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**LANDSCAPE OF MEDICINES
USE & DEVELOPMENT FOR
SNAKEBITE ENVENOMING
(2015-2022)**



FUNDED BY



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INTRODUCTION

Snakebite envenoming (SBE) is a complex and neglected global health challenge. Up to 2.7 million instances of SBE occur annually causing an estimated 81,000 to 138,000 deaths, and nearly triple the number of amputations and other permanent disabilities. The majority of this impact is felt by vulnerable and rural populations in low- and middle-income countries (LMICs) in sub-Saharan Africa, Asia, Latin America and parts of Oceania. SBE has suffered from a critical lack of data and information to inform its prevention, control and treatment, and as such, continues to remain a major public health issue.¹

The reasons for this are myriad. Firstly, there is a wide diversity of snake species globally and considerable variability in the compositions and toxicity levels of their venoms. The result is an equally complex array of clinical manifestations for SBE, with multiple, sometimes compounding syndromic profiles resulting from a single case of envenomation. This makes prevention, diagnosis and treatment challenging, demanding specialised medical expertise and products. While currently available animal plasma/serum-derived antivenom products have been the mainstay of SBE treatment for the last century, and have unquestionably saved countless lives, they are not without issue. This includes high manufacturing costs (requiring live snakes, large animal models, skilled labour, and functional laboratories), a limited framework of specificity (constrained by the venom source), requirements for administration by skilled health workers, and – given their non-human antibody profiles – a highly immunoreactive potential. This limits their feasibility as reliable, effective treatments for SBE.

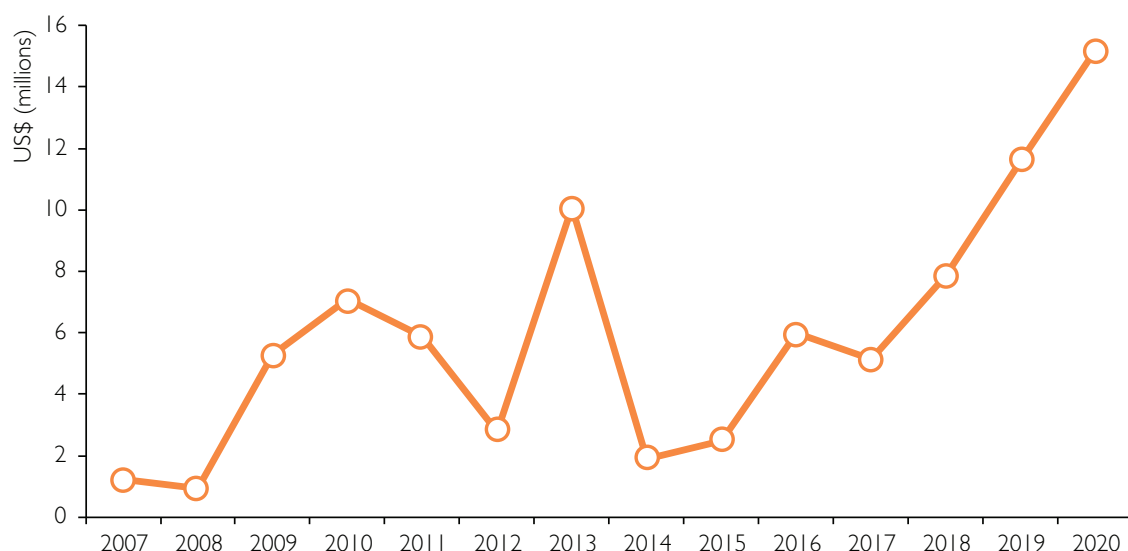
As a result, the current landscape of products on the market is not fit for purpose: antivenoms are neither readily available, accessible, or affordable for target populations, are often inappropriate for the context, do not address all SBE manifestations such as necrosis, and can result in serious secondary health issues, including anaphylaxis and serum sickness. There is a clear need for novel treatments for SBE that can be produced at lower costs, with higher – and broader – specificity, and minimal or zero immunoreactivity, such as recombinant, humanised antibodies, other biologics, and/or small molecule therapies. Although interest and investment in SBE R&D has grown considerably in the last decade, historically this has been limited. There are several reasons for this, including a lack of global attention to the issue, the complexities of snake venom toxinology, challenging ethical considerations for clinical development and design, and a perceived small commercial market, largely based in LMICs. This market failure has – until recently – left a gap in new product development.

In response, a concerted effort in recent years by those working in the field to raise the profile of SBE and stimulate interest and investment in research and development has yielded positive outcomes. This includes the official inclusion of SBE in the World Health Organization (WHO) Neglected Tropical Disease portfolio in 2017, a resolution on SBE adopted by the World Health Assembly in 2019, and the launch of the WHO 2019-2030 roadmap to prevent and control SBE in that same year.² Since then, SBE research has attracted major global health funders, including Wellcome, European Commission and the UK Foreign Commonwealth and Development Office, and a broad array of academics and product developers. This has resulted in some promising avenues of research. As this space grows, there is a continued and growing need to provide the sector with data and information to guide funding decisions and research agendas.

As part of this, in 2019, Wellcome and Policy Cures Research partnered to deliver the first global funding landscape for SBE research. This showed that between 2007-2017, funding for SBE R&D totalled \$49 million (see Figure 1).³ Since then, as part of a now ongoing commitment to collect and report on global SBE R&D funding, SBE has been integrated into the flagship G-FINDER project which reports annually on global funding trends for neglected disease R&D.⁴ Between 2018-2020,

investment in SBE R&D has experienced encouraging growth, rising from \$10m in 2019 – an increase of more than 60% (\$3.8m) over 2018, its first year in the G-FINDER survey – to an historical height of \$15m in 2020. This is an increase of more than a third from the previous year.⁵

Figure 1. Global funding for SBE R&D 2007-2020



In light of recent advocacy wins and increases in annual investment, an updated and detailed review of the SBE pipeline could serve as a powerful tool for the ongoing coordination and advancement of the medicines landscape. Several reviews on various aspects of the SBE R&D landscape have been undertaken over the years. This includes reviews of the clinical status of available antivenom products in sub-Saharan Africa in 2015⁶ and 2019⁷; systematic reviews of clinical outcomes measures in SBE randomised controlled trials⁸, the SBE diagnostic pipeline⁹, small molecules therapies and repurposed drugs (in 2021)¹⁰; as well as comprehensive reviews of plant polyphenols¹¹, and traditional medicine plant-derived snake venom toxin inhibitors as potential SBE therapeutics (in 2022)¹². The most comprehensive overview of all novel small molecules and biologics reported to date with snake toxin neutralisation abilities was published in 2016¹³, with updates in 2018¹⁴. While these reviews have been critical sources of information on the landscape of SBE antivenom use and new therapeutics R&D, no comprehensive overview of everything under development or in use has been undertaken since. Nor does a comprehensive, interactive database of information that profiles all marketed products or investigational candidates within the SBE landscape currently exist.

Recognising this gap, Policy Cures Research, with support from Wellcome, undertook to research and deliver a comprehensive database of SBE drug and biologic candidates that have been investigated (in either discovery/preclinical or clinical development) since 2015, or have been available for clinical use during this period. Given the nascent, and nuanced field of SBE R&D, our philosophy was to include as much information about the landscape of research as possible, with the broadest possible inclusion criteria – incorporating various types of molecules or biologics tested for or used with direct action against snake venom toxins with product development in mind. In the midst of the momentum in SBE R&D, this work provides an important source of data and information to help coordinate and prioritise R&D, and facilitate and accelerate promising products through the pipeline.

METHODOLOGY

Our goal was to create a comprehensive database profiling a) all products registered and/or available for snakebite envenoming (with direct action on toxins) since 2015 ('products'), and b) all drugs and biologics investigated as potential snakebite therapeutics (with direct action on toxins) since 2015 ('investigational candidates'). Products and candidates could be applicable for use in any context, including high-income country (HIC) and low- and middle-income country (LMIC) contexts.

For inclusion in the dataset, products and candidates needed to:

- Be synthetic or natural small molecules (drugs) or immunoglobulin (Ig) (animal plasma/serum-derived or recombinant) or non-immunoglobulin (non-Ig) (animal, natural or recombinant) based biological therapies (biologics), with no restrictions: entries could be entirely new chemical or biological entities (NCEs) or existing/repurposed/label extensions
- Have a direct inhibitory action on snake venom toxins, neutralising venom components to have a therapeutic effect on snakebite envenoming
- Have evidence of research and development (candidates) towards product development, or use (products) at any point since 2015
- Be either investigated for potential clinical use and/or used currently in clinical treatment of snakebite envenoming from WHO medically important category 1 or 2 snakes (or both) only

Specific exclusions were:

- Adjunct and supportive therapies which only modify immune responses and symptoms caused by snake venom toxin
- Devices, diagnostics and other non-medicine-related biomedical products with an indication for SBE
- Basic and fundamental research which was not geared towards product development

We undertook a series of partially sequential, partly overlapping, but mutually reinforcing steps to develop a database of product and candidate profiles. These were: (1) identify and validate products and candidates through multiple sources that are or were in use or in development since 2015; (2) collect information on the products' and candidates' preclinical and/or clinical development, and associated data; (3) research additional context around the products and candidates (e.g., immunisation/production strategy, paraspecificity, region of use and/or registration, etc.) to build out multi-field entry profiles; (4) validate and sense check candidate profiles through independent, external reviews by experts in the field.

Data requirements

These four research steps were borne out of an initial data requirement gathering exercise, whereby we agreed to and defined data fields to be captured for each candidate, where available and verifiable (see Table 1).

For each field, we developed a definition, data input description and sample data type classification (for example, numeric, free-text, or defined list, etc.), as well as guidance notes where relevant, to ensure standardised data entry across researchers/enumerators. Fields were developed in collaboration with a specially convened expert advisory group (EAG) for this project, comprised of leading SBE academics, researchers and product developers working within the sector (see Annexe 1).

