development partners or no PDP development partner as compared to projects with at least one pharmaceutical company (Figure 21; Figure 23; Figure 27; Figure 29). More detailed analysis of financial participation and partnering relationships is needed to understand the relative contribution of pharmaceutical and biotechnology participants in the development of neglected disease products.

Preliminary work to this end has been conducted. Case studies of biotechnology company participation in neglected disease product development suggest that there are many benefits to biotechnology companies working in this space that motivate

<table>
<thead>
<tr>
<th>Table 4. Estimation of Pharmaceutical versus Biotechnology Contributions for Product Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LARGE MULTINATIONAL PHARMACEUTICAL COMPANIES</strong></td>
</tr>
<tr>
<td>Reported Neglected Disease R&amp;D Contribution</td>
</tr>
<tr>
<td>Active Organizations Identified in This Study</td>
</tr>
<tr>
<td>Calculated Approximate Contribution per Company</td>
</tr>
<tr>
<td>Average Products per Company</td>
</tr>
<tr>
<td>Calculated Approximate Contribution per Product</td>
</tr>
</tbody>
</table>

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35 Moran M et al. (2011) Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, Policy Cures, Australia

36 See Figure 3.


participation. Moving forward, more systematic analysis of the 104 active biotechnology companies in this space is needed to understand how and why biotechnology companies are participating in neglected disease R&D. Furthermore, analysis to understand what would increase engagement of the more than 3,800 additional biotechnology companies not yet working in neglected disease R&D is needed. As biotechnology companies appear to fill niche areas in the neglected disease pipeline—such as pre-clinical drug development and vaccine development where large pharmaceutical company involvement is minimal—specific effort should be made to continue to grow biotechnology company engagement.

Equivalent case studies are not available for large pharmaceutical companies, but the Access to Medicines Index provides broader analysis of pharmaceutical company activities that promote access to medicines to those in need. The Access to Medicines Index includes a sub-score for R&D for diseases with known market failures, including 14 of the diseases also analyzed here. While the disease list, year, and study methodology differ between the current analysis and the 2010 Access to Medicines Index report, it is interesting to note that the top three scoring companies for R&D in the Access to Medicines Index are the same three large pharmaceutical companies with the highest level of participation in the development of neglected disease products identified in our study (Table 5). Further analysis of how neglected disease R&D contributes to overall pharmaceutical company medicines access strategies and other corporate-social responsibility initiatives is warranted.

The financial contribution of pharmaceutical companies is significant and growing. However, pharmaceutical company participation appears to be the result of extensive participation by a few companies rather than broad participation across the large pharmaceutical company sector. Future efforts aimed to engage pharmaceutical developers in neglected disease R&D should focus on increasing the breadth of companies participating in product development.

Table 5. Pharmaceutical Company Access to Medicines Index R&D Scores and Number of Active Neglected Disease Projects

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>2010 ACCESS TO MEDICINE INDEX R&amp;D SCORE (OUT OF 5.0)</th>
<th>PRODUCTS IN DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>4.0</td>
<td>15</td>
</tr>
<tr>
<td>Novartis AG</td>
<td>3.3</td>
<td>13</td>
</tr>
<tr>
<td>Sanofi</td>
<td>2.8</td>
<td>12</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Pfizer Inc.</td>
<td>2.2</td>
<td>5</td>
</tr>
<tr>
<td>Eisai Co.</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>1.8</td>
<td>3*</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>1.8</td>
<td>7</td>
</tr>
<tr>
<td>Roche Holding Ltd.</td>
<td>1.8</td>
<td>2</td>
</tr>
<tr>
<td>Gilead Sciences</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Due to our definition of biotechnology companies, Crucell is counted as a biotechnology company as it was purchased less than 3 years ago by Johnson & Johnson. Crucell has 4 products in development which would bring the Johnson & Johnson total to 7 products.

43 Moran M et al. (2011) Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?, Policy Cures, Australia
The aim of this study was to describe quantitatively what types of organizations are developing drugs and vaccines for neglected diseases. The broader intent of the Global Health Primer database is to enable a public discussion of key issues in neglected disease R&D, such as:

- Progress being made towards development of products that meet the health needs of the poor;
- The cost and value of neglected disease R&D efforts;
- The level and type of neglected disease product developer participation;
- The extent to which countries, and developer sectors within those countries, are playing a role in neglected disease R&D;
- Trends in developer participation and pipeline progress over time.

