

## GLOBAL FUNDING FOR SNAKEBITE ENVENOMING RESEARCH 2007-2018

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## METHODOLOGY

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### Background to the survey

Each year since 2007, the G-FINDER project has provided policy-makers, donors, researchers and industry with a comprehensive analysis of global investment into research and development (R&D) of new products to prevent, diagnose, control or cure neglected diseases in developing countries.

Following a coordinated international campaign, snakebite envenoming (SBE) was added to the WHO's list of Neglected Tropical Disease in 2017. This recognition has increased public awareness, but financial and clinical data on SBE remains scarce while treatment options in low- and middle-income countries (LMICs) are still largely ineffective, unaffordable and inaccessible.

In 2019, SBE is – for the first time – included in the G-FINDER survey. In addition to this, the Wellcome Trust has identified SBE as an area which requires further research and commissioned Policy Cures Research to conduct a landscape analysis of funding for snakebite envenoming (SBE) research.

### The survey scope

#### DEFINING RESEARCH AREAS

The scope of this project was determined in consultation with the Wellcome Trust and independent international experts (listed in Annexe A). The project was based on the G-FINDER survey for neglected disease biomedical R&D, and was expanded to include operational (OR), implementation (IR) and health systems and policy research (HSPR) as areas of interest identified by the Wellcome Trust and experts.

Definitions of biomedical R&D were drawn from the existing G-FINDER Neglected Disease scope document. Definitions for OR, IR and HSPR were based on established and accepted definitions, further validated by independent international experts. Investments that did not meet the project scope were excluded from the results.

A comprehensive list of inclusions, exclusions and restrictions is outlined in the detailed Snakebite Envenoming scope document which can be found in Annexe C.

#### TYPES OF RESEARCH INCLUDED

This project quantifies SBE research investments in two main overarching categories, each broken down into a number of further categories:

- Biomedical R&D
  - Basic research
  - Product development (from pre-clinical research through to post-registration studies):
    - Drugs
    - Biologics
    - Diagnostics
- Research for implementation
  - Operational research
  - Implementation research

- Health systems and policy research

Other SBE-related research (e.g. non-biomedical product R&D, such the development and testing of personal protective equipment) that did not fit the two categories above but which otherwise met the inclusion criteria was categorised under 'Other research'.

A detailed explanation of what types of R&D activities are included in each of the product development categories, as well as specific inclusions and exclusions for all areas is provided in the Snakebite Envenoming scope document.

The purpose of the survey was to track and analyse global investment in the R&D of new health technologies and research for implementation for SBE in LMICs. Investment in research which did not target medically important snakes in LMICs was excluded, as there is a commercial market for such products. Investment in venomics research for pharmaceutical purposes not related to the development of products for SBE was similarly excluded. General therapies to treat pathologies resulting from SBE such as painkillers and treatment of acute renal failure were also excluded as they cannot be ring-fenced to SBE treatment only. Investment that was not research related was excluded, although we recognise the vital importance of activities such as advocacy and antivenom donations, investment in these activities falls outside the scope of the project.

## Conducting the survey

### IDENTIFICATION OF SURVEY RECIPIENTS

Recipients were identified through various avenues including the G-FINDER contacts database; clinical trial registries and desk-based research. We also focused on identifying survey recipients from LMICs with a particular focus on South and Central American and North African countries. The initial list of survey recipients was validated and updated by independent international experts.

Additional survey recipients were identified by the SBE research community during the survey period through existing contacts, and data reported back to Policy Cures Research from participants.

### DATA COLLECTION

This project operated according to two key principles: capturing and analysing data in a manner that is consistent and comparable across all funders and financial years; and presenting funding data that is as close as possible to 'real' investment figures.

Data was collected in two ways:

1. Through the SBE-specific survey Excel spreadsheet which collected investment data for SBE biomedical R&D and research for implementation for FY2007-FY2018
2. Through the 2019 G-FINDER survey (online platform and Excel spreadsheet) which collected FY2018 biomedical R&D investment data only

For some organisations with very large datasets, the reporting tools were difficult to use. The Policy Cures Research team was therefore asked to use publicly available databases to identify the relevant funding. For the US National Institutes of Health (NIH), grants were collected using the Research Portfolio Online Reporting Tools (RePORTER). Information on funding from the US Department of Defense was collected using third-party databases including SBIR, USASpending and Govtribe. Funding from the European Commission was retrieved from the Community Research and Development Information Service (CORDIS) public database. Information about the projects funded by Innovate UK and the Australian

National Health and Medical Research Council were extracted from spreadsheets available on their website. Funding from the UK National Institutes of Health was identified from the NIHR Funding and Awards Open Data platform. Similarly, funding from the US National Science Foundation was identified through its online search tool. Grants from the Swiss National Science Foundation (SNSF) were identified through the P<sup>3</sup> database. Supplementary information was provided by SNSF.

All participating organisations were asked to only include disbursements (or receipts), rather than commitments made but not yet disbursed. In general, only primary grant data was accepted. Data from all sources was subject to verification using the same processes and inclusion criteria.

## THE SURVEY PLATFORM

Survey recipients were asked to enter grant-by-grant expenditures incurred during their financial year that had the largest overlap with the relevant year (as opposed to the last calendar year).

Survey recipients were asked to enter details for every SBE investment they disbursed or received, including:

1. a research type (e.g. biomedical R&D, operational research), from a predefined list
2. a product type (e.g. drugs, non-product related), from a predefined list
3. a research activity within the product type (e.g. discovery and pre-clinical, clinical development), from a predefined list
4. the name of the funder or recipient of the grant
5. a brief description of the grant
6. a grant identification number
7. currency of the grant
8. the grant amount

Due to the nature of some SBE research taking place under other projects, for example field surveys conducted during studies designed for purposes other than snakebite, some organisations provided estimates of costs as spending on SBE could not be defined separate to the total project cost. Where survey recipients could not provide data to this level of detail, they were asked to provide the finest level of granularity they can.

## Validation and analysis

### VALIDATION

All entries were verified against the inclusion criteria. Cross-checking was conducted using manual reconciliation – which matched investments reported as disbursed by funders with investments reported as received by product developers and intermediaries – followed by a manual grant-level review of project descriptions.

### DATA AGGREGATION

All pharmaceutical industry funding data was aggregated and anonymised for confidentiality purposes. Rather than being attributed to individual companies, pharmaceutical company investment was instead reported as ‘aggregated industry’.

## INFLATION ADJUSTMENTS

Funding data was adjusted for inflation and converted to US dollars (US\$) for the relevant financial year to eliminate artefactual effects caused by inflation and exchange rate fluctuations, allowing accurate comparison of year-on-year changes. All reported data was also adjusted for inflation using consumer price index (CPI) estimates from the International Monetary Fund (IMF)<sup>1</sup> and any data entered by survey participants in their local currency was converted to US\$ based on the average annual exchange rate of the relevant financial year as reported by the IMF,<sup>1</sup> Bank of England,<sup>2</sup> United Nations Treasury<sup>3</sup> and OANDA.<sup>4</sup>

## Limitations

While the survey methodology was based on the ongoing G-FINDER survey, which is in its twelfth year, there are limitations to the data presented, including survey non-completion and non-comparable or missing data.

## SURVEY PARTICIPATION

Some SBE research funding may not have been captured because organisations active in the field were either not identified or invited and did not participate. However, we are confident that the vast majority of SBE research funding globally since 2007 has been captured.

Policy Cures Research conducted a landscape review prior to the survey, which was reviewed and validated by independent international experts, and any additional organisations identified during the survey period were subsequently invited. Survey follow-up was prioritised to secure the participation of all large funders active in this area and additional priority target groups.

In total, 62 organisations responded to the survey. Of these, 47 organisations reported funding data, while the remaining 15 organisations confirmed they had not funded or conducted research during the period. Organisations reporting funding data included 37 funders, 2 fund managers (PDPs) and 23 product developers.

Participants originated from 19 countries with good coverage across sectors and regions, including:

- Academic research organisations from Australia, Benin, Canada, Costa Rica, France, India, Morocco, Switzerland, Tunisia, UK and US
- Government research institutions from Brazil, France, Morocco, South Africa and Spain
- Philanthropic foundations and NGOs from Swaziland, Switzerland and UK
- PDPs from Switzerland and US
- Public sector government organisations from Argentina, Australia, Brazil, France, India, Netherlands, Nigeria, Switzerland, UK and US and the European Commission
- Private sector industry companies from Australia, Colombia, Spain, UK and US.

## TIME LAGS IN FUNDING PROCESS

Time lags exist between disbursements and receipt of funding as well as between receipt of funds and the moment they are actually spent. Thus, grants by funders will not always be recorded as received by recipients in the same financial year and there may be a delay between investments as reported by the survey and actual expenditure on research programmes by product developers and researchers. Nevertheless, as this report analyses trends over an extended period, the impact of time lags is minimal.

**NON-COMPARABLE DATA**

A total of 1,298 grants or expenditure items for SBE research were reported for the period from 2007-2018. Despite funding being reported in each of the survey years, data may not always be strictly comparable from year to year. As shown in Table 1 below, there has been variation in the participation/reporting of data by survey participants for each year over the duration of the survey period, and not all organisations reported data for each year that was covered by the survey. Although we believe the majority of this variation is a true representation of the entry of new organisations to the field, some of this effect is likely due to the retrospective nature of the survey.

**Table 1. Number of organisations reporting data per year 2007-2018**

2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
9	10	12	14	15	17	18	17	16	26	28	40

This variation in reporting is due to a number of reasons including:

- Recall bias
- Lack of participation – for some organisations collecting data from earlier years was too resource-intensive to complete
- Systematic issues in record keeping – some organisations did not have the capacity to report data on earlier years such as LSTM whose systems could only go back to 2009, although they confirmed that funding had been received prior to this.