Table 1. Data fields captured for each product or candidate (where available and applicable)

Product or Candidate profile	
Identifier	Development lifecycle
Candidate ID (internally assigned number)	Current R&D stage
Candidate name	Highest R&D stage
Alternative names	Development status
Chemical name	Developers
CAS number	Known funders
Patent	Preclinical results status
Adis Insight ID	Type of preclinical results
Adis Insight URL	Preclinical results source(s)
Use-case	Inactive development type
Disease	Inactive development reason
Main product type	Researched in pregnant women or lactating women
Sub product type	If marketed, regulatory approval type/level
Indication	Evidence tested in clinical trials (Y/N)
Investigated for other indications (Y/N)	If yes, does clinical trial evidence pre-date 2015 (Y/N)
Other indications	Registration details (products only)
Thermostability	Clinical use status
Technical profile	Approval status
Archetype	Approving authority
Target	National Authority Approval status (and date)
Route of administration	US FDA approval status (and date)
Mechanism of action	EMA approval status (and date)
MeSH headings / pharmacological class	Japanese MHLW approval status (and date)
Key features and challenges	Other stringent Regulatory authority approval (and date)
Recent updates	Stringent Regulatory Authority (SRA) approval (and date)
Snake species (product derived from)	WHO pre-qualification (and date)
Snake family (product derived from)	Countries where the product is approved
Snake species risk category (product derived from)	Region of use
Immunising venom protocol (monospecific/polyspecific)	Approved for use in pregnant or lactating women
Region (snake/venom derived from)	FDA pregnancy labelling/pregnancy risk summary
Country (snake/venom derived from)	Linked clinical trial (CT) data (if applicable)
WHO immunising species	CT number
WHO paraspecificity species	CT title
Ig final product type/preparation	CT description
Ig format - animal derived	CT phase
Ig format – recombinant	CT status
If Ig format - recombinant ‘other’, specify	CT last updated
Production technique and/or immunisation strategy	CT start date
Snake species (product tested in)	CT start type (anticipated/actual)
Snake species effectiveness (any efficacy data)	CT end date
Snake family effectiveness (any efficacy data)	CT end type (anticipated/actual)
Snake species risk category effectiveness (any efficacy data)	CT recent updates
Direct action on toxins (Y/N)	CT source
Target toxin class	CT sponsor
Target toxin class	CT collaborator
Syndromic profiles	CT locations

Key scope and data decisions

As research unfolded and some new end-user requirements for the database were introduced, it was necessary to revisit, stress test, and occasionally make ongoing, minor adjustments or clarifications to the inclusion and exclusion criteria, as well as various database fields. Each change or refinement was made with the aim of maximising standardisation and utility across profiles. In general, and when conflicting options arose, our approach erred on the side of inclusivity, in line with our aim to capture the broadest view possible of the SBE R&D landscape. We also made no judgments based on therapeutic potential, including all molecules and biologics tested for direct action against snake venom toxins (as products or as potential therapeutics), regardless of their effectiveness as available products or feasibility as marketable ones. Modifications and decisions were documented, and include the following:

Refinements related to inclusions/exclusions

- Only botanical and natural extracts with isolated compounds and metabolites identified and tested for direct action on toxins were included. Crude botanical extracts (e.g., ethanolic preparations) were excluded, even when tested for direct action on snake venom toxins and neutralisation capacity.
- All levels and types of efficacy data were included, whether *in vitro*, *in vivo*, lethality, toxicity, partial or full. This was a practical decision, as well as one of inclusivity, to enable efficient input of (already) multiple levels of data.
- Novel immunogens to improve immunisation techniques for immunoglobulin-based products were excluded, unless the resulting antibodies or antisera generated were tested for snake venom neutralisation ability (the latter being the candidate entry).
- Observational and single clinical case studies were included for context, but were not considered 'evidence of clinical development' for registered products. Evidence of clinical development included only controlled clinical trials.
- Discovery and very early research, and research programmes or projects with no specific lead candidate identified but with a clear intention towards product development were included as candidates. This was specifically to ensure the broadest view of the R&D landscape for SBE was captured, especially given the nascent stage of most SBE R&D. To avoid duplication, where projects were also able to be validated by unique lead candidates subsequently identified in the literature, the lead candidate was included and the project entry then excluded.
- Multiple potential candidate entries identified in one piece of research – e.g., a series of antibody fragments developed and tested, or multiple plasma-derived antisera with varying venom profiles generated and tested – were entered as unique entries only where it was feasible (i.e., numbers were few enough to not overly distort the landscape) and made sense to do so (i.e., units included different product types or subtypes or had very different profiles). Where not feasible, or where separation didn't make sense (i.e., where product types were in a series, venom profiles were similar, or where the intention was clearly for one end product such as a polyspecific antivenom), only one entry was created.
- Any candidate or product with evidence of use or development were included, even if they were essentially inactive. For example, FAV-Afrique and Favirept were included – despite their last vials said to have expired around 2016 and both being technically discontinued – based on their use within the project timeframe as well as their future status for re-introduction (i.e., making them active products).
- Products or candidates with action against envenoming from snakes outside of risk categories 1 and 2 but where need and medical importance clearly exists (e.g., sea snakes), were excluded to preserve the focus on snakes with high medical importance.

- Candidates or products with different formulations or different routes of administration were entered as separate entries if the products were substantially different in bioavailability and R&D progress (e.g., varespladib vs methyl-varespladib). Lyophilised and liquid formulations of the same antivenoms were not disaggregated.

Refinements related to data fields

- **Archetype:** “Repurposed” products or candidates were any molecules or biologics previously investigated (“repurposed (investigational)”) or marketed (“repurposed (approved)”) for any other condition (this includes approval as dietary supplements or food additives). These two repurposed categories were included to better capture work within the SBE R&D landscape that leverages products that are not yet marketed but where substantial research already exists. “New chemical or biological entities (NCEs)” were products or candidates not already marketed or investigated for any condition (unless an NCE marketed for SBE).
- **Current R&D stage:** SBE marketed products were assigned either “preclinical” or “post-marketing human safety/efficacy studies (without prior clinical studies)”. The latter was created specifically to reflect the different product development and regulatory pathway for antivenom products for SBE compared with products for other neglected diseases. The gold standard (and current minimum requirement) for antivenom approval requires only preclinical venom-induced neutralisation lethality studies *in vivo*. Most clinical studies (if undertaken) are therefore conducted post-marketing without preceding Phase I – Phase III human trials. For this reason, the “post-marketing human safety/efficacy studies (without prior clinical studies)” label is not synonymous with Phase IV, given no prior phase development progress is required to progress to marketing authorisation. SBE investigational candidates were assigned labels that follow traditional R&D pathways “discovery & preclinical”, and “Phase I, II or III” (even though it is unlikely that – at least for novel traditional animal-plasma derived antivenoms – there will be a requirement for more than minimum preclinical data for approval in the foreseeable future).
- **Valency/specificity:** Following expert advice, we defined product ‘valency’ in its strictest (traditional) sense, as a reflection of the number of species of snakes used in the venom immunising protocol (for immunoglobulin biologics), i.e., single snake species source as monospecific and multi-snake sources as polyspecific. We renamed this field as “immunising venom protocol” to improve clarity. We included separate sections for “snake species (product tested in)” and “snake species effectiveness (any efficacy data)” to capture entries’ snake specificity/paraspecificity.
- **WHO immunising species/WHO paraspecificity species:** We found discrepancies between sources related to marketed antivenoms’ immunising snake species and listed paraspecificity, including between manufacturers’ websites and the WHO. For comprehensiveness and to avoid the need to judge accuracy, we included both, adding two additional fields to capture information from the WHO source.
- **Region of use/registration:** For a more accurate view of the spread of available SBE products, we added a field for “region of use”, alongside “region of registration”. The former allowed us to better reflect the fact that sometimes antivenoms are produced by an institute or manufacturer well outside of the region of intended use, meaning these are not synonymous. However, data in general, including on regulatory approval status and location, was difficult to find and so we relied heavily on information from the WHO. It was challenging to reflect this in the selected fields, so where possible we added notes in the “key features and challenges” section of the product profiles.

Methods and sources

Step 1: Initial candidate and product identification

Multiple sources were used to find and identify a total of 127 marketed or available products and 196 investigational candidates.

a) We searched Adis Insight¹⁵ – a leading drug development database – to retrieve an up-to-date output of relevant drugs and biologics under investigation for snakebite envenoming. The platform returns detailed information on drugs, candidate deals, clinical trials, safety, patents, and other historical information useful for building candidate or product profiles. Information is full via subscription (our approach) or limited via open source. We searched utilising Adis Insight's inbuilt 'by indication' function, which classifies medicines using a standardised list of indications. Accordingly, free-text searches by indication are not possible. We therefore used search terms that were the most relevant, available indications in the database for snakebite envenoming. These were: "snake venom poisoning", "snake bite poisoning", "snake bites" and "poisoning by venomous snakes"ⁱ. We also searched using the 'by drug class' search function (also not free-text), with the pre-formed relevant search terms "snake venoms", "polyvalent snake antitoxins", "polyvalent snake antivenins", and "polyvalent snake antivenom". Lastly, we searched using the free-text option 'All Text' with the search term "snake".

"Drug" and "trial" outputs were retrieved, triangulated and de-duplicated, and unique products, candidates and associated data formatted, extrapolated, and transposed into our database. Adis Insight search results were retrieved in March 2022 (see Table 2).

Table 2. Number of products and/or candidates retrieved from Adis Insight

	Products	Candidates
Number of unique returns from search terms via Adis Insight	43	
Number of unique entries identified via Adis Insight as in scope	4	4

b) We searched the WHO Snakebite Information and Data Platform¹⁶, specifically the table on Antivenom and Manufacturers. The database is a comprehensive overview of risk category 1 and 2 snakes, their associated geographical distribution and potential health impact and disease burden. It also lists marketed and available antivenom products with known use and/or use efficacy against specific snake species, as well as information on registration and WHO assessment status. The data platform is 'snake focused' as opposed to 'antivenom focused', and as such data retrieved needed to be de-duplicated and re-oriented to identify all available marketed products. Results were retrieved in March 2022 (see Table 3).

Table 3. Number of products and/or candidates from the WHO Snakebite Information and Data Platform

	Products	Candidates
Number of unique antivenoms retrieved via the WHO SBE data platform	120	0
Number of unique antivenoms identified via WHO SBE data platform as in scope	120	0
Number of additional profiles identified via WHO SBE data platform not already identified via Adis Insight	116	0

i "Poisoning" was the terminology offered by Adis Insight.

c) We exported datasets from the WHO International Clinical Trials Registry Platform (ICTRP)¹⁷ the most comprehensive list of global clinical trials available. The following search terms were used to retrieve datasets – which were then merged and de-duplicated into one – related to SBE in March 2022: “snake”; “snakebite”; “envenoming”; “snakebite envenoming”; “antivenom”; and “antiserum”. Clinical trials were scoped for relevance, which we defined as an investigation of one or more drugs or biologics with a primary and/or secondary outcome measure matching treatment of snakebite envenoming, and where the mechanism of action was direct action on snake venom toxin (i.e., not adjunct or supportive therapies). This data search served a dual function of uncovering additional products and/or candidates for inclusion that had not yet been identified (see Table 4), as well as capturing and linking clinical trial data to candidates and products marked for inclusion in the database (see Step 2 below). We performed a similar search of clinicaltrials.gov, but since this information is already contained within ICTRP, no additional candidates or products were identified outside of the figures quoted below.