The types of data analyzed here have the potential to inform funder and policymaker decision making for neglected diseases product development. Funders and policy makers often have to make difficult decisions regarding the allocation of grant money, incentives, and other financial resources for neglected disease R&D. Evidence is needed to determine whether it is better to stay the course with existing strategies or intervene with specific policy or program interventions to improve R&D efficiency and effectiveness. The Global Health Primer database, therefore, provides a key element of the evidence base to support donor and policy maker decision making in this space.

We understand that product and developer data and trends are just one subset of the useful data that can be examined to inform funder and policy maker decision making. Unfortunately, the lack of interoperability between data sets limits our collective ability to examine progress, efficiency, and effectiveness of neglected disease R&D. We note, for example, that the G-FINDER report on funding for neglected disease R&D reports large funding contributions from emerging economies, including India and Brazil. We would expect that money to be distributed locally, yet we were surprised to find few product developers in emerging economies as reported here. Differences in data collection, definitions, and data time frames make it difficult to definitively connect financial and pipeline data. Discussions between PolicyCures, which operates the G-FINDER report, and BIO Ventures for Global Health (BVGH) with its Global Health Primer, have begun. As large dataset holders begin to work together to standardize definitions and explore data compatibility, more useful information for policymakers and funders will likely emerge.

Beyond data interoperability, there is a woeful lack of metrics available for examining the collective neglected disease R&D value chain. Only PDPs are regularly externally evaluated, but the lack of consistency in those evaluations makes it difficult to draw conclusions about the effectiveness of the PDP model or neglected disease R&D efforts as a whole. Instead of focusing on evaluation of the productivity of individual organizations, BVGH has chosen to first focus on bigger picture questions. For example: “Is the neglected disease R&D portfolio resulting in needed products becoming available for delivery to the poor?” There are many nuances to answering this and other broad questions in neglected disease R&D. However, if we are indeed outcome driven, we should not shy away from tracking and asking these broader questions before drilling down to the performance of individual organizations.

If we can focus first on whether or not we are succeeding in our ultimate goal of bringing life-saving interventions to market, we can then tailor our line of follow-up questioning to focus on
very specific bottlenecks that need to be overcome in the value chain. Follow-on questions as to how to shorten the time between phases of R&D (which may be disease specific), address vast differences in scientific difficulty (which may be product type and disease specific), attract new types of expertise into entrenched R&D communities, and many more will be easier to prioritize in the context of broader success metrics. As we identify examples of models that have overcome bottlenecks, we can disseminate information on those best practices among different players in the value chain. For those hurdles where existing models have failed, we can develop calls to action for funders and policy makers. Tens of thousands of lives are lost each month to neglected diseases, so even a very modest increase in R&D efficiency or effectiveness has the potential to make a large impact.

Some of the findings presented here regarding participation of developer types in neglected disease R&D were consistent with our expectations, while others were surprising. As an organization with a mission to increase biotechnology company engagement in the global health space, we were gratified to identify 104 biotechnology companies participating in 41% of neglected disease drugs and vaccines in development. Using the Global Health Primer database, we now have a way to track trends in biotechnology company involvement and solid evidence on which to base proposals for incentives and initiatives to increase participation.

We were surprised to find that PDPs were involved in only 40% of the neglected disease drugs and vaccines identified in this study and that industry participation did not correlate strictly with PDP involvement. Given the enormous investment made in the PDP mechanism, we expected a larger percentage participation of PDPs in the overall pipeline. The number of products in development without a PDP partner points to a need to support other developers with sufficient finances to be successful. A countervailing argument is that the PDPs are working on the projects that hold the most promise for success and that are most targeted toward the populations in need. For example, a drug that needs to be infused daily in a clinic location for 30 days would be of far less value to global health than a drug for the same disease
given orally once per day for three days. We had no way of evaluating the quality of the products covered in this analysis or their appropriateness for use in low resource settings in the developing world. Also not captured in our analysis are the contributions PDPs make that benefit all products in a field, such as screening tools, shared testing protocols, animal models, validated assays, clinical trial sites, clinical protocols, and the many other resources that contribute to the development of the "commons." These assets comprise the “boring” work of product development but they are highly unlikely to be created alone by any of the other developer types. The creation of shared resources is an example of the qualitative analysis of “developer value” that is missing from this analysis but that warrants further study.