**MISSING AND INACCURATE DATA**

This project can only report the data as it is given to us. Although strenuous efforts were made to check the classification, accuracy and completeness of grants, in a survey collecting 12 years of data, it is likely that some data will still have been incorrectly entered or that funders may have accidentally omitted some grants. We believe that the checks and balances built into the data collection and validation process mean that mistakes, if present, have a minor overall impact.

## LANDSCAPE OF SBE RESEARCH ORGANISATIONS

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The purpose of this landscape analysis was to identify organisations which are currently active in SBE research, and the types of research they undertake. For this reason, we have only included and classified organisations based on the most recent five years (2014-2018) of data from the survey of global funding for SBE research. Organisations which were invited to the survey but did not participate were also included and classified where reliable information was available from external sources.

Table 2. Landscape of SBE researchers by research and product type, 2014-2018

Organisation	Basic research	Biologics	Drugs	Diagnostics	Unspecified R&D	IR	OR	HSPR	Other research	Country
<b>Government research organisations</b>										
Argentinian National Scientific and Technological Research Council (CONICET)	✓									Argentina
Institute of Biomedicine of Valencia (IBV) <sup>A</sup>	✓									Spain
Butantan Institute	✓	✓					✓	✓		Brazil
Ezequiel Dias Foundation (FUNED)	✓	✓		✓						Brazil
French Research Institute for Development (IRD)	✓	✓								France
Indian National Institute of Animal Biotechnology (NIAB)				✓						India
Indian Translational Health Science and Technology Institute (THSTI)				✓						India
Instituto Nacional de Producción de Biológicos (ANLIS)	✓	✓								Argentina
Nigerian Federal Ministry of Health <sup>C</sup>	✓					✓	✓			Nigeria
Oswaldo Cruz Foundation (FIOCRUZ)					✓					Brazil
Senegalese Ministry of Health and Prevention		✓								Senegal
South African Vaccine Producers (SAVP)*		✓								South Africa
<b>Academic and other research organisations</b>										
Animal Venom Research International (AVRI) <sup>#,5</sup>								✓		United States of America
Australian Venom Research Unit (AVRU) <sup>A</sup>		✓						✓		Australia
Bangor University	✓									United Kingdom
Bayero University, College of Health Sciences <sup>#,6,7</sup>	✓							✓		Nigeria
Bio-Ken Snake Farm (including James Ashe Antivenom Trust) <sup>#,A,8</sup>	✓							✓		Kenya
Brazilian Federal University of Ceara	✓									Brazil

\* Organisation reported zero data but have expressed potential to undertake R&D

# Organisation was invited to the survey but did not participate; categorisation is based on external sources

A Partner of Global Snakebite Initiative

B Identified by Robert Harrison (LSTM) as active but did not participate in survey

C Partner of the EchiTAB Study Group

Organisation	Basic research	Biologics	Drugs	Diagnostics	Unspecified R&D	IR	OR	HSPR	Other research	Country
<b>Academic and other research organisations</b>										
Brazilian State University of Campinas	✓								✓	Brazil
Brazilian State University Paulista	✓		✓							Brazil
Charles Campbell Toxinology Centre (CCTC) <sup>#,A,9</sup>	✓	✓						✓		Papua New Guinea
Clemson University	✓									United States of America
Clodomiro Picado Institute <sup>A,C</sup>	✓	✓								Costa Rica
Federal University of São Francisco Valley			✓							Brazil
Federal University of São Paulo	✓									Brazil
Florida State University	✓									United States of America
Goethe University Frankfurt	✓									Germany
Haffkine Institute for Training, Research and Testing	✓									India
Health Action International (HAI)								✓		Switzerland
HEPS-Uganda <sup>#,10</sup>								✓		Uganda
Herminio Ometto Foundation	✓									Brazil
IAVI	✓									United States of America
Imperial College London	✓		✓							United Kingdom
Indian Institute of Science <sup>#,B,11</sup>	✓									India
Institut Pasteur		✓								France
Institut Pasteur de Côte d'Ivoire <sup>#,12</sup>	✓									Cote D'Ivoire (Ivory Coast)
Institute of Clinical Research Benin (IRCB)		✓						✓		Benin
JSS Academy of Higher Education and Research				✓						India
Leiden University <sup>#,B,13</sup>	✓									Netherlands

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Organisation	Basic research	Biologics	Drugs	Diagnostics	Unspecified R&D	IR	OR	HSPR	Other research	Country
<b>Academic and other research organisations</b>										
Lille 1 University	✓									France
Liverpool School of Tropical Medicine (LSTM) <sup>A,C</sup>	✓	✓	✓	✓				✓		United Kingdom
Madras Crocodile Bank Trust and Centre for Herpetology <sup>#,A,14</sup>	✓							✓	✓	India
Mahidol University <sup>#,15</sup>	✓	✓				✓				Thailand
Médecins Sans Frontières (MSF)	✓	✓								Switzerland
Mexican National Polytechnic Institute		✓								Mexico
National Autonomous University of Mexico (UNAM)		✓								Mexico
National University of Singapore (NUS) <sup>#,B,16</sup>	✓									Singapore
Nitte Mahalinga Adyanthaya Memorial Institute of Technology			✓							India
Northeastern National University	✓									Argentina
Nove de Julho University	✓									Brazil
Ohio State University	✓									United States of America
Paris Diderot University	✓									France
Queen Saovabha Memorial Institute <sup>#,17</sup>	✓									Thailand
San Jose State University		✓								United States of America
Sardar Patel Medical College		✓								India
SASTRA University		✓								India
Snakebite Healing and Education Society								✓		India
Scientific Institute of Rabat <sup>#,18</sup>	✓									Morocco
Technical University of Denmark <sup>#,B,19</sup>	✓			✓						Denmark

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<b>Academic and other research organisations</b>										
Texas A&M University	✓									United States of America
Tezpur University			✓	✓						India
Tropical Medicine Institute, Universidad Central de Venezuela <sup>#,20</sup>	✓									Venezuela
University Hospital Of Martinique	✓									Martinique
University of Arizona		✓								United States of America
University of Buenos Aires	✓									Argentina
University of Central Florida	✓									United States of America
University of East Anglia	✓									United Kingdom
University of Geneva	✓			✓						Switzerland
University of Kelaniya <sup>#,B,21</sup>	✓									Sri Lanka
University of Newcastle	✓	✓	✓							Australia
University of Oxford <sup>C,22</sup>	✓									United Kingdom
University of Sao Paulo	✓									Brazil
University of Sciences and Technology, Algeria <sup>#,23</sup>	✓									Algeria
University of Toronto	✓	✓								Canada
VU University Amsterdam <sup>#,B,24</sup>	✓									Netherlands

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Organisation	Basic research	Biologics	Drugs	Diagnostics	Unspecified R&D	IR	OR	HSPR	Other research	Country
<b>Pharmaceutical and biotechnology companies</b>										
Indriyam Biologics		✓		✓						India
INOSAN Biopharma SA		✓								Spain
Instituto Bioclon <sup>#,25</sup>		✓								Mexico
Kyntox Biotech				✓						India
Laboratorios Probiol*	✓									Colombia
Leopard Tech Labs	✓									India
Lorven Biologics Private Limited		✓								India
Luna Innovations		✓	✓							United States of America
MicroPharm Ltd <sup>*A</sup>		✓								United Kingdom
Ophirex Inc			✓							United States of America
SPRIM		✓								Mexico
Wiener Lab Group		✓								Argentina

\* Organisation reported zero data but have expressed potential to undertake R&D

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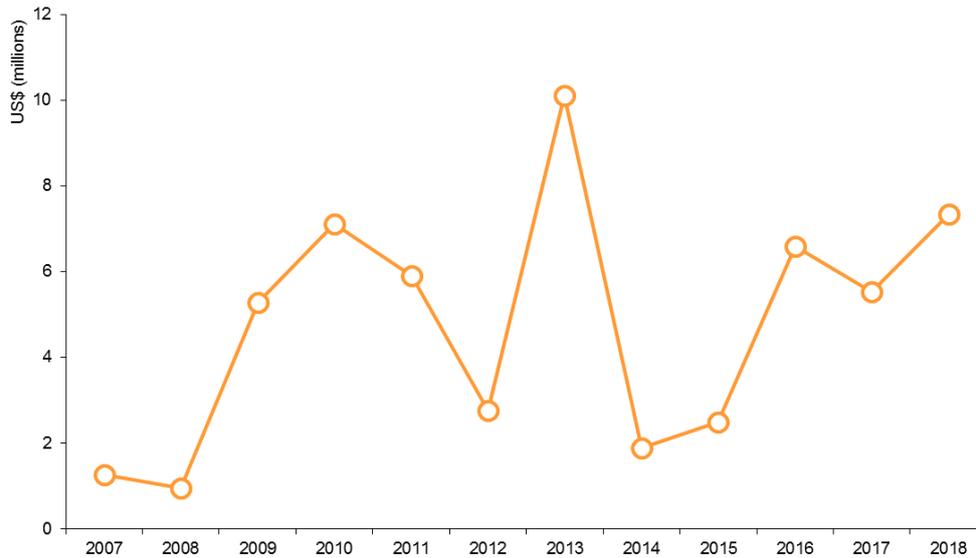
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# FINDINGS: GLOBAL FUNDING FOR SBE RESEARCH 2007-18

## FUNDING OVERVIEW

Figure 1. Total funding for SBE research 2007-2018



- Reported global funding for snakebite envenoming (SBE) research during the period 2007-2018 totalled \$57m. Overall, annual funding for SBE research has been relatively modest (averaging less than \$5m per year over the last 12 years, and only exceeding \$10m once during this period) and sensitive to changes from the small pool of funders which contribute to this area.