Table 4. Number of candidates and products from ICTRP

	Products	Candidates
Number of unique clinical trials returned via ICTRP		103
Number of unique clinical trials identified as in scope		32
Number of unique profiles identified via in scope clinical trials	19	4
Number of additional profiles identified via ICTRP not already identified via Adis and WHO SBE data platform	1	3

d) We searched PubMed¹⁸ for relevant literature to validate already identified products or candidates and uncover new ones for inclusion. We anticipated this would include several entries – particularly candidates in discovery and preclinical development – and thus considered search terms that would return information on novel or innovative R&D. We searched using the same search terms as those in our other searches related to the condition/disease (“snakebite”, “envenoming”), combined with additional terms related to indication (“treatment”, “therapy”), product type (“antivenom”, “drug”, “biologic”), and innovation (“innovation”, “discovery”, “preclinical”, “novel”). Using these terms, we performed the following search combinations (using all available terms and combinations):

- “condition” (i.e., “snakebite”)
- “condition” + “indication” (e.g., “snakebite” + “treatment”)
- “condition” + “product type” (e.g., “snakebite” + “antivenom”)
- “condition” + “indication” + “innovation” (e.g., “snakebite” + “treatment” + “novel”)
- “condition” + “product type” + “innovation” (e.g., “snakebite” + “antivenom” + “novel”)

PubMed searches were conducted in March 2022. All searches were combined and de-duplicated, and returned paper titles and abstracts reviewed for relevance. Relevant publications were reviewed in full. Unique and in scope candidates or products were added to the database, or additional data on existing entries already entered in the database was captured (see Table 5).

Table 5. Number of publications (total/relevant*) retrieved, and candidates and products (additional) identified from PubMed

	Products	Candidates
Number of publications (total/relevant*) retrieved		1109/454
Number of additional candidates identified via PubMed not already identified elsewhere	7	167

* Relevant papers are those in which we identified additional or validated existing candidates or products

e) We searched the grant databases of three of the largest global funders of medicines development: the United States National Institutes of Health (US NIH)'s RePORTER¹⁹; the European Commission's CORDIS²⁰; and the Bill & Melinda Gates Foundation's (BMGF) grants database (data supplied from the Foundation); as well as those of two major global funders of SBE therapeutics R&D with available online data: Wellcome's grant funding²¹ and the US Department of Defense's (DOD) via USASpending.gov²². This served to validate existing and find new candidates (particularly those in preclinical/discovery stage). For all databases, we searched using the same search terms as described above, in various combinations. For RePORTER, we retrieved all grants dating from 2015 to present. For CORDIS, we retrieved the Horizon 2014–2020 dataset. For BMGF, we searched datasets ranging from 2014–2020 inclusive (dates supplied and available for review). For Wellcome, we retrieved all grants available for review (from 2005 to present), and for the US DOD, we retrieved grants from 2015 to present. We also searched our own internal G-FINDER R&D funding database for relevant projects. G-FINDER began systematically tracking SBE R&D funding in 2018 and at the time of this project, had data available to 2020. We identified other funders and developers through this review and searched their websites to fill gaps.

All datasets were retrieved and scoped for relevance in March 2022. Profiles were created for new candidates or information added to existing candidates, as appropriate (see Table 6).

Step 2: Linking preclinical and clinical development data

For candidates or products in clinical development, we collected relevant clinical trial data through a few sources. Primary candidate identification through Adis Insight (Step 1) also provided linked clinical trials. These were scoped for relevance, and manually uploaded to the clinical trial entries in our database. Next, we datamined the datasets retrieved from the WHO ICTRP and clinicaltrials.gov as described above. We scoped every clinical trial entry in the datasets. Relevant trials were marked for inclusion and assigned to a candidate or product (or multiple if more than one was being investigated). We cross checked ICTRP clinical trials with those from Adis Insight and clinicaltrials.gov to rule out duplicates. Clinical trial data review was performed between March and June 2022. For candidates or products in preclinical development, results were sourced through PubMed searches between March and June 2022 (see Step 3).

Step 3: Completing candidate and product profiles

Much of the information needed to complete profiles was provided through Steps 1 and 2. In addition, we utilised academic literature search engines/tools to source greater detail and context for the candidates or products identified in Steps 1 and 2. Primarily, we searched PubMed using the candidate or product name/s, and reviewed relevant literature retrieved (including that already sourced in Step 1: to verify and cross reference information as needed. Additional information was searched for via relevant regulatory websites, such as the US Food and Drug Administration (FDA)²³ and European Medicines Agency (EMA)²⁴ as appropriate, as well as a number of reliable online sources, including DRUGBANK Online²⁵, PubChem²⁶, the US National Library of Medicine's Medical Subject Headings (MeSH) portal²⁷, and other websites as needed. Technical information on products was primarily sourced from developer websites and where possible, directly from antivenom product pamphlets/inserts.

Additional profile information was conducted between March and June 2022, concurrently with the steps outlined above.

Table 6. Number of grants, candidates and products retrieved from donor databases/sources

	Products	Candidates
RePORTER		
Number of grants returned via RePORTER	84	
Number of grants identified as in scope	14	
Number of unique candidates identified via in scope grants	1	5
Number of additional candidates identified via in scope grants not already identified elsewhere	0	4
CORDIS		
Number of grants returned via CORDIS	22	
Number of grants identified as in scope	2	
Number of unique candidates identified via in scope grants	0	1
Number of additional candidates identified via in scope grants not already identified elsewhere	0	1
BMGF		
Number of grants returned via BMGF	1	
Number of grants identified as in scope	0	
Number of unique candidates identified via in scope grants	0	0
Number of additional candidates identified via in scope grants not already identified elsewhere	0	0
WELLCOME		
Number of grants returned via WELLCOME	29	
Number of grants identified as in scope	13	
Number of unique candidates identified via in scope grants	1	12
Number of additional candidates identified via in scope grants not already identified elsewhere	0	10
US DOD		
Number of grants returned via US DOD	34	
Number of grants identified as in scope	4	
Number of unique candidates identified via in scope grants	1	1
Number of additional candidates identified via in scope grants not already identified elsewhere	0	0
G-FINDER		
Number of grants sourced from G-FINDER	95	
Number of grants identified as in scope	70	
Number of unique candidates identified via in scope grants	0	9
Number of additional candidates identified via in scope grants not already identified elsewhere	0	6

Step 4: External validation and sense checking

Following database completion, a series of internal and external, independent reviews were undertaken to clean and validate the data. Internally, each candidate and product profile was reviewed for content, consistency, and logic by a minimum of two individuals. Data cross checking and cleaning was conducted in a rigorous, sequential manner. Some steps served to clean and standardise the data, while others were intended to identify content or subject matter error. Illustrative content checks included, for example, reviewing archetype against highest R&D stage (i.e., all ‘repurposed (approved)’ entries needing logically to have a highest R&D stage as ‘marketed’), or reviewing snake venom sources against country and region of origin and specificity (i.e., monospecific antivenoms logically listing only one snake species, one country, and one region as venom source).

An external review was also undertaken. We sought independent, specialist input from members of the project's expert advisory group (see Annexe 1). The entire database was reviewed to validate entries or identify known missing candidates or products; review essential, standard labels; provide additional industry information to fill gaps as appropriate; and for each, recommend corrections, improvements, or additional details. External review was undertaken between June and July 2022.

Materials and platforms

Our data was entered and stored in a bespoke database built in Microsoft CRM Dynamics. Data was transposed (when needed) to Microsoft Excel and Word. Our analyses were performed using Microsoft Excel.

Limitations

Our aim was to identify all drugs and biologics in use or in development for SBE since 2015, which we approached by utilising the comprehensive, multi-pronged search strategy described above. However, due to the nuanced nature of the SBE medicines R&D landscape and inherent biases and weaknesses in available information, the database has some limitations.

Firstly, due to the proprietary nature of (and lack of publicly available information on) many, particularly preclinical, candidate investigations, we anticipate the data may have gaps with respect to the full body of research. We also acknowledge that nearly all the data sources used rely on self-reporting by investigators, which have their own inherent limitations, including potential for reporting biases arising from changes in adherence and utilisation over time, as well as publication biases towards positive results. Other data may have been overlooked due to English-language bias, especially for Central and South American products where much of the available information was in Spanish and Portuguese. Lastly, information overall – particularly for available products – was often extremely hard to obtain, sometimes dictating that we rely heavily on secondary sources to fill gaps.

Secondly, our deliberate decision to be as inclusive as possible means also that within the database we are not always comparing like with like. Examples include: projects and programmes of work versus a clear lead drug candidate; alternative animal models giving rise to genuine novel biologics (e.g., chicken antibody and antibody fragment candidates) versus alternative animal models as precursor research to more traditional approaches (e.g. some rabbit antisera candidates, also acknowledging some publish findings with this type of research and others don't); and single molecules or isolates under investigation versus combined related series of molecules or biologics. Despite these differences, this approach has enabled us to present the most comprehensive database of molecules, biologics and streams of work with therapeutic potential possible, fulfilling our intention to capture what is going on in the SBE R&D landscape in the broadest sense.

Thirdly, direct action on snake venom toxins *sensu stricto* was a major inclusion criterion for this undertaking. This meant, however, that some R&D with alternative mechanisms of action – but similar outcomes and therapeutic potential – were necessarily omitted. This includes, as an example, acetylcholine esterase inhibitors like neostigmine, which offer potential anti-3FTx (three finger toxin) capabilities by altering internal physiological processes (increasing concentration of acetylcholine at the synaptic cleft) as opposed to acting directly on the toxin itself. Other adjunct and supportive therapies that have the potential for profound corrections in the physiologic and syndromic effects of snake venom toxins were also excluded on this basis. Candidates like this could and should be investigated and dealt with elsewhere to broaden the view of the R&D landscape for next generation SBE therapeutics.

Lastly, readers should also note the data is up to date – and analyses drawn from the status of products and candidates – as of mid-2022.

