Diarrhoea is one of the six conditions identified in the fourth Millennium Development Goal: reduce child mortality, that lead to the majority of child deaths. In 2010, diarrhoeal diseases caused 1.1 million deaths and 66.5 million years of productive life lost in developing countries. Diarrhoeal infections can be spread through food or water contamination, or from person to person as a result of poor hygiene. The most at-risk populations are children, particularly malnourished children and people living with human immunodeficiency virus (HIV). Whilst preventive measures such as clean drinking water and sanitation can reduce the risk of infection, research and development (R&D) of new tools is equally important, particularly for vaccines as they can prevent infection.

This factsheet examines funding for diarrhoeal disease R&D globally from 2007-2011 and discusses the need to increase the focus on under-funded disease areas, have greater funding diversity and have a more balanced distribution of funding between basic research and product development. The G-FINDER data analysed in this factsheet only includes diseases that disproportionately affect developing countries, where there is neither commercial interest in R&D nor suitable products available. The following diarrhoeal diseases are included in the G-FINDER survey: rotavirus, Enterotoxigenic E. coli (ETEC), cholera, shigella, cryptosporidium, Enteroaggregative E. coli (EAggEC), and giardia (see table 1).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Basic Research</th>
<th>Drug</th>
<th>Vaccines (Preventive)</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td></td>
<td></td>
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<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
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<tr>
<td>Shigella</td>
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</tr>
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</tr>
<tr>
<td>Enteroaggregative E. coli (EAggEC)</td>
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<td></td>
<td>✓</td>
</tr>
<tr>
<td>Giardia</td>
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<td></td>
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<td>✓</td>
</tr>
<tr>
<td>Multiple diarrhoeal diseases</td>
<td>✓</td>
<td></td>
<td>Restricted</td>
<td>✓</td>
</tr>
</tbody>
</table>

1. G-FINDER figures are adjusted for inflation and reported in 2007 US dollars. The majority of the analysis presented in this factsheet is based on data reported by regular participants of the G-FINDER survey, however the complete funding figures (including irregular participants) are presented graphically in Figure 1.
Over the 2007-2011 period, diarrhoeal diseases received a total of $677m in R&D funding. Total funding for diarrhoeal disease R&D increased from $102m in 2007 to a peak of $171m in 2009, and then decreased to $141m in 2011. Diarrhoeal diseases represented only a small portion ($141m, 5%) of the total funding pie for R&D of neglected diseases in 2011. This is a serious underinvestment given that diarrhoea is the second leading disease causing death in children under five years of age and that we are still lacking key tools to prevent and treat these diseases.3

The public sector is the dominant funder (providing 53% [$358m] of funding), and is largely responsible for the funding increases from 2007 to 2011. Philanthropic funders accounted for almost a third (29%, $196m) and the pharmaceutical industry for almost a fifth (18%, $122m) of diarrhoeal disease R&D funding.

Public funding more than doubled from $43m in 2007 to $88m in 2011, largely due to increases from US National Institutes of Health (US NIH). Over the five year period, the US NIH increased funding for diarrhoeal disease R&D from $31m to $53m. The French institute Inserm also saw a substantial increase in funding, from a low base of $0.3m in 2007 to $9m in 2011.

Philanthropic funding came almost exclusively from the Bill & Melinda Gates Foundation (99% over the 2007-2011 period). However, funding from the Gates Foundation decreased by 30% – from $44m in 2007 to $31m in 2011 – with fluctuations most likely reflecting the cyclical nature of their grants. This decrease in funding was most apparent in cholera R&D funding, where funding dropped from $16m in 2009 to $1m in 2011, with the registration of the International Vaccine Initiative’s (IVI) Shanchol™ cholera vaccine in 2009.4

There have been positive improvements from industry with a 65% increase from $13m in 2007 to $22m in 2011. Industry funding peaked in 2009 at $33m, due to a funding increase for rotavirus vaccines as candidates moved into later (more expensive) stage trials.

Funding is fairly concentrated with just three funders accounting for 81% of funding: the US NIH at 35% ($235m), the Gates Foundation at 29% ($194m), and the pharmaceutical industry at 18% ($122m).