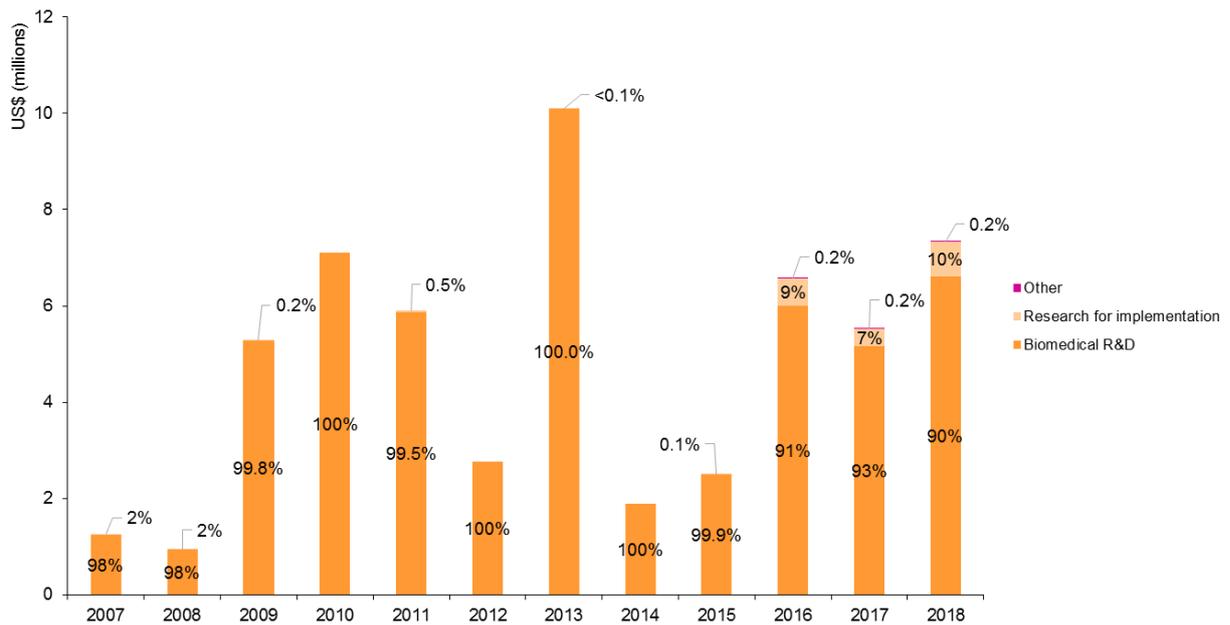
Figure 2. Impact of private sector funding on total SBE funding 2007-2018



- The variability of annual SBE research funding becomes less extreme when industry investment is excluded, and the drivers behind the three distinct funding peaks can be seen more clearly.

- The 2009-2011 and 2013 peaks in overall funding for SBE R&D were both driven primarily by industry investment in discovery & preclinical research of antivenoms, as well as the establishment of public research institutions in Brazil.
- In contrast, the increase since 2014 has been driven by public sector funders in the US and Europe. The increase in 2018 in particular – which took non-industry investment in SBE R&D to a record high – is linked to first time funding from two European public sector funders (UK DFID and the French ANR). These two organisations have traditionally been top funders of neglected disease biomedical R&D but have not historically funded SBE research, which could indicate a shift in perspective following the internationally coordinated advocacy campaign and subsequent inclusion of SBE on the WHO Neglected Tropical Disease list.

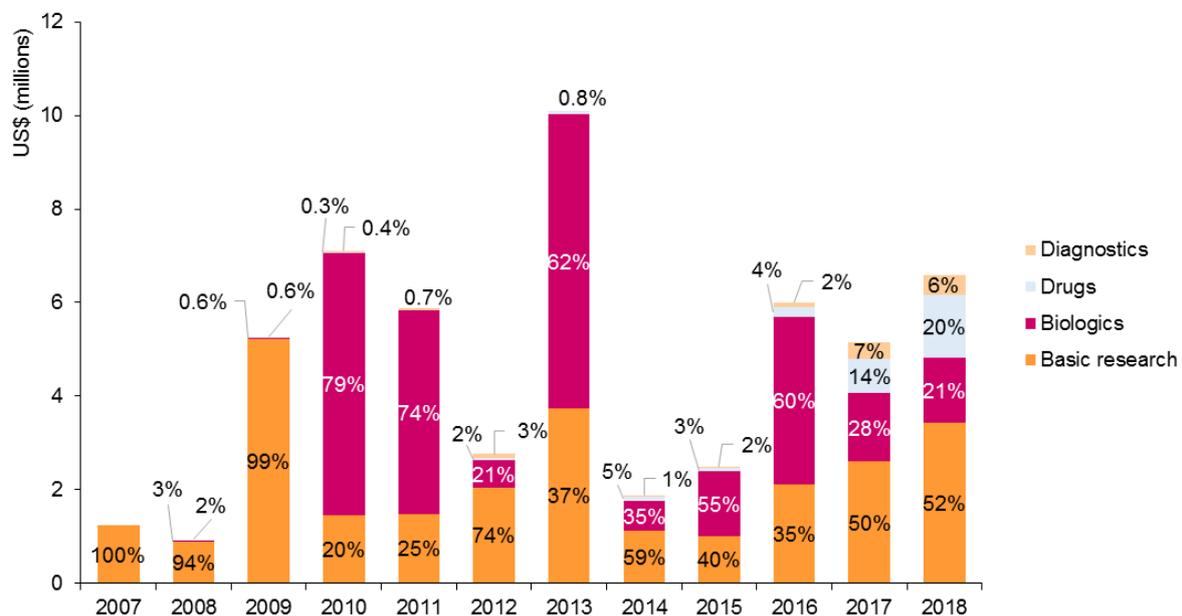
Figure 3. Total SBE funding by research type 2007-2018



- Funding for SBE research was almost exclusively for biomedical R&D from 2007-2015. Since 2016, funding for research for implementation has been growing but still remains significantly less than funding for biomedical R&D.
- Of total investment from 2007-2018, 97% (\$55m) was invested in biomedical R&D, with just 3.0% (\$1.7m) going towards research for implementation. Less than \$0.1m (<0.1%) went to other SBE research (non-biomedical product R&D).

## FUNDING FOR SBE BIOMEDICAL R&amp;D

Figure 4. SBE biomedical R&amp;D by product 2007-2018



- Total funding for SBE biomedical R&D over the last 12 years was \$55m.
- Just under half of all biomedical R&D funding from 2007-2018 was for basic research (\$26m, 47%), followed by biologics (\$25m, 46%) – with these two areas collectively accounting for 93% of all biomedical R&D funding over the 12 year period. The next largest share of funding was for drugs (\$2.7m, 4.8%), and diagnostics accounted for the remaining \$1.1m (2.0%).
- The two peaks in funding for basic research were linked to Brazilian public investment to set up research infrastructure applicable to SBE research; INCTTOX was formed in 2009, and in 2013 the new CeTICS centre was established at the Butantan institute.
- Industry investment in discovery & preclinical research was the driving force behind each of the increases in funding for biologic R&D seen in 2010, 2011, 2013 and 2016.
- Investment in drug R&D for SBE was negligible until 2016 when the Wellcome Trust invested in this area for the first time, and has since been increasing as a result of growing US DOD funding to US-based SMEs.
- Similarly, investment in diagnostic R&D has only taken off in the last three years with new funding from the UK NIHR and Indian BIRAC for the development of regionally-specific diagnostic kits.

Table 3. Top 12 funders of SBE biomedical R&D 2018

Funder	US\$ (millions)												2018 % of total
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	
US DOD	-	-	-	-	-	-	-	<0.1	0.4	0.8	0.9	1.1	16
UK DFID	-	-	-	-	-	-	-	-	-	-	-	0.8	11
Aggregate industry	-	-	-	5.0	4.2	0.1	5.8	<0.1	-	2.0	0.2	0.7	10
French ANR	-	-	-	-	-	-	-	-	-	-	-	0.6	9.6
US NSF	<0.1	-	-	-	-	-	-	-	-	0.2	0.7	0.5	7.2
Australian NHMRC	-	-	-	0.1	0.1	0.5	0.5	0.3	0.6	0.3	0.4	0.4	5.7
UK NHS	-	-	-	-	-	-	-	-	-	-	0.3	0.3	5.2
Wellcome Trust	0.2	<0.1	<0.1	-	-	-	-	-	-	0.2	0.4	0.3	4.9
Spanish CSIC	-	0.4	<0.1	<0.1	0.2	0.1	0.3	<0.1	0.1	0.1	0.2	0.3	4.7
UK MRC	-	-	-	-	-	-	-	0.1	0.3	0.3	0.7	0.3	4.5
Brazilian FAPESP	0.3	0.3	2.5	0.4	0.3	0.9	2.5	0.8	0.5	1.4	0.4	0.3	4.2
Swiss SNSF	-	-	-	-	0.2	0.2	-	-	-	-	-	0.3	4.0
Subtotal of top 12 <sup>^</sup>	1.2	0.9	5.3	7.1	5.9	2.8	10	1.8	2.4	5.8	5.0	5.8	88
<b>Total biomedical R&amp;D funding</b>	<b>1.2</b>	<b>0.9</b>	<b>5.3</b>	<b>7.1</b>	<b>5.9</b>	<b>2.8</b>	<b>10</b>	<b>1.9</b>	<b>2.5</b>	<b>6.0</b>	<b>5.2</b>	<b>6.6</b>	<b>100</b>

<sup>^</sup> Subtotals for 2007-2017 top 12 reflect the top funders for those respective years, not the top 12 for 2018.