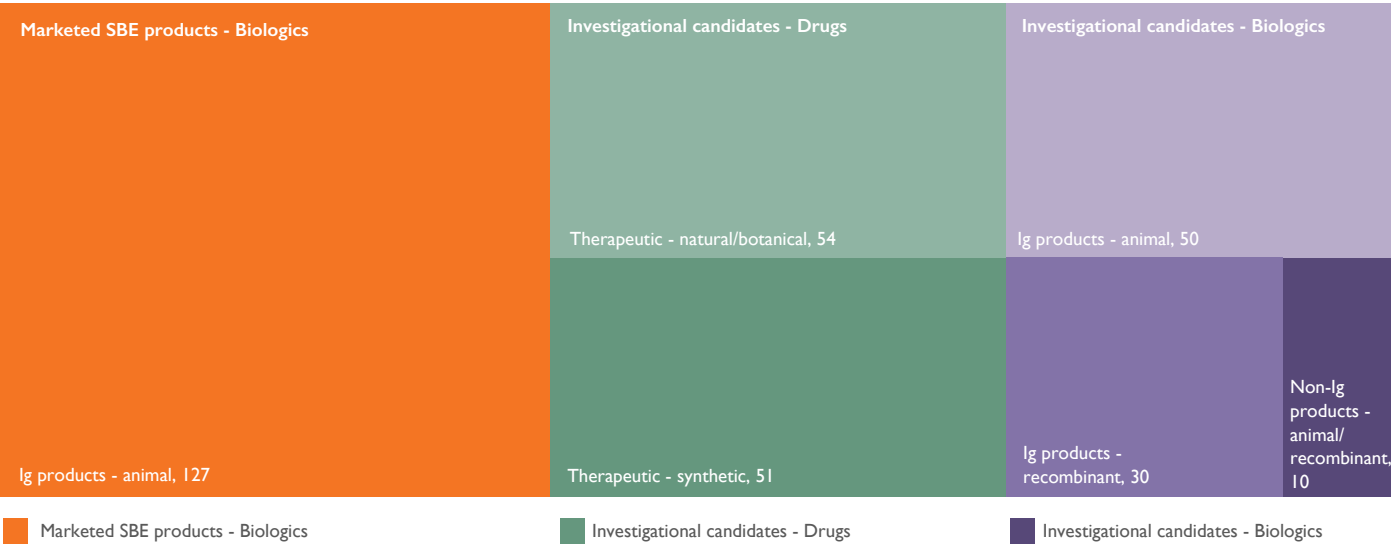
FINDINGS

Overview

Through the methodology detailed above, we identified a total of 127 products marketed and/or available for use since 2015 along with 196 candidate medicines (drugs and biologics) that have been actively investigated in the same period. These figures, as well as the variety of product types, approaches and targets they encompass, represent an encouragingly diverse R&D portfolio for a field of research much smaller in size than and quite distinct from many other neglected diseases.

The landscapes of marketed/available products and investigational candidates have striking differences however, reflecting major variations in product and sub-product type (see Figure 2), R&D stage distribution, and geographic relevance, among others. Given how distinct these portfolios are, the findings are discussed separately, each serving to answer different research questions relevant to the sector regarding the landscape of SBE R&D.

Figure 2. Marketed products and investigational candidates for SBE by product and sub-product type



Available products

In total, we identified 127 products with an indication for the treatment of SBE, approved or available for use between 2015-2022. This also included currently discontinued products if they were found to be marketed and/or available at any point during this period. All the products identified were classified as animal plasma/serum derived immunoglobulin-based antivenoms. There was no evidence of available or approved recombinant-based biological products or approved drugs for the treatment of SBE.

Most of the available products (111, 87%) have evidence of being approved by either stringent (SRA) or national regulatory authorities (NRA) (see Figure 3). Two of these – Favirept and FAV-Afrique – were originally produced by Sanofi Pasteur but are currently both officially discontinued. The last batch of FAV-Afrique was produced in January 2014 and expired in June 2016, with a similar timeline for Favirept.²⁸ However, in January 2018 MicroPharm announced the acquisition of several of Sanofi

Pasteur's antivenom products, including FAV-Afrique and Favirept, with the aim of re-introducing the products in 2024 and 2025, respectively.²⁹ For the remaining 16 products (13%) clear regulatory approval was not able to be ascertained, despite their availability (see Annexe 2 for all product inclusions with clinical use status). This includes products intended for use in Asia and Africa. More than two-thirds (11) of the products with unclear approval status are intended for use in South Asia (5) and South East Asia (6), manufactured in India and Vietnam respectively.

Figure 3. Clinical use status of available products



In practice – and part of the unique SBE landscape – some products are unofficially available in different countries and are used without having regulatory approval. For example, we found no evidence of products with approval for use in Laos, despite seven products unofficially being available and used within the country for SBE, without any regulatory approval. Countries that lack domestic manufacturing capacity are more likely to import unregistered products (with potential limited specificity and application to snakes and SBE within their context). On top of general supplier prioritisation of markets where products are already approved, this leaves some countries with limited access to appropriate or quality assured antivenoms. On the other hand, some products aren't registered in the countries where they are actually intended for use. This is reflective of a fragmented regulatory system and antivenom market, where – in part – manufacturers may seek to save costs by avoiding product registration in multiple jurisdictions.³⁰ The variation and uncertainty in clinical use status is concerning and highlights the complexities in SBE product development as well as clinical management and market regulation. In reality, this means that despite the large number of available antivenoms sold, bought and used on the market globally, many are not meeting needs in terms of quality, appropriateness and availability.

Encouragingly, the distribution of products (region of intended use) maps reasonably well onto the distribution of disease burden; the areas with the highest burden also have the largest volume of products available for use (see Figures 4 and 5). Nearly half of all products (61, 48%) are intended for use in the three regions with recognised high burdens of SBE: South East Asia (23, 18%), South America (20, 16%) and sub-Saharan Africa (18, 14%). Products intended for use in South Asia (11, 8.7%) and East Asia (13, 10%) also represent a significant proportion, mostly due to Indian, Chinese and Taiwanese products, which are manufactured for domestic use. Products also exist for areas with lower SBE burden such as Europe and North America, as well as products for very specific locations including BothroFav, an antivenom designed against *Bothrops lanceolatus* which is almost exclusively found in Martinique in the Caribbean. While the quantum of available products and global distribution may appear positive, it is important to keep in mind that a number of them are essentially the same product, with only slight variations made by local manufacturers for different geographies. Furthermore, these products are exclusively immunoreactive biologics, characterising a landscape lacking in diversified therapeutic solutions, manufacturing techniques and specialised geographic adaptations.

Figure 4. Number of available products by intended region of use

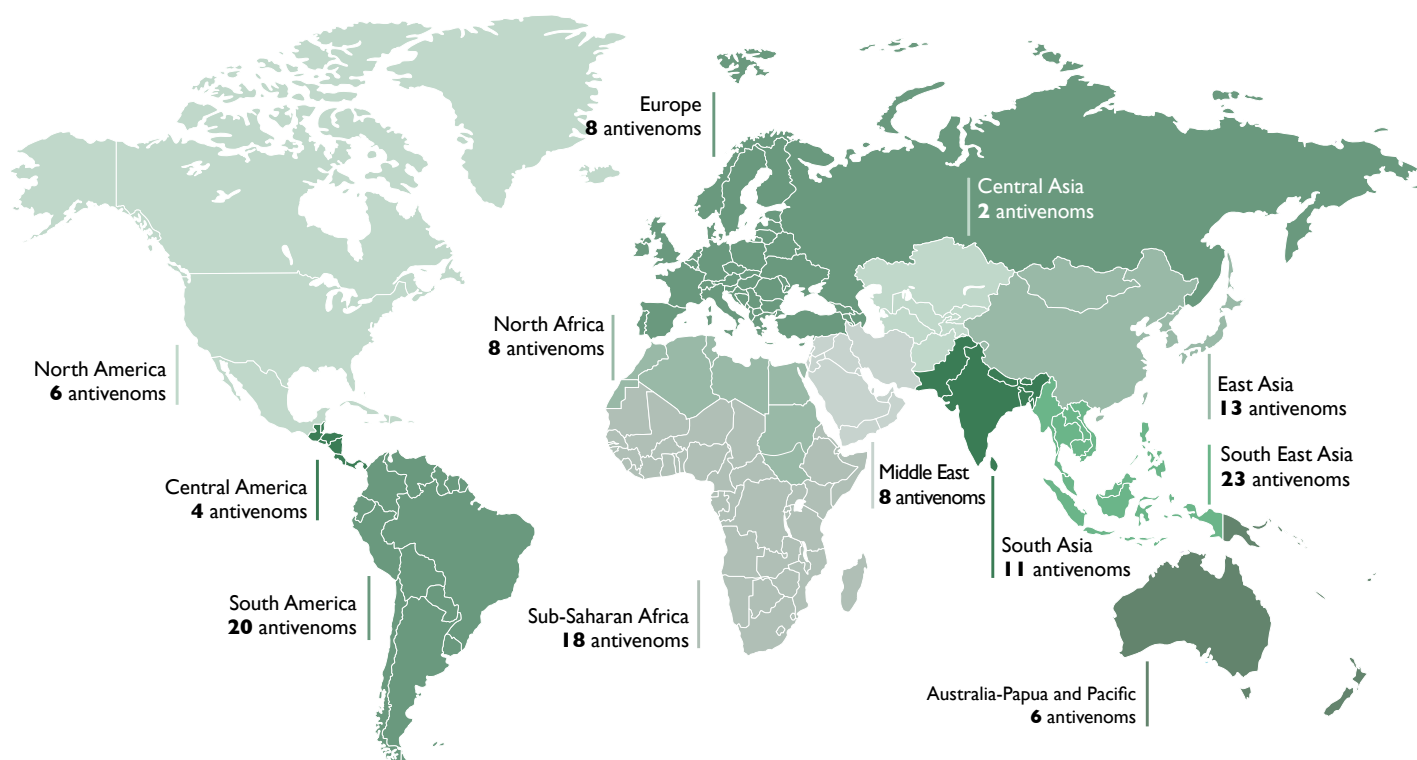
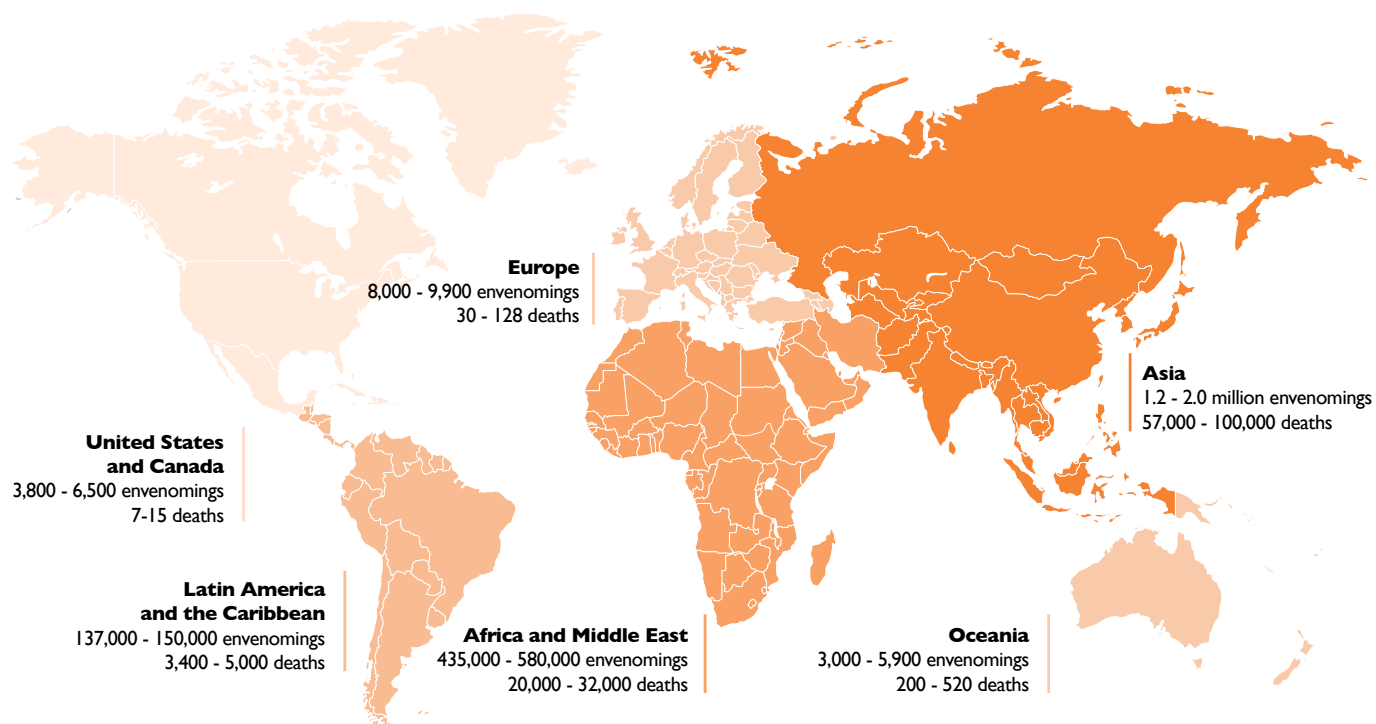