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* Figures are adjusted for inflation and reported in 2007 US dollars
* Regular participants are those who have reported to G-FINDER in every year of the survey. In order to avoid artefactual changes related to data collection, funding from irregular participants is not included in our trend analysis.
From 2007 to 2011, funding was predominantly directed at three diarrhoeal diseases: rotavirus (27%, $185m), cholera (18%, $120m) and shigella (15%, $99m); with an additional 27% ($186m) going to R&D for multiple diarrhoeal diseases. Funding fluctuations over the five-year period were attributable to increases in funding for rotavirus, cholera, shigella, and *cryptosporidium* (see overleaf for snapshots of disease specific trends).

Funding distribution for diarrhoeal disease R&D is influenced by a number of external factors. In particular, rotavirus has greater industry support for two reasons: a) it is a semi-commercial disease due to its prevalence in high-income countries and b) the GAVI Alliance supports the introduction of rotavirus vaccines in developing countries, which provides an incentive for industry involvement in R&D. Other diarrhoeal diseases do not have as much industry support and in addition, have a smaller burden of disease.

The R&D gaps for EAggEC and ETEC (where there is insufficient commercial investment) are limited to diagnostics and vaccines, while an R&D gap for giardia only exists for diagnostics; this narrow scope partially explains their small funding share. However, it is still concerning that some research areas receive minimal amounts of funding. For example, EAggEC vaccine R&D only received one grant of $7,124 over the 2007-2011 period and giardia diagnostics received less than $500,000 in funding per year from 2007 to 2011. The actual cost of developing a vaccine is estimated to be $600-$800 million over 10 – 15 years; whilst the development of a diagnostic tool is estimated to cost $2-$50 million over 3 – 5 years.

![Figure 2. Funding by diarrhoeal disease (2007-2011)](image)

These peaks and drops reflect the funding priorities of different funders (see overleaf for snapshots of disease specific trends). Industry and philanthropic funders align their funding decisions with the movement of product candidates through the pipeline, for example, providing additional funds for expensive late-stage clinical trials. Public funders, such as the US NIH, are often investigator driven and focus more on basic research and therefore, their funding allocations might not reflect strategic pipeline decisions or disease priorities.
DIARRHOEAL DISEASE PRODUCT DEVELOPERS

From 2007 to 2011, the majority of funding for diarrhoeal disease R&D was distributed to four types of developers: academic research institutions received just over a third ($250m, 37%), product development partnerships (PDPs) and other intermediaries a quarter ($168m, 25%), multinational companies (MNCs) just under a fifth ($118m, 17%), and public sector government received just under a tenth ($54m, 8%) of funding.

Funding for academic research institutions more than doubled from $19m in 2007 to $46m in 2011, with a peak of $80m in 2009. These fluctuations are largely dependent on the US NIH, which was the most dominant funder and accounted for 62% of funding to academic research institutions over the five-year period. Almost all of this US NIH funding (99%) went to US academic research institutions as US NIH funding is investigator driven. For example, the 2007-2009 increase ($60m, 312%) was due to increased US NIH funding for basic research for cholera, cryptosporidium and shigella.

PDP funding relies heavily on the Gates Foundation which provides 91% ($153m) of total PDP funding for diarrhoeal diseases, with the second largest funder, the UK Department for International Development (DFID) providing 7% ($11m). There are only two PDPs active in R&D for diarrhoeal diseases, PATH (including OneWorld Health [OWH] funding) and IVI. PATH received two-thirds of funding for PDPs in 2007-2011 ($110m, 65%), whilst IVI received 16% ($27m). IVI's funding decreased dramatically from $12m in 2007 to $0.9m in 2011, perhaps attributable to the completion of late stage
Encouragingly, industry developers have become increasingly involved in R&D for diarrhoeal diseases, with self-funding for MNCs doubling from $11m in 2007 to $22m in 2011. This is partially explained by increased investment in late stage rotavirus vaccine clinical trials due to the ‘pull’ effect of the GAVI market for rotavirus vaccines. Increased funding for shigellosis vaccines in discovery and preclinical stages also explained this trend to a lesser extent.