The PDP model and several parallel initiatives, such as the "CEO roundtable," have focused their efforts on engaging large pharmaceutical companies in neglected disease R&D. This makes sense from many perspectives as pharmaceutical companies have more money available to invest in the projects they support and can share in-kind expertise across the product development value chain. Our analysis showed that approximately 65% of large pharmaceutical companies are engaged in neglected disease R&D. However, our data also showed that these companies are more involved in drug development than vaccine development, and that just four companies work on over 72% of the products with pharmaceutical company participation.

Sector wide efforts, such as those developed for the pharmaceutical industry, may benefit engagement of other developer types, such as the biotechnology sector and major funders of academic/research institutions. For example, Dr. Francis Collins, Director of the National Institutes of Health (NIH), has gained approval and funding for the National Center for Advancing Translational Science (NCATS). This program aims to accelerate development of new therapeutics and includes several special initiatives focusing on neglected diseases, including the Cures Accelerating Network (CAN) and the Therapeutics for Rare and Neglected Diseases (TRND) program. These programs recognize that for rare and neglected diseases the "valley of death" between early discovery in academic institutions and government laboratories and the development of those discoveries into products is vast. Our analysis shows that academic/research institutions participate at a high level across the neglected disease pipeline, suggesting that advances in support for translational research by the NIH will have a direct benefit for the neglected disease R&D pipeline. Continued support for translational research efforts, should remain on the global health advocacy agenda. With the substantial involvement of biotechnology companies identified in our analysis, a more focused strategy toward this sector could engage a broader range of biotechnology companies as well.

As BVGH continues to track developers and products with the Global Health Primer and its associated database, we will grapple with additional layers of data complexity, such as capturing scientific complexity, breadth and quality of a portfolio (e.g., how many different mechanisms of action are targeted), the relationships between the various developers, and the relationship between funding and outcome. BVGH is just one organization in a broad community of individuals and organizations devoted to applying the best available science and human resources to solving some of the world's oldest and deadliest diseases. Although there are many questions that remain to be asked and worked through, we hope these data will contribute in a positive way to both discussion and action by the global health community to improve neglected disease R&D.
METHODOLOGY

PRODUCT AND DISEASE SCOPE

The analysis presented here is based on data from the BIO Ventures for Global Health Global Health Primer database of drugs and vaccines in development for neglected diseases. Products in development for neglected diseases included in the Global Health Primer are identified through a variety of sources, including product development partnership websites and reports, interviews with disease experts and organizations actively involved in neglected disease product development, searches of public databases of press releases, scientific literature, and clinical trials databases, and attending scientific and global health focused meetings. Products are updated in the online database on a quarterly basis. All analyses presented here are based on data exported from the database on September 13, 2011.

Neglected diseases are categorized as a single group due to neglect rather than their biological or medical basis. Therefore, the term “neglected” has been difficult to define and challenging to gain consensus around, even within the global health community. For the purposes of this study, 23 diseases were included. The full list of diseases and product scope are summarized in the table below. The diseases include the so-called “big three” (HIV, malaria, and tuberculosis), the World Health Organization (WHO) list of “neglected tropical diseases,” and several major causes of diarrhea and pneumonia. From the WHO list, no products in development were identified for cysticercosis, dracunculiasis (guinea-worm disease), echinococcosis, or yaws, therefore these diseases are not presented in this study. Diarrhea and pneumonia were selected for inclusion as these represent the number one and two leading causes of death in children less than five years of age and disproportionately affect the developing world.