Figure 5. Geographical distribution of estimated SBE burdenⁱⁱ



ⁱⁱ Figure source: José María Gutiérrez et al., "Snakebite Envenoming," Nature Reviews Disease Primers 3 (September 14, 2017): 17063, <https://doi.org/10.1038/nrdp.2017.63>.

Due to the natural inter-species variation in venom composition, SBE has often been viewed as a local issue, which has driven geo-specific production of antivenoms for endemic species. As such, domestic manufacturers tend to cater to sub-national or sub-regional antivenom needs, as opposed to the manufacture of products designed for wider geographic coverage. Indeed, about 107 products (84%) are manufactured domestically for national or regional use (see Table 7). For example, the Queen Saovabha Memorial Institute is a Thai antivenom manufacturer which produces antivenom products for species of concern in Thailand and the close region. Its products are officially used in Thailand, Malaysia, Indonesia and Vietnam. Likewise, there is domestic production of antivenoms in a number of East and South East Asian Countries such as China, Taiwan, South Korea, Japan, Vietnam, Indonesia, Myanmar and the Philippines for domestic markets. The pattern is similar for the Americas.

The remaining 20 available products (16%) are made by manufacturers not in the intended region of use, including manufacturers from India (VINS Bioproducts, Biological E, Premium Serum and Vaccines), the Americas (Inosan Biopharma, Laboratorios Silanes and Clodomiro Picado Institute), as well as MicroPharm, which is UK-based. The exported products are designed for use in the Middle East and North Africa (MENA) and sub-Saharan Africa regions where there is limited manufacturing capacity. While filling an important gap, lack of domestic manufacturing capacity can create a reliance on international producers, which in some instances, can beget vulnerability to supply and suitability.

Table 7. Breakdown of domestic and international manufacturing by manufacturer type

	Public	Private	Total
Domestic	68	39	107
International	1	19	20
Total	69	58	127

Close to half of all SBE products (46%, 59) are produced by geographically diverse, small pharmaceutical and biotechnology companies (excluding public sector pharmaceutical companies) from places like China, Australia, Colombia, Mexico, Uzbekistan, Spain, India, Indonesia, Japan, US, UK, Poland, Israel and Korea. The remaining products available are produced by public sector organisations (54%, 69), including government research institutions, academic organisations and public sector pharmaceutical companies.

For SBE, R&D and regulatory pathways for antivenoms are unique and not entirely linear. Currently, products only need to demonstrate preclinical efficacy in animal models before progressing to market, with no additional requirements for completing Phase I-III clinical trials (dictating that we assign antivenoms as either ‘preclinical’ or ‘post-marketing human safety/efficacy studies’ – see methodology). Within this non-traditional development and regulatory pathway, the availability of either preclinical and clinical evidence for available and marketed products is limited. Just under half (57, 45%) of all products have available preclinical data (any preclinical analysis, *in vivo* or *in vitro*, assessing venom neutralisation or preclinical assay comparisons conducted on multiple antivenoms post-marketing) (see Table 8). It’s important to note that the value and results of the preclinical data were not assessed: preclinical data was counted regardless of whether the results were positive or negative. For the remaining 70 products (55%) we were not able to identify preclinical data at all, the minimum standard for antivenoms to be approved for market use.

Table 8. Availability of preclinical and clinical data for SBE products

Data	Number
Both preclinical and clinical data available	29
Only preclinical data available	28
Only clinical trial data available	12
Neither available	58
Total	127

Of those with available preclinical data, 29 (51%) also have available clinical trial data. This includes products like EchiTab-Plus and EchiTabG, which were tested in a randomised controlled, double-blind non-inferiority trial for *Echis ocellatus* envenoming in Nigeria and demonstrated satisfactory clinical effectiveness.³¹ Availability of data should not however be construed as greater product quality or efficacy. For example, while ASNA-C also has preclinical and clinical data available, a post-marketing surveillance study found low-levels of neutralisation and high-levels of adverse reactions. All other 28 (49%) products do not have available clinical trial data at all, including one instance where clinical trial data could not be authenticated.³²

Some products appeared to have no preclinical data but do have clinical data available (12), notably two monovalent products from the Queen Saovabha Memorial Institute, which are being evaluated in a Phase II/III randomised controlled trial against their polyvalent counterparts.³³ Worryingly, for 58 products we were not able to identify any preclinical or clinical data in the public domain.

The SBE product development and manufacturing landscape is clearly unique. As such, other neglected diseases should not be used as a reference point for comparing or understanding the state of the market. The paradox in SBE is the homogeneity of the current product landscape, compromised of similar but geographically bespoke animal-derived immunoglobulin products, in contrast with the heterogeneity of the manufacturing landscape with its fragmented market and variable regulatory compliance. This has contributed to the inconsistency of preclinical and clinical outputs for registered products and a deepening concern for safety and efficacy. In turn, this has driven variability in demand, which has affected manufacturer outputs, itself reliant on expensive and outdated techniques. The data here affirm that the product landscape has much room to improve in order to respond to a range of unmet needs. Novel products including both drugs and biologics, as well as advances in manufacturing techniques and approaches would ultimately improve availability and access, particularly in remote and peri-urban areas in LMICs which bear the largest burden.

Investigational candidates

We identified 196 investigational candidates that have been tested for direct action against snake venom toxins (and with potential therapeutic application for SBE in mind) at any stage of development since 2015. Given the complexity of the SBE research landscape, we kept the scope intentionally broad, including unique ‘investigational candidates’ of varying types of molecules and biologics, including: single isolates (e.g. plant extract isolates, synthetic whole small molecules); whole biologics (e.g. single whole antibodies); related collections of molecules where combining was logical (e.g., a series of promising peptides, aptamers, antibody fragments, or immunoglobulin products identified under one research/candidate aim); and candidate-focused projects geared towards therapeutics development (even in the absence of a clear lead candidate, in some cases).

Of the investigational candidates we identified, there is a relatively even split between R&D into novel drugs (small molecule therapies (SMTs)) (105, 54%) and biologics (91, 46%) (see Table 9). Considering that all currently available and marketed SBE therapeutics are biologics (specifically, animal plasma/serum-derived immunoglobulin-based antivenoms), this split – and slight skew

towards SMTs – is indicative of a broadening SBE R&D landscape, which has shifted considerable attention towards identifying new therapeutics across a wide range of product types. These include both novel biologics and new and repurposed SMTs that could be combined therapies and/or have universal applicability.

Table 9. Number of SBE investigational candidates by product and product sub-type

	Number	% Total	% Product type
Drugs	105	54%	100%
Therapeutic – natural/botanical	54	28%	51%
Therapeutic – synthetic	51	26%	49%
Biologics	91	46%	100%
Immunoglobulin products – animal plasma/serum derived	51	26%	56%
Immunoglobulin products – recombinant	30	15%	33%
Non-immunoglobulin products – animal/natural/recombinant	10	5.1%	11%
Total	196	100%	

This increasing research diversity is evident in the variability of product types under investigation. Within biologics almost 90% (81, 89%) are immunoglobulin products, 51 of which are animal plasma/serum-derived and encompass a wide range of therapeutic potential and development progress, including (amongst others): novel whole immunoglobulins using new animal models (e.g. in chickens, sheep), precursor antibody research to new antivenoms or recombinant products (e.g. in chickens, mice and rabbits), antisera raised with novel immunisation techniques (e.g. DNA, recombinant toxins), and novel equine or ovine antivenoms that are pathology-specific (e.g. venom induced consumption coagulopathy (VICC)) and are aimed at improved efficacy (e.g. utilising venom from more locally relevant snakes, combining marketed antivenoms with peptides, or freeze-dried). Thirty are recombinant immunoglobulin products, comprised of a range of recombinant antibodies and antibody fragments, including camelid nanobodies (VHH), chicken single-chain variable fragments (scFvs), humanised Ig and scFvs, and plant derived/expressed fragments (VHH and scFvs). The heterogeneity within and between these groups can make it hard to aggregate and compare, but taken together they do largely reflect the current R&D landscape of novel antivenoms that leverage traditional immunoglobulin-driven antivenom philosophies, with efforts focused on improving cost, production capacity and sensitivity.

Only 10 biologics (11%) are non-immunoglobulin products, whether animal/naturally derived or recombinant, including early work on snake blood, human and opossum inhibitor proteins. At this stage these mainly represent experimental research to test basic neutralisation capability, with a long view to therapeutic potential in the future.