**DIARRHOEAL DISEASE PRODUCT PIPELINE**

The diarrhoeal disease vaccine and diagnostic pipeline is active with a healthy range of candidates. There are six rotavirus vaccine candidates in the pipeline, with two in late stage development. ROTAVAC is the most advanced candidate, having just completed Phase III clinical trials, and is in development by Bharat Biotech, India's Department of Biotechnology and PATH. Another advanced candidate is RV3 which is in Phase IIb trials in Indonesia and is in development by the Murdoch Children's Research Institute, BioFarma and Universitas Gadjah Mada. There are a number of other vaccine candidates in the pipeline including at least ten for ETEC, seven for shigella, two for cholera and one for *cryptosporidium*. There are also at least three cholera diagnostics in the pipeline, all of which are being developed by academic research institutions or small pharmaceutical and biotechnology firms (SMEs).

**CASE STUDY:**

Program for Appropriate Technology in Health (PATH)

PATH has recently been involved with manufacturers in China and India to develop new oral rotavirus vaccines that are safe, effective, and affordable. The most advanced candidate, ROTAVAC, has generated favourable results in a Phase III clinical trial and is being considered for licensure by the Indian national regulatory authority. ROTAVAC’s manufacturer, Bharat Biotech previously announced a price of $1 per dose, which will make the vaccine affordable and accessible in low-resource settings.

PATH’s research and development portfolio on diarrhoeal diseases also encompasses the following activities:

- **Fast-tracking development of three rotavirus vaccine candidates that will be administered by intramuscular injection.** These “non-replicating” rotavirus vaccines could overcome the reduced efficacy of live, oral vaccines in low-income settings, which may be due to elevated maternal antibodies, potential interference by other oral vaccines, and co-infections of the digestive system.

- **Partnering with public- and private-sector partners on vaccines against the main bacterial causes of diarrhoea, ETEC and shigella.**

- **Developing a drug candidate for treating secretory diarrhoea as a result of diseases like cholera.** The drug, which is designed to reduce fluid loss, is currently being evaluated in Phase II clinical studies.

- **Collaborating with technology partners on novel diagnostic technologies for diarrhoeal diseases to support the introduction of new diarrhoeal drugs.**
CONCLUSION & RECOMMENDATIONS

Responding to the diarrhoeal disease challenge facing children in low- and middle-income countries requires a multi-pronged approach, which should encompass water treatment and hygiene measures, alongside treatments such as oral rehydration. This approach should also include R&D solutions that can provide preventive vaccines to halt these diseases in their tracks, new tools for diagnosis, and facilitate appropriate treatment with drugs. This will require:

- **Increased focus on under-funded disease areas.** There should be more funding directed at smaller disease areas that are not semi-commercial such as *cryptosporidium*, EAggEC and even giardia (which only needs diagnostics). Whilst PDPs and industry are quite active in product development for some diseases, there should be a greater development focus for diseases that are under-funded.

- **Greater funding diversity.** Funding is currently highly concentrated with the top 3 funders accounting for 81% of funding, and some diseases dominated by just one funder, such as *cryptosporidium* where the US NIH provides 93% of funding. Reliance on a few key funding organisations is risky and can limit the range of priorities addressed. Public funders should continue to increase funding for diarrhoeal disease R&D, whilst philanthropic funding would benefit from the introduction of new funders and diversification. Likewise, whilst there have been positive increases in funding from industry, they should expand their disease focus beyond semi-commercial diseases.

- **Balanced distribution of funding between basic research and product development.** Whilst both basic and applied research are needed to deliver a product, funding should be distributed according to the state of the science and the maturity of the product pipeline. Also, funding for basic research should be better aligned with product development needs to maximise public health impact. For example, if the disease pipeline is mature, then funding should be directed to late stage candidates to fund these expensive trials. Philanthropic and industry funders tend to prioritise their funding according to these needs, but public funding may have a greater impact if it also prioritised R&D based on pipeline needs and disease priorities.

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