- No reported funding

- In total, 52 organisations provided funding SBE biomedical R&D from 2007-2018. The geographical distribution of funders over the entire period was balanced with 27 organisations from HICs and 25 from LMICs. LMICs included: Argentina, Benin, Brazil, Burkina Faso, Cote d'Ivoire, Costa Rica, India, Mexico, Nigeria, Senegal and Tunisia.
- Brazilian FAPESP and industry have historically been the two top funders, but the makeup of the top funders has changed over time as the number of funders investing in this area of research grows. In 2007, only six organisations reported providing funding for SBE biomedical R&D – four of which were LMIC-based (Brazilian FINEP, Brazilian FAPESP, Institut Pasteur de Tunis and the Clodomiro Picado Institute).
- Gradually, more HIC funders have contributed funding to SBE biomedical R&D. Of the top 12 funders in 2018, seven organisations were European, four of which were UK-based. Only one funder – Brazilian FAPESP – was from an LMIC, with the remaining three funders coming from the US and Australia.
- Excluding industry investment, almost all biomedical R&D funding from the top 12 funders in 2018 was given to organisations based in the funder's own country (although a number of the research projects funded were undertaken abroad in countries with a high SBE burden).
- Just over a third (\$2.5m, 38%) of total funding in 2018 was contributed by the top three funders: the US DOD (\$1.1m, 16%), UK DFID (\$0.8m, 11%) and industry (\$0.7m, 10%). This is a much lower concentration from the top three funders than is seen in any of the neglected infectious diseases traditionally tracked in the G-FINDER report.
- The US DOD was the largest funder of biomedical R&D in 2018, and has steadily increased its funding - largely investment for broad spectrum drugs and antivenoms - every year since 2014.
- In 2018, two new European public funders invested in SBE research for the first time: the UK DFID gave funding to IAVI for a new consortium focusing on monoclonal antibody (mAb) therapies for SBE, and the French ANR which exclusively gave funding for basic research to francophone researchers.

Table 4. Top 12 recipients of SBE biomedical R&D funding 2018

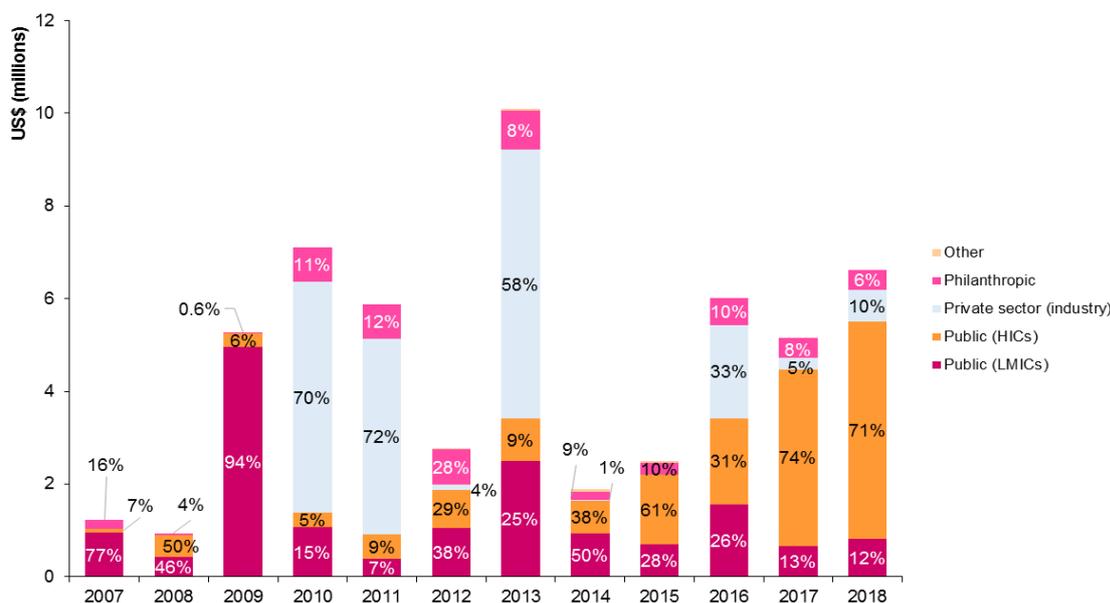
Recipient	US\$ (millions)												2018 % of total
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	
Aggregate industry	-	-	-	5.0	4.2	-	4.6	0.1	0.5	2.9	1.0	1.3	19
Liverpool School of Tropical Medicine (LSTM)	0.2	-	0.3	0.8	-	<0.1	0.2	0.3	0.5	0.5	1.2	0.9	13
IAVI	-	-	-	-	-	-	-	-	-	-	-	0.8	11
University of Newcastle, Australia	<0.1	<0.1	<0.1	0.1	0.1	0.2	0.2	<0.1	0.3	0.3	0.3	0.3	4.8
Biomedical Institute of Valencia	-	0.4	<0.1	<0.1	0.2	0.1	0.3	<0.1	0.1	0.1	0.2	0.3	4.7
Lille 1 University	-	-	-	-	-	-	-	-	-	-	-	0.3	4.5
University of Geneva	-	-	-	<0.1	0.3	0.3	-	<0.1	<0.1	<0.1	-	0.3	4.4
Institut Pasteur	-	-	-	-	-	-	-	-	-	-	-	0.2	3.4
University Hospital Of Martinique (UHM)	-	-	-	-	-	-	-	-	-	-	-	0.2	3.2
Mexican National Polytechnic Institute	-	-	-	-	-	-	-	-	-	-	0.2	0.2	3.1
Florida State University	-	-	-	-	-	-	-	-	-	<0.1	0.2	0.2	2.6
National Autonomous University of Mexico (UNAM)	-	-	-	-	-	0.1	0.1	-	-	-	-	0.1	2.2
Subtotal of top 12 <sup>^</sup>	1.2	0.9	5.3	7.1	5.9	2.7	9.9	1.7	2.4	5.7	4.4	5.1	77
Total biomedical R&D funding	1.2	0.9	5.3	7.1	5.9	2.8	10	1.9	2.5	6.0	5.2	6.6	100

<sup>^</sup> Subtotals for 2007-2017 top 12 reflect the top funders for those respective years, not the top 12 for 2018.

- No reported funding

- In total, 62 organisations received funding for SBE biomedical R&D from 2007-2018.
- Excluding industry, only two organisations from the top 12 in 2018 – LSTM and the University of Geneva – received funding from more than one funder, highlighting a reliance on single funders.
- The top three recipients in 2018 received 44% of all funding provided in 2018. This was the lowest concentration across all years, reflecting a sharp increase in the number of recipient organisations.
- The top recipient of SBE biomedical R&D funding in 2018 was industry, most of which was for drug development. Funding to industry in 2018 was exclusively external funding received with no self-funded research reported.
- The second-largest recipient was LSTM, which received funding for all four product categories in 2018, highlighting the diverse research being undertaken at this institution.
- Two universities from Mexico made it into the top 12 as a result of funding from industry for R&D into biologics.

Figure 5. SBE biomedical R&D funding by sector 2007-2018



- In total, the public sector accounted for well over half (\$32m, 58%) of all investment in SBE biomedical R&D from 2007-2018. The next largest share was from the private sector (industry), which was responsible for a third of total funding (\$18m, 33%), with the remainder coming from the philanthropic sector (\$5.2m, 9.4%).
- Public funding was evenly provided by HICs and LMICs, with both income groups providing \$16m (50% of total public funding) over the whole period.
- Industry funding has largely been driven by peaks in investment in discovery & preclinical research over just a few years rather than consistent amounts. Almost all (94%) industry investment over the 12 year period was provided in just four years (2010, 2011, 2013 and 2016).
- Public funding from LMICs has been relatively consistent over time, aside from two notable spikes in Brazilian public investment to set up research infrastructure applicable to SBE research.
- In contrast, the bulk of all funding from HIC public funders has come in recent years, with just under three-quarters (74%) of all HIC public funding coming in the four year period from 2015-2018, despite funding from HICs being reported for all twelve years. HIC funding has steadily been increasing since 2014 and peaked in 2018 at \$4.7m.
- Funding from philanthropic has been relatively consistent since 2010, but has never exceeded \$1.0m per year.

## FUNDING FOR SBE RESEARCH FOR IMPLEMENTATION

Figure 6. SBE research for implementation by research type 2007-2018



- Reported funding for SBE research for implementation has been negligible for most of the period from 2007-2018. There has been a marked increase in the amount of funding reported for health systems and policy research in the last three years, but funding for operational and implementation still remains very small.
- There is a clear gap in funding in this area with no funding reported in 2010, 2012 or 2014 for any of the research for implementation categories, and funding for implementation research reported in only 2011.

Table 5. Funders of SBE research for implementation 2018

Funder	US\$ (millions)													2018 % of total
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018		
UK NHS	-	-	-	-	-	-	-	-	-	-	0.3	0.3	48	
The Hennecke Foundation	-	-	-	-	-	-	-	-	-	-	-	0.1	17	
The Lilian Lincoln Foundation	-	-	-	-	-	-	-	-	-	-	-	0.1	17	
Sir Halley Stewart Trust	-	-	-	-	-	-	-	-	-	<0.1	<0.1	<0.1	6.6	
Snakebite Healing and Education Society	-	-	-	-	-	-	-	-	-	-	-	<0.1	5.1	
Wellcome Trust	<0.1	<0.1	<0.1	-	-	-	-	-	-	-	-	<0.1	3.6	
World Health Organization (WHO)	-	-	-	-	-	-	-	-	-	-	-	<0.1	2.1	
Aggregate industry	-	-	-	-	-	-	-	-	-	-	<0.1	-	-	
Dutch DGIS	-	-	-	-	-	-	-	-	-	0.5	-	-	-	
Nigerian Federal Ministry of Health	-	-	-	-	<0.1	-	-	-	-	<0.1	-	-	-	
African Society of Venomology (ASV)	-	-	-	-	-	-	-	-	-	<0.1	-	-	-	
Cameroon Ministry of Public Health	-	-	-	-	-	-	-	-	-	<0.1	-	-	-	
<b>Total research for implementation funding</b>	<b>&lt;0.1</b>	<b>&lt;0.1</b>	<b>&lt;0.1</b>	<b>-</b>	<b>&lt;0.1</b>	<b>-</b>	<b>&lt;0.1</b>	<b>-</b>	<b>&lt;0.1</b>	<b>0.6</b>	<b>0.4</b>	<b>0.7</b>	<b>100</b>	

- No reported funding

- There were only seven funders of research for implementation for SBE in 2018, and only 16 funders in total who reported investment in this area over the full period covered.
- Six of the seven funders of SBE research for implementation in 2018 were from HICs, and all funding from these six organisations was awarded to HIC-based recipients.
- The Nigerian Federal Ministry of Health was the only participant to report any funding for implementation research, which was in 2011.