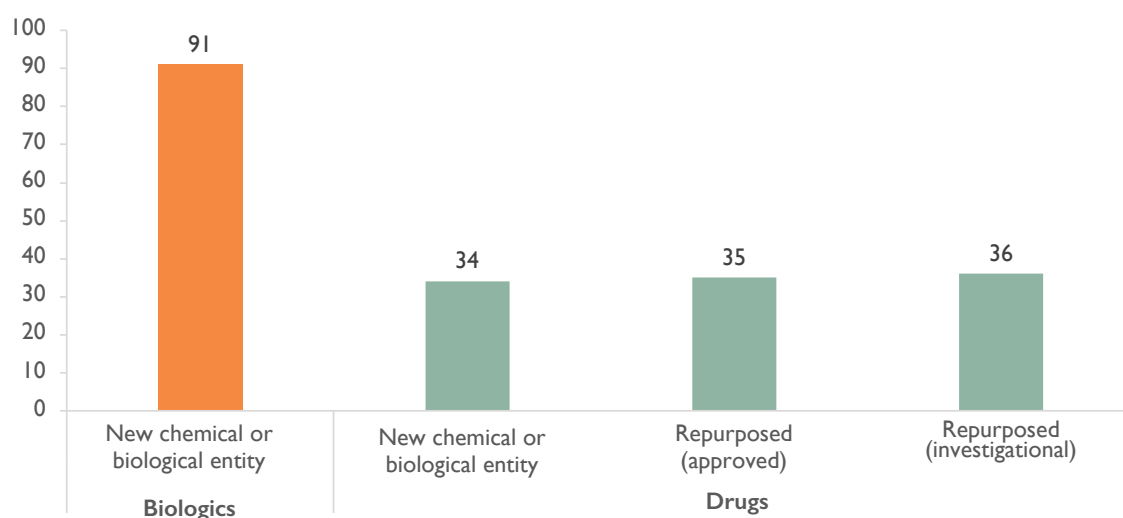
Drug R&D comprises 54 natural or botanical derived SMT candidates (51% of drug candidates) and 51 synthetic (49%). There is also considerable heterogeneity between and within these. Synthetic SMTs include some of the most advanced and discussed SBE candidates, which draw on a variety of repurposed drugs (e.g., the phospholipase A₂ (PLA₂) targeted varespladib and methyl-varespladib, the metal chelator DMPS, as well as the matrix metalloproteinase inhibitors batimastat and marimastat); highly toxin-specific synthetic peptides, enzymes, DNA aptamers and nanoparticles; as well as some very upstream computational predictive molecular docking modelling matched with approved drug screening (e.g., ketoprofen, dexketoprofen, etc). Although much of this is early stage, effective repurposed drugs could progress quickly given their established safety data.

Natural and botanically derived SMTs include a multitude of novel and well-characterised small molecules, such as plant polyphenols (e.g., chlorogenic acid, rosmarinic acid), specific plant extract

isolate compounds (e.g., BRS-p19, fucoidan, mimosine, quercetin), and vitamins and minerals, including zinc, vitamin C, vitamin E and vitamin B-complex. These, particularly the latter, may have limited potential as standalone therapies, but nonetheless have been tested with SBE therapeutics in mind for their direct action on snake venom toxins, and thus fulfilled the criteria for inclusion. The overall volume of botanical or natural SMTs – on par with synthetic SMTs – is possibly elevated by the sheer number of crude plant extracts used already as traditional medicines for treatment of SBE – each possessing multiple potential isolated metabolites – rather than being indicative of the weight of research interest in this area.

Overall, while just under two-thirds (125, 64%) of all SBE investigational candidates are new chemical or biologics entities (herein ‘NCEs’), a sizeable portion – just over a third – are repurposed (71, 36%), all of which are drugs (see Figure 6).

Figure 6. SBE investigational candidates by product and archetype

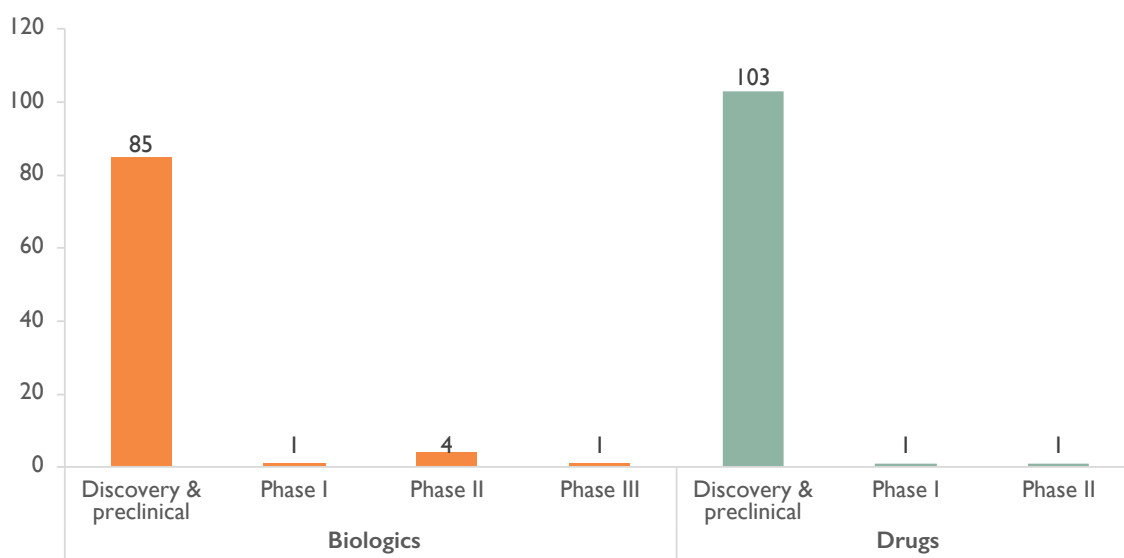


It is largely unsurprising that all 91 biologic candidates are NCEs, which reflects the nuanced nature of SBE biological therapy and production approaches, focused on deriving or creating de novo antibodies or whole proteins with very specific anti snake venom capabilities, and therefore little medical applicability or interest outside the context of snakebite. However, given such therapies are relatively expensive to produce, and under usual R&D pathways as NCEs would require hefty safety data to progress, most of these are likely to be a way off progressing as next generation therapeutics.

It is positive therefore that within this shift toward SBE drug R&D, over two-thirds under investigation are repurposed drugs (71, 68% of drug candidates). Just under a half of these repurposed drugs are already approved for use in humans (35, 49%), with the rest already having been under investigation for other conditions at various stages of development (36, 51%). While these cover drugs with an arguable range of potential therapeutic application, they do also include a number of candidates – some with extensive human safety data – that have gained significant attention in the search for next generation therapeutics. These include the repurposed investigational drugs varespladib, batimastat, marimastat and prinomastat, the approved drugs dimercaprol and disulfiram, and the only two drugs currently in clinical development for snakebite: DMPS (unithiol) and methyl-varespladib. With relatively simple production capacity and an existing pathway to progress through clinical development, repurposed SMTs offer promise in the search for complementary or standalone SBE therapeutics.

Nearly all SBE candidates are in very early stages of development, with 96% (188) in either preclinical or discovery phase (see Figure 7). This is not so surprising given the weight of SBE investigational candidates overall is on NCEs, which normally require rigorous human safety data to progress, and on a sizeable number of biologics, which are notoriously expensive to produce, especially in the case of venom-dependent, immunoglobulin-based antivenoms.

Figure 7. SBE investigational candidates by product type and R&D stage



Just eight candidates in total are in clinical development, investigating safety and efficacy in humans: two synthetic drugs and six animal plasma/serum-derived immunoglobulin (traditional type antivenom) biologics. These include two candidates in Phase I (the metal chelator DMPS/unithiol and a novel F(ab')₂ antivenom against the Indochinese/Siamese Russel's viper); five in Phase II (the orally bioavailable PLA₂ targeted drug methyl-varespladib, and four novel antivenoms with specificity to snakes in South Asia (Pakistan, Sri Lanka), South America (Brazil) and the Australia-Papua region (Papua New Guinea)); and just one reported as being in Phase III (a novel F(ab')₂ antivenom for North American (USA-specific) coral snake envenoming). However, only four candidates appear active, with the rest having completed trials with further progress unknown (see Table 10).

Some interest and momentum surround these candidates, but this hasn't always translated to progress. For example, the Instituto Clodomiro Picado (ICP) monospecific Papua New Guinea (PNG) taipan antivenom was developed specifically to overcome cost barriers of the Seqirus monospecific Australian taipan antivenom – the only antivenom currently available for taipan envenoming in PNG. But despite advancing through Phase I and Phase II randomised trials in 2014 and 2016 with positive results, the product has not progressed further. Nor does any one candidate offer promise across all snakebites. For example, while varespladib/methyl-varespladib is a potent PLA₂ inhibitor, the variability of snake venom toxins within and between species means it is likely that clinical results that are promising for some snakebites may yield more subtle or no clear benefit for similar bites even in the same region.

Ultimately, the limited number of candidates that have progressed to clinical trials is concerning. No botanical or naturally derived SMTs are in clinical development, nor are any other biologics outside of the traditional antivenom paradigm of costly, labour intensive, and immune-reactive animal plasma/serum derived immunoglobulin products. This means new snakebite therapeutics, particularly those that are cheaper to produce, less immunogenic and – ideally, broadly applicable – are currently some way off becoming a reality.

Table 10. SBE investigational candidates in clinical development*

Phase	Name	Product type and sub-type	Archetype	Primary developers/ investigators	Status
Phase I	DMPS (Unithiol)	Drug - synthetic	Repurposed (approved)	Liverpool School of Tropical Medicine (UK)	Active – Phase I trial (“TRUE-1”) registered 2021. Recruiting. Expected completion end 2022.
	Novel F(ab') ₂ antivenom (against <i>Daboia russelii siamensis</i>) (China)	Biologic – Ig product (animal plasma derived)	New chemical or biological entity	Shanghai Serum Biotechnology Co Ltd (China)	Active – Phase I registered 2020. Not yet recruiting.
Phase II	Methyl-Varespladib	Drug - synthetic	Repurposed (investigational)	Ophirex, Inc. (USA)	Active – Phase II trial (“BRAVO”) registered 2021. Recruiting.
	Novel bivalent snake antivenom (IgG) (against <i>Daboia russelii</i> & <i>Echis carinatus</i>) (Pakistan)	Biologic – Ig product (animal plasma derived)	New chemical or biological entity	Antisnake Venom and Antirabies Serology Laboratory, Sindh (India)	Completed – Phase II trial conducted in 2015. Results published 2017. Further progress unknown.
	Novel freeze-dried trivalent antivenom (FDTAV) (against <i>Bothrops</i> , <i>Lachesis</i> , <i>Crotalus</i>)	Biologic – Ig product (animal plasma derived)	New chemical or biological entity	Butantan Institute (Brazil)	Completed – Phase IIb trial conducted 2003-2008, retrospectively registered 2017. Results published 2017. Further progress unknown.
	Novel ICP-AVRI-UOP Sri Lankan polyspecific antivenom	Biologic – Ig product (animal plasma derived)	New chemical or biological entity	ICP (Costa Rica), University of Peradeniya (Sri Lanka), Animal Venom Research International (Sri Lanka)	Active – Phase II/III trial registered 2016, updated in 2019. Recruitment pending 2019.
Phase II	Novel PNG taipan antivenom (against <i>Oxyuranus scutellatus</i>)	Biologic – Ig product (animal plasma derived)	New chemical or biological entity	ICP (Costa Rica)	Completed – Phase II trial completed 2016. Results not published. Further progress unknown.
Phase III	Snake (<i>Micrurus</i>) North American immune F(ab') ₂ Equine	Biologic – Ig product (animal plasma derived)	New chemical or biological entity	University of Arizona (USA)	Completed – Phase III trial completed 2016. No official results published. Further progress unknown.