Table 6. Diseases and Products Included

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>DRUGS?</th>
<th>VACCINES?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIG THREE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Microbicides only</td>
<td>Y</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Malaria</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td><strong>OTHER NEGLECTED TROPICAL DISEASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buruli ulcer</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Dengue</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>HAT</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Leprosy</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>STH: Hookworm</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>STH: Ascariasis &amp; Trichuriasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Trachoma</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td><strong>OTHER IMPORTANT DISEASES OF POVERTY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>Y</td>
<td>N/A</td>
</tr>
<tr>
<td>Cholera</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td>ETEC</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td>Shigellosis</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>N/A</td>
<td>Y</td>
</tr>
<tr>
<td>Pneumococcal disease</td>
<td>N/A</td>
<td>Y</td>
</tr>
</tbody>
</table>

The neglected diseases included in this study are summarized here. Diseases are divided into three general categories. The numbers of products identified are listed. Those product types not researched for inclusion are designated by not applicable (N/A); STH=Soil Transmitted Helminths
DEFINITIONS

Organizations analyzed in this study were categorized as academic/research institutions, government agencies, product development partnerships (PDPs), biotechnology companies, pharmaceutical companies, other non-profits, or other industry. As definitions of these organization types are difficult to standardize across the global health sector, a full list of organizations and their categorization for the purposes of this study are included in Supplementary Information 1. A summary of organization type definitions is included here for reference:

- **Academic/research institutions** included teaching and research-focused institutions as well as research hospitals.

- **Government agencies** included a wide range of research groups, ministries, and other government operated organizations.

- **PDPs** included public health-focused organizations who are facilitating product development.

- **Biotechnology companies** were defined as small to medium biologics or pharmaceutical companies with an annual revenue of less than $10 billion and that focus on novel product development. Companies with a primary focus on in-licensing, generics, contract services, or other non-discovery aspects of product development were re-categorized as “other industry.” Biotechnology companies that were purchased by multinational pharmaceutical companies less than three years ago remain designated as biotechnology companies in this report to reflect that products currently in development at these organizations likely originated from the biotechnology company rather than the large pharmaceutical company. Because all acquisition integrations take various forms over various periods of time, we chose three years as a simple, objective determination of when transition into the larger company should be recognized.

- **Pharmaceutical companies** were defined as large multinational drug and vaccine developers. Companies with a primary focus on in-licensing, generics, contract services, or other non-discovery aspects of product development were re-categorized as “other industry.”

- **Other non-profits** include all non-academic, non-government, non-PDP non-profits participating in product development such as foundations, and other multilateral agencies.

- **Other industry** includes all biopharmaceutical industry companies excluded from the definitions of biotechnology and pharmaceutical companies provided above. This category includes contract research organization (CROs) and other pharmaceutical services providers.
LIMITATIONS

Organizations are tracked as product developers based on public reporting of their participation. Although every effort is made to identify all products in development for neglected diseases, it is difficult to validate the success of this effort. By comparison with a non-public database, we believe the information is fairly complete. Projects or products for which public information is not available are not included in the dataset which may cause underrepresentation of early stage projects or projects conducted entirely in the private sector, although we think this unlikely due to the corporate social responsibility benefits for companies to disclose neglected disease research. As PDPs have the most comprehensive public pipelines, products with PDP developers may be over represented. Furthermore, organizations may define "participation" in product development differently. For instance, some organizations list funders as development partners while others may list only those organizations actively completing parts of the development process. In the case of the Global Health Primer dataset, developers were listed inclusively as reported by the developers.

The organizations analyzed here also only represent a snapshot of product development known to us as of a given date. As discussed earlier, trend data would provide more depth to the analysis and thus allow improved decision making based on changes in direction over time.

HIV drug development is excluded from both the Global Health Primer and this study. At present, billions of dollars have been, and are being, invested in the development of HIV drugs and is generally not considered to be "neglected" by the pharmaceutical industry.

A key limitation to the data is that we have no information as to the role that the various developers play in each project. Thus a project where a company may only license a product to another for development is counted the same as a project where a company is committing considerable funds to develop a new drug or vaccine. Thus, the results should not be over-interpreted as to the depth of involvement of the various developers nor the quality of the projects assessed in this study.
Developing New Drugs & Vaccines for Neglected Diseases of the Poor:
The Product Developer Landscape

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