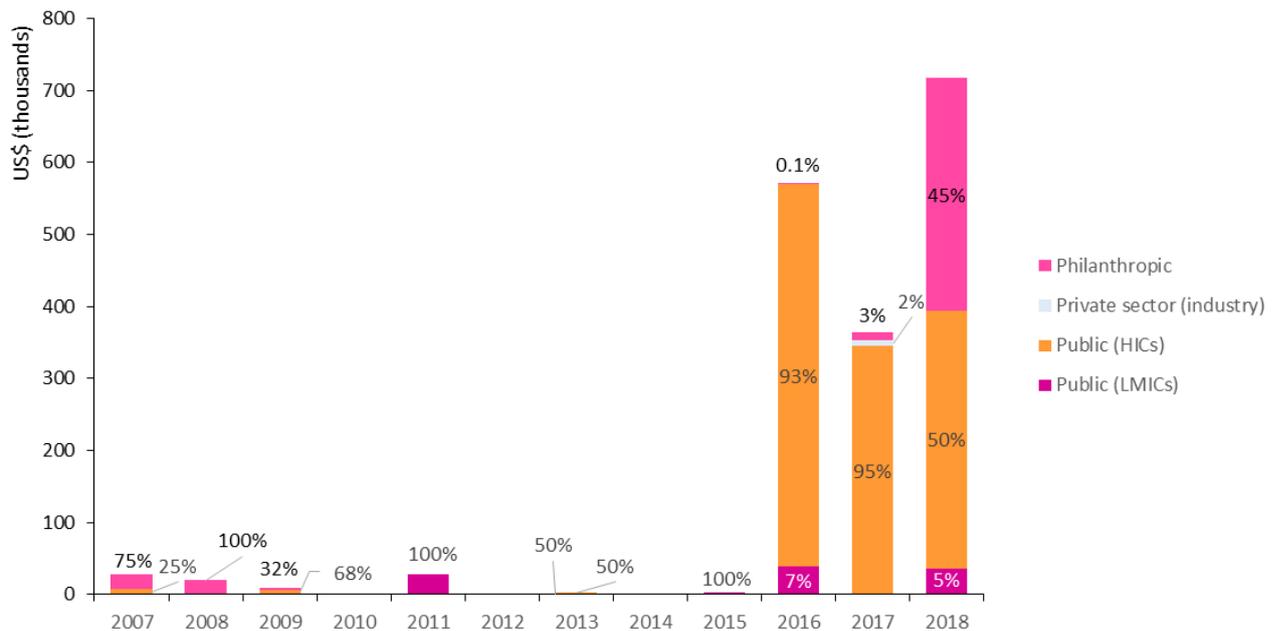
Table 6. Recipients of SBE research for implementation funding 2018

Recipients	US\$ (millions)													2018 % of total
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018		
Liverpool School of Tropical Medicine (LSTM)	-	-	-	-	-	-	-	-	-	<0.1	0.4	0.4	54	
Health Action International (HAI)	-	-	-	-	-	-	-	-	-	0.5	-	0.3	35	
University of Melbourne (including AVRU)	-	-	-	-	-	-	-	-	-	-	-	<0.1	5.7	
Snakebite Healing and Education Society	-	-	-	-	-	-	-	-	-	-	-	<0.1	5.1	
Butantan Institute	-	-	-	-	-	-	-	-	<0.1	<0.1	<0.1	-	-	
Institute of Clinical Research Benin (IRCB)	-	-	-	-	-	-	<0.1	-	-	<0.1	-	-	-	
Nigerian Federal Ministry of Health	-	-	-	-	<0.1	-	-	-	-	<0.1	-	-	-	
French IRD	<0.1	-	<0.1	-	-	-	<0.1	-	-	-	-	-	-	
University of Newcastle, Australia	<0.1	<0.1	<0.1	-	-	-	-	-	-	-	-	-	-	
<b>Total research for implementation funding</b>	<b>&lt;0.1</b>	<b>&lt;0.1</b>	<b>&lt;0.1</b>	<b>-</b>	<b>&lt;0.1</b>	<b>-</b>	<b>&lt;0.1</b>	<b>-</b>	<b>&lt;0.1</b>	<b>0.6</b>	<b>0.4</b>	<b>0.7</b>	<b>100</b>	

- No reported funding

- Only four organisations received funding for research for implementation in 2018, and the only LMIC recipient (Snakebite Healing and Education Society, India) was self-funded research. In total, just nine organisations received funding for research for implementation from 2007-2018.
- LSTM received over half of all research for implementation investment in 2018 (and essentially all investment in 2017) as a result of a NIHR project.
- The majority of organisations only engaged in health systems and policy research, and just three organisations were active across more than one area of research for implementation:
  - The Butantan Institute and French IRD were both active in health systems and policy research and operational research, while the Nigerian Federal Ministry of Health engaged in implementation research and operational research.

Figure 7. SBE research for implementation funding by sector 2007-2018



- The largest share of SBE research for implementation funding was contributed by public funders from HICs (\$1.2m, 72%), followed by philanthropic organisations (\$0.4m, 22%). The remaining funding came from public funders in LMICs (\$0.1m, 6.1%).
- The private sector was largely absent from this landscape, only funding health systems and policy research in 2017.

## FUNDING FOR OTHER NON-BIOMEDICAL R&D

Brazilian FAPESP was the only funder which reported investment into other (non-biomedical product development) research related to SBE. This was for a three-year project testing the feasibility and acceptability of protective clothing to prevent snakebite in pineapple farmers.

## ANNEXE A – INDEPENDENT INTERNATIONAL EXPERTS

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EXPERT	ORGANISATION
Jordan Benjamin	Asclepius Snakebite Foundation
Dr Jean-Philippe Chippaux	French Institute of Research for Development
Ben Waldmann	Health Action International
Dr David Williams	Global Snakebite Initiative

## ANNEXE B – SURVEY PARTICIPANTS

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- AntivenomSwazi Foundation
- Argentinian Ministry of Science, Technology and Productive Innovation (MINCYT)
- Argentinian National Institute of Biological Production (ANLIS)
- Australian Department of Foreign Affairs and Trade (DFAT)
- Australian National Health and Medical Research Council (NHMRC)\*
- Biomedical Institute of Valencia (IBV)
- Biotechnology Industry Research Assistance Council (BIRAC)
- Brazilian Center for Production and Research of Immunobiology (CPPI)
- Brazilian Development Bank (BNDES)
- Brazilian Innovation Agency (FINEP)
- Brazilian Ministry of Health: Department of Science and Technology (DECIT)
- Brazilian Support Foundation for Research in the State of Bahia (FAPESB)
- Brazilian Support Foundation for Research in the State of Minas Gerais (FAPEMIG)
- Brazilian Support Foundation for Research in the State of Rio Grande do Sul (FAPERGS)
- Brazilian Support Foundation for Research in the State of São Paulo (FAPESP)
- Brazilian Support Foundation for Scientific and Technological Development in the State of Ceará (FUNCAP)
- Brazilian Support Foundation for the Development of Scientific and Technological Actions and Research in the State of Rondônia (FAPERRO)
- Butantan Institute, Fundacao Butantan
- Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM)
- CSL Ltd (including Seqirus)
- Drugs for Neglected Diseases initiative (DNDi)
- Dutch Ministry of Foreign Affairs (DGIS)
- European Commission (EC)\*
- Ezequiel Dias Foundation (FUNED)
- French National Research Agency (ANR)
- French Research Institute for Development (IRD)
- Gates Foundation\*
- Hamish Ogston Foundation
- Health Action International (HAI)
- Indian Department of Biotechnology, Ministry of Science and Technology (DBT)
- Indian Department of Science and Technology (DST)
- IndianSnakes.org
- Innovate UK\*
- INOSAN Biopharma SA
- Institut Pasteur
- Institut Pasteur de Maroc
- Institut Pasteur de Tunis
- Institute of Clinical Research Benin (IRCB)
- International AIDS Vaccine Initiative (IAVI)
- Kofi Annan Foundation
- Laboratorios Probiol SA
- Liverpool School of Tropical Medicine (LSTM)
- Médecins Sans Frontières (MSF)
- MicroPharm Ltd
- Nigerian Federal Ministry of Health
- Ophirex Inc
- Snakebite Healing and Education Society

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\* Denotes organisations where funding data was taken from publicly available sources

- South African National Health Laboratory Service (NHLS, including South African Vaccine Producers (SAVP))
- Swiss National Science Foundation (SNSF)\*
- The Wellcome Trust
- UK Department for International Development (DFID)
- UK Department of Health and Social Care (DHSC)\*
- UK Medical Research Council (MRC)
- UK National Health Service (NHS, including National Institute for Health Research (NIHR))\*
- University of Arizona
- University of Costa Rica (including the Clodomiro Picado Institute)
- University of Geneva
- University of Melbourne (including the Australian Venom Research Unit, AVRU)
- University of Toronto
- US Department of Defense (DOD)\*
- US National Institutes of Health (NIH)\*
- US National Science Foundation (NSF)\*

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\* Denotes organisations where funding data was taken from publicly available sources

## ANNEXE C – SNAKEBITE ENVENOMING SCOPE DOCUMENT

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This document sets out the types of research activities that are included in our survey of the global investment landscape for snakebite envenoming (SBE) research. These research activities fall into two main overarching domains, each with different sub-domains:

- I. Biomedical research & development (R&D)
  1. Basic research
  2. Product development
  
- II. Research for implementation
  3. Operational research (OR)
  4. Implementation research (IR)
  5. Health policy and systems research (HPSR)

Data on biomedical R&D for FY2018 is being collected as part of the 2019 G-FINDER survey of funding for neglected disease R&D. Data on historical investments in biomedical R&D for SBE, and all data on research for implementation for SBE is being collected via a separate, targeted survey.