*As of Sept 2022

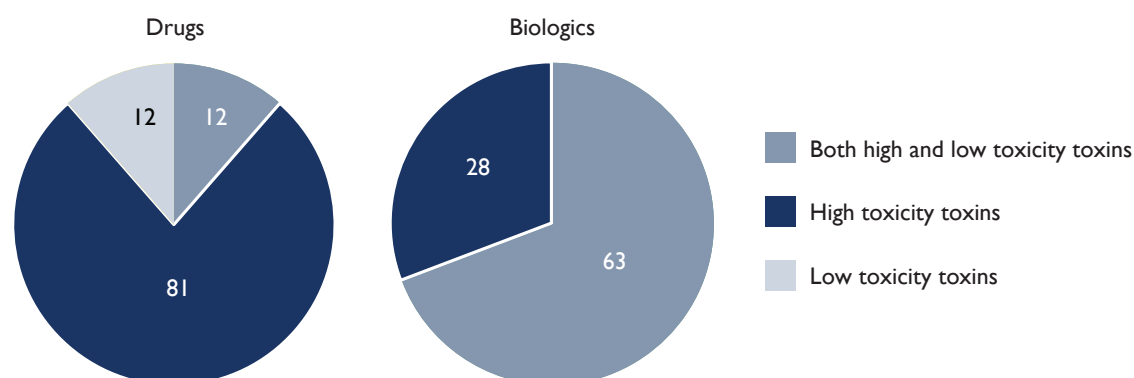
We also captured information about candidates' target toxins to better understand the spread and intention of R&D across snake venom sub-components (and by extension, snake types). Snake venom includes a broad range of toxins with varying degrees of toxicity (lethality, syndromic effects) and abundance (within and between snake species), and therefore public health importance. This includes – based on recent classifications³⁴ – high toxicity toxins with high abundance (phospholipase A₂ (PLA₂), snake venom metalloproteinase (SVMP), three-finger toxin (3FTx) and serine proteinase (SVSP) toxin families), high toxicity toxins with lower abundance (dendrotoxins and sarafotoxins), low toxicity toxins with high abundance (L-amino acid oxidases (LAAO), C-type lectin-like proteins (SNACLECS), cysteine-rich secretory proteins (CRISPS), disintegrins, and bradykinin-potentiating peptides (BPPs)), and low toxicity toxins with low abundance (hyaluronidase, 5' nucleotidase, nerve growth factor (NGF), phosphodiesterase and natriuretic). For this reason, it would be logical for R&D into new SBE therapeutics to focus on high toxicity, high abundance toxins to achieve the greatest impact.

We measured candidates first by whether they targeted 'high toxicity toxin', 'low toxicity toxins' or 'both high and low toxicity toxins', and then, if specified, by the toxin itself. We found that over half (109, 56%) of all SBE investigational candidates specify 'high toxicity toxins' as major targets, well over a third cite 'both high and low toxicity toxins' (75, 38%), and just 12 (6.1%) target 'low toxicity toxins' (see Figure 8).

Drug R&D is dominated by a focus on high toxicity toxins (81, 77% of drugs). Given the rational design of drugs, and the public health impact of high toxicity toxins, this focus is not surprising. Drugs specifying low toxicity toxins (12, 11%) are largely those identified via predictive computational models and botanicals with low toxicity toxin affinity described through comprehensive molecular characterisation studies. The rest cite both high and low toxin specificity, either because they contained evidence of specificity against multiple snake venom toxins, or for the most part because the molecules were tested for action on crude whole snake venom, which contains both high and low toxicity toxins in a wide range of proportions (and as such, was the default allocation for these type of candidates).

For this same reason, candidates with specificity to 'both high and low toxicity toxins' dominate the biological candidate profiles (63, 69%), where the majority are animal plasma-derived immunoglobulin products (43, 68%) raised and tested against crude snake venom, which contains all snake venom toxins. In contrast, most biological candidates specifying 'high toxicity toxins' as targets are comprised of recombinant antibodies or antibody fragments (15, 54%) intentionally designed with high toxicity toxin targets in mind. Given the deliberate engineering (and cost) involved in biological therapy design and production, it is not surprising that there are no biologics specifically designed to solely target low toxicity toxins.

Figure 8. SBE investigational candidates by product and broad toxin class target

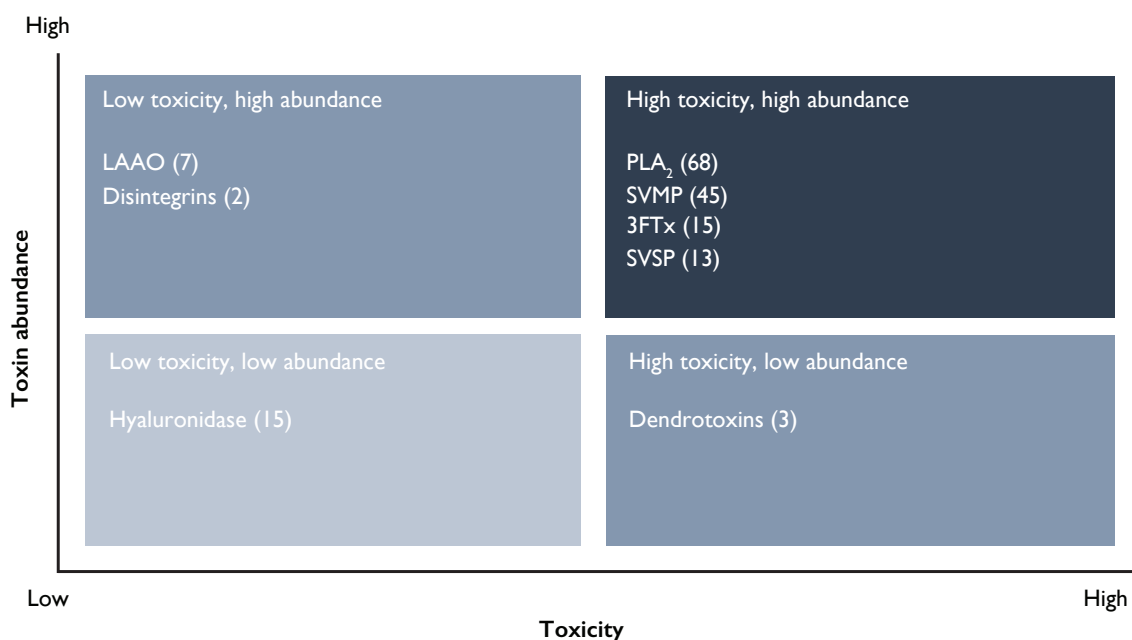


Next, where possible, we also collected information on specific toxin classes targeted. Almost a third of candidates (58, 30%) do not provide information as to which specific toxins they are targeting, with most of these representing those being tested against crude snake venom (where all classes of toxins are present but unspecified as targets). For candidates that do however – 68 cite PLA₂ as a target toxin, the most cited of all specified toxins – followed by SVMPs (45 candidates), and 3FTxs (15 candidates). Thirteen candidates specify SVSPs. This concentration of R&D in high toxicity, high abundance toxin-targeting therapeutics aligns well with an expected focus that would maximise impact (see Figure 9).

On the other hand, 15 candidates cite low toxicity, low abundance hyaluronidase as a target, which marks it on par with and above high toxicity, high abundance 3FTxs and SVSPs respectively. However, this number may artificially be inflated by candidates sourced from just a few studies – particularly those where multiple naturally-derived compounds were isolated and tested from single crude plant extractions and where broad anti-snake toxin abilities were being characterised – rather than any heavy research focus into this toxin. All other specific toxins – high toxicity, low abundance dendrotoxins and high abundance, low toxicity toxins LAAO and disintegrins – are cited by less than 10 candidates each.

While the overall focus of SBE therapeutics R&D falls on high toxicity and abundance toxins, given snake venom composition varies considerably between, and even within, snake species, it is encouraging to see some research interest in other types (and combinations) of toxins outside of these top four. Some effort is likely needed to further break down specific toxin targets for the large number of biologics and drugs that target crude snake venom in order to gain a more complete picture of the health of the landscape. That said, identifiable trends appear to support a focus on high impact next generation products.

Figure 9. Number of SBE investigational candidates that cite each specific toxin class as a target*ⁱⁱⁱ



*Candidates can have multiple targets

ⁱⁱⁱ Modified from original figure in: José María Gutiérrez et al., “The Search for Natural and Synthetic Inhibitors That Would Complement Antivenoms as Therapeutics for Snakebite Envenoming,” *Toxins* 13, no. 7 (June 29, 2021): 451, <https://doi.org/10.3390/toxins13070451>.

DISCUSSION

SBE has only recently been recognised as a global health priority, being formally listed by the WHO among the highest priority neglected tropical diseases in 2017. Within a broader view of neglected disease product R&D, and with limited global awareness of this health issue historically, it would be reasonable to expect the volumes of available medicines as well as new therapeutic candidates under investigation to be small. As this current work demonstrates however, neither is the case for SBE. That said, both landscapes require careful interpretation and are not immediate cause for celebration, as these figures directly reflect the complexities (and shortcomings) of SBE-related product R&D, which is unlike other neglected diseases in its nuanced and not entirely clear clinical profiles, product needs, development pathways and regulatory environment.