This project **ONLY** includes SBE research that is explicitly targeted at low- and middle-income countries (LMICs) needs. For the purpose of this project, the [World Bank's definitions](#) of LMICs are used.

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## I Biomedical research & development

Biomedical R&D includes both basic research and product development. Product development is further subcategorised depending on the type of technology being developed, as well as the stage of research.

For the purposes of this project, **ONLY** product development R&D into drugs, biologics and diagnostics are included.

For a detailed description of activities included under the biomedical R&D category please go to the [Annexe D](#).

### 1 Basic research

*Studies that increase scientific knowledge and understanding about the disease, disease processes, pathogen or vector, but which are not yet directed towards a specific product.*

**Examples:**

Project title	Project description
Vulnerability to snakebite envenoming: a global mapping of hotspots. <sup>22</sup>	A quantitative study estimating and mapping the global burden of snakebite envenoming.
Proteomic Characterization of Two Medically Important Malaysian Snake Venoms, Calloselasma rhodostoma (Malayan Pit Viper) and Ophiophagus hannah (King Cobra). <sup>26</sup>	A high-throughput proteomic study characterizing and quantifying the composition of venom and their pathological activities.

### 2 Product development

*Research activities and processes necessary to develop and improve new biomedical technologies designed to diagnose, prevent, cure or treat disease; including discovery and design, preclinical and clinical or field development, and other activities essential for successful development and uptake of new technologies.*

*The following activities are included under product development:*

- **Drugs**
  - Discovery and preclinical
  - Clinical development - Phase I
  - Clinical development - Phase II
  - Clinical development - Phase III
  - Clinical development - Baseline epidemiology
  - Clinical development - Unspecified
  - Post-registration studies
- **Biologics**
  - Discovery and preclinical
  - Clinical development - Phase I
  - Clinical development - Phase II
  - Clinical development - Phase III

- Clinical development - Baseline epidemiology
- Clinical development - Unspecified
- Post-registration studies
- **Diagnostics**
  - Discovery and preclinical
  - Clinical evaluation
  - Operational research for diagnostics

**Examples:**

Project title	Project description
In vivo neutralization of dendrotoxin-mediated neurotoxicity of black mamba venom by oligoclonal human IgG antibodies. <sup>27</sup>	A preclinical study trialling a recombinant antivenom based on human immunoglobulin G (IgG) monoclonal antibodies to neutralise neurotoxicity of black mamba venom in rodents.
Varespladib (LY315920) Appears to Be a Potent, Broad-Spectrum, Inhibitor of Snake Venom Phospholipase A2 and a Possible Pre-Referral Treatment for Envenomation. <sup>28</sup>	An in vivo proof-of-concept study of Varespladib as a broad-spectrum PLA2 inhibitor in rodents.
Use of Molecular Diagnostic Tools for the Identification of Species Responsible for Snakebite in Nepal: A Pilot Study. <sup>29</sup>	A pilot study testing the use of PCR to immunologically identify snake species responsible for snakebite.

## II Research for implementation

In public health, research for implementation is used to understand the barriers that prevent access to life-saving tools, and identify ways of removing those barriers. The research methodologies and tools that are utilized vary according to the type of problem to be addressed.

Although there is no single, universally accepted definition of research for implementation, it is generally agreed to represent a continuum consisting of three distinct but potentially overlapping domains (operational research, implementation research, and health systems and policy research), as described below.

### 3 Operational research (OR)

Adapted from Zachariah et al. 2009<sup>30</sup>

Operational research is “the search for knowledge on health interventions, strategies, or tools that can enhance the quality, effectiveness, or coverage of programmes *in which the research is being done*.” Accordingly, operational research is specific to the context and setting (e.g. programme, location) in which it is conducted. Operational research is strongly linked to monitoring and evaluation of health programmes, and often uses data that is routinely collected as part of programmatic activities.

The key elements of operational research are that the research questions are generated by identifying the constraints and challenges encountered during the implementation of programme activities (prevention, care, or treatment), and the answers provided to these questions should have direct, practical relevance to solving problems and improving health-care delivery.

Operational research involves three main types of methods: descriptive, case-control, and retrospective or prospective cohort analysis. Basic science research and randomised controlled trials should not be included as operational research. The randomised controlled trial determines efficacy of an intervention in a strictly controlled environment with inclusion and exclusion criteria, whereas operational research should assess effectiveness within routine settings. From a biomedical/health technology perspective, operational research is focused on existing approved products, rather than investigational candidates.

#### Examples:

Project title	Project description
Incidence and treatment of snakebites in West Bengal, India. <sup>31</sup>	A retrospective study to understand the factors associated with poor prognosis of snakebite cases treated with antivenom in a single tertiary hospital in the Paschim Medinipur district of West Bengal.
The effect of pre-hospital care for venomous snake bite on outcome in Nigeria. <sup>32</sup>	A prospective study to identify common first aid practices in response to snakebite and their impact on clinical outcomes in Northern Nigeria.

## 4 Implementation research (IR)

Adapted from TDR Implementation Research Toolkit 2017<sup>33</sup> and Proctor et al. 2011<sup>34</sup>

Implementation research is the systematic approach to recognising, understanding and addressing health system and implementation bottlenecks, identifying optimal implementation options for a given setting, and promoting the uptake of research findings into policy and practice. Implementation research is demand-driven and underlying research questions are framed according to needs identified by relevant stakeholders and/or implementers in a given health system. It is often multidisciplinary, and can be applied at multiple levels of healthcare systems and community practices. Although it is relevant to local contexts and needs, implementation research typically results in generalizable knowledge that can be applied across different contexts and settings through scale-up and other implementation processes.

In one of the more well-established frameworks for implementation research, Proctor et al identified eight different dimensions of implementation outcomes: acceptability; adoption; appropriateness, feasibility, fidelity, cost, coverage and sustainability.

### Examples:

Project title	Project description
Cost-Effectiveness of Antivenoms for Snakebite Envenoming in 16 Countries in West Africa. <sup>35</sup>	Assessment of cost-effectiveness of providing antivenoms in West Africa by comparing costs associated with antivenom treatment against their health benefits in decreasing mortality.
Snakebite: An Exploratory Cost-Effectiveness Analysis of Adjunct Treatment Strategies. <sup>36</sup>	An exploratory study using threshold approach to compare the cost-effectiveness of two approaches to manage snakebite: 1) antivenom and supportive care and 2) antivenom/adjunct combination strategy with supportive care.
Acceptability study of protective boots among farmers of Taungdwingyi Township. <sup>37</sup>	Acceptability study of fang-proof protective boots amongst farmers in Myanmar to prevent envenomation from Russell's viper.

## 5 Health Policy and Systems Research (HPSR)

Adapted from Alliance for Health Policy and Systems Research Briefing Note 1, 2007<sup>38</sup> and Health Policy and Systems Research – A Methodology Reader<sup>39</sup>

Health policy and systems research seeks to understand and improve how societies organize themselves in achieving collective health goals, and how different actors interact in the policy and implementation processes to contribute to policy outcomes. It is by nature multidisciplinary, with a strong emphasis on social sciences, economics, and anthropological investigations. It is distinct from biomedical R&D and clinical effectiveness studies, as well as from routine surveillance and epidemiological studies. Although it can overlap with elements of implementation research, it differs in that it is not primarily concerned with service or programme delivery.

HSPR can focus on the health system as a whole or one or more of its constituent parts. Traditional approaches to HSPR focused on the six health systems 'building blocks' (service delivery; information and evidence; medical products and technologies; health workforce; health financing; leadership and governance), but there is increasing recognition of the need to also focus on people (as individuals, families, communities and larger populations) and

institutions, as well as the connections between health systems and other related systems (e.g. education, economic development, ecology, etc.).<sup>40</sup>

HSPR can be situated at the international, national, subnational or local levels, or their intersections. In the local arena, HSPR looks not only at service provision and systems of local health governance, but all activities related to the provision, protection, and promotion of health in local communities and households, including community-based approaches for populations outside traditional health systems.<sup>41</sup>

### Examples

Project title	Project description
Consequences of Neglect: Analysis of the Sub-Saharan African Snake Antivenom Market and the Global Context. <sup>42</sup>	A global survey to understand the status and the associated factors affecting the production of antivenom manufactured specifically for sub-Saharan Africa.
Needs and availability of snake antivenoms: relevance and application of international guidelines. <sup>43</sup>	A survey of antivenom manufacturers, National Health Authorities and poison centres to determining key factors limiting the successful implementation of WHO Guidelines within the international industry and state institutions
A study of the current knowledge base in treating snake bite amongst doctors in the high-risk countries of India and Pakistan: does snake bite treatment training reflect local requirements? <sup>44</sup>	A descriptive study to evaluate the snakebite management skills amongst doctors in India and Pakistan; and to determine if there are critical gaps in treating snakebite cases, and if so, how to address them.
Community-based audits of snake envenomations in a resource-challenged setting of Cameroon: case series. <sup>45</sup>	A descriptive study highlighting community-based audits as a pivotal tool for resource-constraint settings to gather data and indicate key public health interventions to curb snakebite-related mortality.

### III Other

Other SBE-related research that cannot be categorised using the definitions above (but which is not outside the scope of the survey – see ‘Exclusions’ below) should be included as *other research*.

### Examples

Project title	Project description
Prevention of krait bites by sleeping above ground: preliminary results from an observational pilot study. <sup>46</sup>	Non-pharmaceutical tools and interventions intended to prevent snakebite envenoming
Evaluation of Snake Repellents against the Principal Venomous Snakes of India in Laboratory Condition. <sup>47</sup>	Products that are developed for veterinary purposes to prevent snakebite envenoming

## IV Exclusions

Our analysis will not include investment in research that is not designed to develop products that will address snakebite envenoming in LMICs. As such, funding for the following research activities would be excluded:

- Venomics research for pharmaceutical purposes not related to the development of products to treat snakebite envenoming (e.g. Drug development from Australian elapid snake venoms and the Venomics pipeline of candidates for haemostasis: Textilinin-1 (Q8008), Haempatch™ (Q8009) and CoVase™ (V0801).<sup>48</sup>)
- R&D into products for snakes which are not medically important in LMICs (e.g. Randomized, Double-Blind, Placebo-Controlled Study: CroFab® vs Placebo for Copperhead Snake Envenomation (Copperhead).<sup>49</sup>)
- R&D into general supportive, nutritional and symptomatic therapies.

## ANNEXE D – G-FINDER NEGLECTED DISEASE R&D SCOPE DOCUMENT

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### BASIC RESEARCH

*Studies that increase scientific knowledge and understanding about the disease, disease processes, pathogen or vector, but which are not yet directed towards a specific product.*

### NATURAL HISTORY AND EPIDEMIOLOGY

- Basic mechanisms of disease transmission
- Disease prevalence in relation to human genotype, strain variation, and inoculation rates
- Genetic diversity and phylogeny
- Epidemiological research on the roles of human behaviour and effects of specific host genotypes on disease transmission
- Epidemiological research on host genetic factors influencing the prevalence of disease (e.g., sickle cell, HLA type, Rh factor) or the impact of disease in select host genotypes
- Epidemiological research on the distribution of pathogen, vectors and the prevalence of morbidity and mortality due to the disease that is NOT related to the development of a specific product
- Epidemiological research on antigenic variability; population studies of human immunity to the disease
- Epidemiology of drug resistance or evolutionary studies on resistance development for established, existing drugs
- Epidemiological research related to vector behaviour and ecology, and vector control

### IMMUNOLOGY OF DISEASE

- Defining signalling pathways of immune function (mechanisms of systemic and/or mucosal immunity)
- Interaction and impact of the signalling pathways with the pathogen
- Development of assays or tools potentially useful for drug, vaccine, microbicide, or biologic research & development
- Identification of immune correlates of protection, including *in vivo* and *in vitro* studies on the protective immune response (cellular, humoral, and/or mucosal)
- Investigating the immune response to particular antigens; studies of specific antigens or immunogens proposed as vaccine or biologic candidates
- Development of animal models to determine immune correlates of protection
- Genetics of the immune response to the disease and effects of antigen polymorphism or genetic diversity on specific vaccine or biologic candidates (as recognised from field studies)

### BIOLOGY OF DISEASE

- Structure and morphology of different developmental stages
- Host-parasite interactions and the biology of pathogen interaction with the vector host
- Biology of invasion of host cells (entry mechanisms)
- Localisation of pathogen proteins or antigens

- Development of culture and purification tools to assist in study of the pathogen
- Descriptions of pathogenic species and characterisation of strains or subtypes in animal models (course of infection, susceptibility of different hosts)
- *In vitro* studies of interactions between the pathogen and other infectious agents (e.g. Epstein-Barr virus)

## BIOCHEMISTRY OF THE PATHOGEN

- Metabolism and nutrition
- Protein sequencing, enzymology, and protein and enzyme characterisation (including antigen analysis)
- Signal transduction; translation, processing and export of proteins
- Glycosylation, Glycosylphosphatidylinositol (GPI) anchors, transporters, ion channels, mitochondrial metabolism, and electrophysiology studies
- Influence of the pathogen on host-cell biochemistry
- Characterisation of antigen/protein diversity of pathogenic strains and subtypes
- Characterisation of proteins and molecular basis for host-cell invasion
- Analysis & characterisation of drug-resistant strains and studies probing drug resistance mechanism/s or pathways
- Non-specific research on the pathogen or host targets to identify potential drug, vaccine, biologic, or diagnostic targets (i.e. target identification)

## GENETICS OF THE PATHOGEN

- Studies on chromosomes; genomic maps; genetic crosses
- Cloning and sequencing of genes; cDNAs for functional proteins (including drug targets and vaccine candidates)
- Expression of proteins from cloned genes; RNA analyses
- Control and timing of gene expression; post-transcriptional processing
- Analysis and characterisation of genes involved in drug resistance
- Genetics of antigenic variability
- Techniques for the genetic transformation of the pathogen
- Tests for genotyping the pathogen for laboratory use

## BIOINFORMATICS AND PROTEOMICS

- Microarray analysis
- Genome annotation - gene predictions
- Comparative genomics, sequence alignment, genome assembly
- Variation, single nucleotide polymorphisms (SNPs)
- Database applications, data mining tools
- Structural and functional genomics
- Structural and functional proteomics
- Proteome analysis, protein structure alignment

## PATHOPHYSIOLOGY AND DISEASE SYMPTOMS

- Clinical diagnosis and clinical observations of the disease presentation and pathophysiology in humans and in animals
- The role of nutritional status in determining disease severity and treatment effectiveness
- Histopathology of the disease in humans and in animals

- The mechanisms of pathology of the disease including the role of the host immune system, and expression of adhesion molecules
- Development of improved animal models to study disease pathophysiology, to evaluate the biological properties of drugs and microbicides
- Identification of biomarkers for diagnostics or therapeutic monitoring
- Studies of the mechanisms by which particular susceptible/resistant mammalian host genotypes exert their effect
- Research on the effects of host co-morbidities and secondary effects of pathogen invasion (e.g., research on anaemia /neurological effects of malaria)
- Interactions between the disease and other relevant concurrent infections, including determining timing and establishment of infection

## VECTOR BIOLOGY, BIOCHEMISTRY, AND GENETICS

- Characterisation of vector behaviour and ecology
- Studies of vector susceptibility to infection; studies of parasites and pathogens of vectors (including potential biological control agents)
- Identification of genes responsible for disruption of parasite/virus growth, genetic transformation of vectors, and insect transposable elements
- Target identification of vector sites that may become the subject of *in vitro* screening or molecular design
- Development of tests for vector identification, taxonomy and systematics, and for the identification of infected vectors
- Studies evaluating resistance development, including the genetics and transmission of pesticide resistance

## DRUGS

*Research activities and processes necessary to develop and improve new small molecule compounds specifically designed to prevent, cure or treat neglected diseases; including drug discovery or design, preclinical and clinical development and other activities essential for successful drug development and uptake.*

## DISCOVERY AND PRECLINICAL

*Research activities targeted at discovering and optimising investigational small molecule compounds including the processes needed to allow new chemical entities to proceed to human trials; including:*

- Target validation, characterisation, and selection
- High throughput screening, lead optimisation
- Development of analytical tests for assaying drugs, including the development of animal models
- Research on drugs from natural products; identification and characterisation of active ingredient
- Research on the effects of drug treatment on immune status
- Measurement of the activity of potential drugs *in vitro* and in animal models; including safety and efficacy studies necessary to satisfy Investigational New Drug (IND) requirements
- Studies evaluating the activity of new drugs on drug-resistant strains, their effect on genes involved in drug resistance, or their effect on resistance pathways
- Development of tests for drug susceptibility of the pathogen for research purposes
- Drug pharmacokinetic, toxicity and metabolism studies *in vitro* and in animal models, including bioavailability, adsorption, metabolism, and excretion (ADME) studies

- Chemistry and synthesis of drugs, including process and scale-up manufacture, production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) batch for toxicology studies; and other Chemistry and Manufacture Control (CMC) activities required to allow new chemical entities to proceed to human trials
- Preparation of Investigational New Drug (IND) application for regulatory submission
- Optimisation and manufacturing of new formulations to support label-expansion\* for new patient sub-populations (e.g. infants, pregnant women)

## CLINICAL DEVELOPMENT - PHASE I

*First-in-human clinical trials to determine safety and tolerability of investigational new drugs in a small group of patients or healthy volunteers, including:*

- Phase Ia single ascending dose studies to determine pharmacokinetics, pharmacodynamics, and maximum tolerated dose
- Phase Ib multiple ascending dose studies to determine the pharmacokinetics, pharmacodynamics, safety and tolerability of multiple doses
- Trials of food effect or drug-drug interactions

## CLINICAL DEVELOPMENT - PHASE II

*Clinical trials to determine the efficacy, safety and therapeutic dose of investigational new drugs in a small set of human subjects (up to several hundred), including:*

- Phase IIa proof of concept studies to demonstrate clinical efficacy or biological activity
- Phase IIb dose-finding studies to determine dose with optimum biological activity with minimal adverse effects

## CLINICAL DEVELOPMENT - PHASE III

*Clinical trials to support the registration of investigational new drugs or label-expansion of already registered drugs in a trial population large enough to provide statistical significance (from several hundred to several thousand)*

- Regulatory standard clinical trials to assess effectiveness of a new drug against current 'gold standard'
- Regulatory standard clinical trials that support a formal registration for label-expansion\* of an existing drug to a new disease or patient group (e.g. paediatric patients, pregnant women or HIV-positive patients)
- Regulatory standard clinical trials that support formal registration for label-expansion\* of an existing drug to a new use, such as intermittent preventative therapy and pre-exposure prophylaxis

## CLINICAL DEVELOPMENT - BASELINE EPIDEMIOLOGY

*Studies evaluating potential trial site populations to confirm disease incidence, prevalence or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation and presentation of clinical trial data; including:*

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\* Label-expansions refer to changes to drugs or their labels after they have been approved. This includes changes in manufacturing, recommended patient population and/or formulation. To change a label, market a new dosage or strength of a drug, or change the way a drug is manufactured, the company must submit a supplemental new drug application (sNDA) to regulatory authorities to obtain marketing approval

- Epidemiological studies directly linked to the conduct or support of clinical trials of products in development, in order to assess or validate the epidemiology of disease, disease incidence, or health of target populations at trial sites
- Preliminary studies of morbidity and mortality at potential clinical trial sites, where these studies are directly linked to planned product trials
- Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

## CLINICAL DEVELOPMENT - UNSPECIFIED

*Other costs required to support clinical testing of investigational new drugs as needed for regulatory approval; including:*

- Infrastructure and site development costs directly associated with the conduct of clinical trials for drug development in LMICs (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)
- Further pharmaceutical development to generate the final clinical formulation, dosage form and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- Compiling of all non-clinical and clinical data for submission of a New Drug Application (NDA) to regulatory authorities
- Behavioural research prior to registration relating to risk assessment, factors affecting adherence to protocol, and product acceptability
- Protocol development, investigator meetings, Good Clinical Practice (GCP)-monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB), and trial audits

## POST-REGISTRATION STUDIES

*Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved drugs so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled use of new drugs by patients. Also includes studies conducted after regulatory approval that assess drug effectiveness in the wider population or which are necessary to support product use in LMICs.*

- Pharmacovigilance and post-registration studies of newly registered drugs to assess adverse events, toxicology and safety
- Effectiveness studies and head-to-head comparator studies of newly registered drugs (versus other therapies or interventions)
- Cost-effectiveness studies of newly registered drugs
- Treatment interactions and population level studies (of newly registered products e.g., pharmaco-epidemiological and resistance studies)
- Behavioural research post-registration of new drugs relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- Case history reports and assessment of long-term prophylaxis using newly registered drugs in communities in LMICs

## BIOLOGICS

*Research activities and processes necessary to develop and improve investigational biological agents specifically intended to prevent or treat infection; including design, preclinical and clinical development, and other activities essential for successful development and uptake. This includes broadly neutralising monoclonal antibodies (bNAbs); polyclonal antibodies; and other bio-therapeutics such as peptide-, DNA- and RNA-based synthetic molecules. Please see section X for disease-specific restrictions to research activities in this category.*

## DISCOVERY AND PRECLINICAL

*Research activities targeted at discovering and optimising investigational biologics and including the processes necessary to allow a candidate biologic to proceed to human trials; including:*

- Studies supporting novel biologic design including target validation, characterisation and selection
- Candidate screening and lead optimisation
- Development of analytical tests for assaying biologics, including the development of animal models
- Evaluation of biologic technologies (e.g. adjuvants, delivery systems) to improve the immunogenicity or delivery of an identified candidate
- Biologic pharmacokinetic, toxicity and metabolism studies in vitro and in animal models, including bioavailability, adsorption, metabolism, and excretion (ADME) studies
- Preclinical safety and immunogenicity studies with candidate biologics, including use or development of functional assays
- Preclinical animal studies, challenge models, and studies addressing the correlation between in vitro models, animal models and field results necessary to satisfy Investigational New Drug (IND) requirements
- Process development and scale-up manufacture, including production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) batches for regulatory toxicology studies and other Chemistry and Manufacture Control (CMC) activities required to allow a candidate biologic to proceed to human trials
- Research on safety and regulatory considerations (e.g. validation of preclinical assays to permit registration)
- Preparation of an Investigational New Drug (IND) application for regulatory submission
- Optimisation of biologic candidates for global use (cheaper, more stable, ease of administration, addition of LMIC-specific targets)

## CLINICAL DEVELOPMENT – PHASE I

*First-in-human clinical trials to determine the safety and tolerability of investigational new biologics in a small group of patients or healthy volunteers, including:*

- Phase Ia studies assessing safety, dosing and immunogenicity in human volunteers; including, pharmacokinetic dynamics and tolerance in healthy volunteers.
- Phase Ib studies assessing safety, dosing and immunogenicity in clinically exposed or high-risk populations

## CLINICAL DEVELOPMENT – PHASE II

*Clinical trials to determine the efficacy, safety and therapeutic dose of investigational new biologics in a small set of human subjects (up to several hundred), including:*

- Phase IIa challenge studies
- Phase IIb safety and preliminary efficacy studies in exposed populations or those at high-risk of infection

## CLINICAL DEVELOPMENT – PHASE III

*Clinical trials to support the registration of investigational new drugs or label-expansion of already registered drugs in a trial population large enough to provide statistical (typically several hundred), including:*

- Phase III expanded efficacy, effectiveness and safety studies required for registration purposes, including implementation, retention and follow-up of volunteers

## **CLINICAL DEVELOPMENT – BASELINE EPIDEMIOLOGY**

*Studies evaluating potential trial site populations to confirm disease incidence, prevalence or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation and presentation of clinical trial data; including:*

- Epidemiological studies **directly** linked to the conduct or support of clinical trials of biologics in development, in order to assess or validate the epidemiology of disease, disease incidence, or health of target populations at trial sites
- Preliminary studies of morbidity and mortality at potential clinical trial sites, where these studies are directly linked to planned product trials
- Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

## **CLINICAL DEVELOPMENT – UNSPECIFIED**

*Other costs required to support clinical testing of investigational new biologics as needed for regulatory approval; including:*

- Infrastructure and site development costs **directly** associated with the conduct of clinical trials for biologic development in **LMICs** (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)
- Further product development to generate the final clinical formulation, dosage form and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- Compiling of all non-clinical and clinical data to obtain a Biologics License from regulatory authorities
- Behavioural research **prior to registration** relating to risk assessment, factors affecting adherence to protocol, and product acceptability
- Protocol development, investigator meetings, Good Clinical Practice (GCP)-monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB), and trial audits

## **POST-REGISTRATION STUDIES**

*Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved biologics so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled use of new biologics by patients. Also includes studies conducted after regulatory approval that assess biologic effectiveness in the wider population or which are necessary to support product use in LMICs.*

- Studies conducted after regulatory approval that assess biologic effectiveness in the wider population or which are necessary to support product use in LMICs
- Pharmacovigilance and post-registration studies of newly registered biologics to assess adverse reactions, toxicology and safety
- Effectiveness studies and head-to-head comparator studies of newly registered biologics (with other therapies or interventions)
- Cost-effectiveness studies of newly registered biologics

- Treatment interactions and population level studies (of newly registered biologics e.g., pharmaco-epidemiological and resistance studies)
- Behavioural research **post-registration** of new biologics relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- Case history reports and assessment of long-term prophylaxis using newly registered biologics in communities in LMICs

## DIAGNOSTICS

*Research activities and processes necessary to develop, optimise, and validate diagnostic tests for use in resource-limited settings (cheaper, faster, more reliable, ease of use in the field); including discovery and design, preclinical and clinical evaluation, and other activities essential for successful deployment for public health use.*

## DISCOVERY AND PRECLINICAL

*Research activities targeted at discovering and optimising **low-cost**, stable, easy-to-use diagnostics for neglected diseases including the processes necessary to allow a potential product to proceed to clinical evaluation; including:*

- Validation, characterisation, and selection of targets suitable for diagnostic use
- Validation of new diagnostic markers or biomarkers
- Development and testing of **low-cost**, stable, easy-to-use diagnostic tests (e.g. simpler microscopy, improved sample collection/preparation, cheaper ELISA assays), including manufacturing design
- New or improved diagnostics for disease staging and therapy decisions
- New or improved diagnostic tools to identify resistant pathogens
- New or improved diagnostics to identify specific target populations
- Tailoring diagnostic tools for LMIC use, including improved point-of-care tests (rapid test), local laboratory test, reference laboratory tests and central laboratory tests
- Creation of reference material banks

## CLINICAL EVALUATION

*Activities and processes associated with clinical evaluation of investigational diagnostic tools so as to demonstrate sensitivity and specificity in human subjects, together with other costs required to support such clinical trials; including:*

- Clinical efficacy trials
- Small-scale testing in humans to establish sensitivity and specificity and utility
- Technical evaluation of tests and studies evaluating product performance
- Establishment of product specifications, kit development and quality assurance
- Submission of relevant data to regulatory authorities for approval
- Assessment & validation of trial sites to carry out product trials
- Infrastructure and site development costs **directly** associated with the conduct of clinical trials for diagnostic development in **LMICs** (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)

## OPERATIONAL RESEARCH FOR DIAGNOSTICS

*Operational procedures and implementation activities associated with novel diagnostic tools, which are necessary to support World Health Organization recommendations for global public health use including:*

- Larger-scale demonstration studies (assessing specificity, sensitivity and utility of the diagnostic test in LMICs)
- Cost-effectiveness studies assessing the diagnostic test
- Identification of pitfalls of the technology and studies of safety measures needed to support the technology
- Studies to determine at what level of the health care system the technology is applicable (e.g. reference labs, regional labs)
- Identification of training needs
- Collecting evidence for expanding the use of a diagnostic tool in different countries
- Development of equipment and customer support documents
- Head-to-head comparator studies (with current gold standard) and in the context of existing diagnostic algorithms
- Behavioural research relating to risk assessment, factors affecting diagnostics use, and user acceptability (patient and provider)
- Epidemiological studies to assess or validate the epidemiology of disease, disease incidence or health of target populations at potential trial sites, and which are **directly** linked to clinical trials of a new diagnostic

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