Firstly, a landscape of 127 marketed and available products does not in this instance translate to a healthy market for SBE therapeutics. Although there are many, they are uniform (all animal plasma-derived antibody-based antivenoms), flawed (are highly species specific and immunoreactive), are expensive to produce, and exist within a loosely regulated environment where products require only limited safety and effectiveness evidence to enter the market. Just under half (58, 46%), in fact, have neither. While antivenoms do save lives, this current data validates the fact that a shift towards improved regulatory frameworks, purification techniques, and Good Manufacturing Practices (GMP) in the short to medium term, and to more cost effective, safer and broadly effective next generation SBE therapeutics in the longer term, is warranted.

Secondly, it is therefore encouraging that – even with its relatively fresh entry into the limelight of global health priority areas – the landscape for novel SBE therapeutics comprises both a sizeable volume of candidates (196) and diversity across its portfolio. This includes an array of both biological and small molecule product types, such as new plasma-derived antivenoms, recombinant (some humanised) antibody products, whole proteins or peptides, DNA aptamers, synthetic small molecules and botanical extract isolates and compounds. This breadth of interest and investment across next generation SBE therapeutics provides strong, up-to-date evidence of a trend (and progress) towards the use of new scientific approaches and technologies to solve shortcomings of available products.

Nearly all investigational candidates, however, are in discovery or preclinical stages of development (188). This not only indicates these are some way off from being available as new products, but also makes it difficult to see and comment on their progression through the ‘pipeline’. For example, a comprehensive review of biologics and small molecules reported for snake venom neutralisation conducted by Laustsen et al. in 2016 identified 31 small molecules, 49 non-antibody proteins, 48 murine monoclonal antibodies and antibody fragments and 21 non-murine recombinant antibodies and antibody fragments.³⁵ While new candidates have been identified since, according to our research, none of these from the original 2016 paper have yet progressed past preclinical investigation. Although we found more recent published evidence or citations of some of these candidates (a potential signal of ongoing research activity), there has been no evidence of any R&D stage progressions. Indeed, a number are academic projects unlikely to be progressed further, and may never enter into the pipeline.

In fact, we only identified six traditional type animal plasma-derived immunoglobulin antivenoms and two drug candidates in this project that have progressed to clinical development during the review period. Notably, the two drug candidates – methyl-varespladib and DMPS (unithiol) – have only appeared recently, within the last seven years in the SBE R&D landscape. Given these are both repurposed drugs with established human safety data, this may offer an insight into the pace of progress we might expect at current levels of investment for other SBE therapeutics, especially given over a third of all investigational candidates identified were repurposed drugs.

Objective commentary on whether the R&D landscape is actually meeting the sector's needs, however, is not straightforward. Research and analysis would need to review target venom, toxin and syndromic profiles in detail across all candidates, overlayed against more granular burden of disease data for SBE at the national and sub-regional level and the available product distribution landscape to give a sense of whether the direction of SBE research fully matches need. This data is not always easy to obtain. From a geographic perspective, only 75 candidates (38%) had available data on the region from which snake venom was derived (a proxy for the potential region of use), and all of these were (necessarily) immunoglobulin based. Data on specific target toxin classes was also not available for almost a third of all investigational candidates (58, 30%). Likewise, almost half (84, 43%) didn't specify any syndromic profile (we did not assume syndromic profiles even with target toxins specified). Ultimately, the granular epidemiological and ecological data that is needed to better define actual needs, is lacking. The strength of this information as extrapolatable observations – either individually or combined – across the SBE R&D landscape is therefore limited.

It is worth noting, in fact, that there were significant logistical challenges in finding, identifying, and clarifying data for both products and candidates included in this database. The state of information in the public domain severely lacks standardisation, including across nomenclature, interpretation of terminology, and availability of basic information. This contributes significantly to the overall opacity of the landscape, rendering it difficult to accurately identify and profile different products and candidates. SBE products, for example, are rarely marketed with a commercial name, described instead by the species used in the immunisation strategy (e.g., “Soro Antibotrópico”) or in very general terms (e.g., “Indian anti-snake venom”). Likewise, no standardised naming convention exists at all for candidates, especially biological products, which are most often described in the literature in general terms referencing their product sub-type and intended target. An extension of this was thus applied as a naming convention – by us – to candidates within this database where needed to distinguish them as individual entities (e.g., “Camelid nanobodies (VHH) (against *Bothrops jararacussu*)”). It would be useful moving forward to strengthen data harmonisation across the SBE landscape to improve visibility and coordination of R&D efforts.

Despite these issues and limitations, this database provides the most up-to-date and comprehensive view of the landscape of available products and investigational candidates in development for snakebite envenoming over the last seven years. The data also comes at an important moment, ahead of the release of WHO's sub-Saharan Africa SBE Target Product Profile (TPP) – the first in a series of SBE TPPs – expected late 2022.³⁶ In an R&D space dominated by the same traditional antivenom design and variable regulatory pathway, it is a major milestone to have validated guidelines and priorities on the future of product development for SBE, particularly for a region with a significant burden. This database thus provides a useful and timely platform from which to evaluate and prioritise candidates (and products) against current and future TPPs, and in doing so, contribute towards improved coordination of and accelerated progress in SBE therapeutics R&D.

ANNEXE 1 – EXPERT ADVISORY GROUP

Advisory Committee Member	Organisation	Title
Ian Cameron	MicroPharm	Chief Executive Officer
Nicholas Casewell	Liverpool School of Tropical Medicine	Professor
José María Gutiérrez	Instituto Clodomiro Picado, Universidad de Costa Rica	Emeritus Professor
Andreas Hougaard Laustsen-Kiel	Technical University of Denmark	Professor
Matthew Lewin	Ophirex//California Academy of Sciences	Chief Scientific Officer/Medical Director
Julien Potet	Médecins Sans Frontières (MSF) Access	Neglected Diseases Policy Advisor
Devin Sok	IAVI	Vice President, Discovery and Innovation

ANNEXE 2 – INCLUDED PRODUCTS AND CANDIDATES

SBE marketed products

Biologics

Available and approved products

- *Agkistrodon acutus* antivenom - DaMAV-China (Shanghai Serum Bio-technology Co Ltd, China)
- *Agkistrodon halys* antivenom - AhAV (Shanghai Serum Bio-technology Co Ltd, China)
- Anavip (Instituto Bioclon/Laboratorios Silanes, S. A. de C. V., Mexico)
- Anti Snake Venom Serum Central Africa - 6 (Biological E Limited, India)
- Anti Snake Venom Serum Monovalent *Echis ocellatus* (Biological E Limited, India)
- Anti Snake Venom Serum Pan Africa - 10 (Biological E Limited, India)
- Antiveneno *Crotálico* (Instituto Nacional de Produccion de Biologicos, Argentina)
- Antiveneno *Micrurus* (Instituto Nacional de Produccion de Biologicos, Argentina)
- Anti-Viper antivenom - Russell's viper (Myanmar Pharmaceutical Factory (MPF)/ Burma Pharmaceutical Industry (BPI), Myanmar)
- Anti-viper antivenom (Microgen and Ministry of Health, Russian Federation)
- Antiviperine sera (National Center of Infectious and Parasitic Diseases, Bulgaria)
- Antivipmyn Africa (Instituto Bioclon/Laboratorios Silanes, S. A. de C. V., Mexico)
- Antivipmyn TRI Fabotherapic (Instituto Bioclon/Laboratorios Silanes, S. A. de C. V., Mexico)
- ASNA-C (Bharat Serums and Vaccines Limited, India)
- *B. multicinctus* and *B. candidus* antivenom (Vietnam Poison Control Center, Hanoi Medical University)
- Banded krait antivenin, *Bungarus fasciatus* monovalent antivenom - BFMAV (Queen Saovabha Memorial Institute, Thailand)
- BioSave - Serum Anti Bisa Ular Polivalen (PT Bio Farma (Persero), Indonesia)
- Bivalent Haemorrhagic Antivenom - HBAV (CDC, Taiwan)
- Bivalent *Naja/Walterinnesia* Snake AV - Equine (National Antivenom & Vaccine Production Center, Saudi Arabia)
- Bivalent Neurotoxic antivenom - FNAV (CDC, Taiwan)
- BothroFAV (MicroPharm Ltd, United Kingdom)
- *Bungarus* Antivenom (CDC, Taiwan)
- *Bungarus multicinctus* antivenom - BmAV (Shanghai Serum Bio-technology Co Ltd, China)
- Cobra Antivenin (Queen Saovabha Memorial Institute, Thailand)
- CoRaI-ICP Liquid (Instituto Clodomiro Picado, Costa Rica)
- Coralmyrn (Instituto Bioclon/Laboratorios Silanes, S. A. de C. V., Mexico)
- Crotalidae Polyvalent Immune Fab (ovine) (BTG International Inc., United States of America)
- *Echis Coloratus* Equine Antiserum (Kamada Limited, Israel)
- EchiTabG (MicroPharm Ltd, United Kingdom)
- EchiTab-plus-ICP (Instituto Clodomiro Picado, Costa Rica)
- European viper venom antiserum (Imunološki Zavod (Institute of Immunology), Croatia)
- Faboterapico Polivalente Antiviperino (Birmex - Instituto Nacional de Higiene, Mexico)

- Freeze-dried Habu antivenom (KM Biologics Co. Ltd, Japan)
- Freeze-dried Mamushi antivenom (KM Biologics Co. Ltd, Japan)
- Gamma-Vip (Institut Pasteur de Tunis, Tunisia)
- Green Pit Viper Antivenin (Queen Saovabha Memorial Institute, Thailand)
- Haemato-polyvalent snake antivenom - HPAV (Queen Saovabha Memorial Institute, Thailand)
- Hexavalent snake venom immunoglobulin (Razi Vaccine & Serum Research Institute, Iran)
- Indian Snake Anti Venom - I.P (VINS Bioproducts Ltd, India)
- Inoserp MENA (INOSAN BIOPHARMA S. A., Spain)
- Inoserp PAN-AFRICA (INOSAN BIOPHARMA S. A., Spain)
- IPA VIP Antiviperin Sera (Institut Pasteur d'Algerie, Algeria)
- King cobra antivenin (Queen Saovabha Memorial Institute, Thailand)
- Kovax Freeze-Dried Agkistrodon (Korean mamushi) Equine Antivenom (KoreaVaccine Co Ltd, Republic of Korea)
- Malayan krait antivenin (Queen Saovabha Memorial Institute, Thailand)
- Malayan Pit Viper Antivenin (Queen Saovabha Memorial Institute, Thailand)
- Monovalent caprine antivenom against *C. rhodostoma* (Twyford Pharmaceutical)
- Monovalent *D. acutus* antivenom - DaMAV-Taiwan (CDC, Taiwan)
- Monovalent *Daboia siamensis* antivenom - DsMAV-Taiwan (CDC, Taiwan)
- Monovalent *Naja philippinensis* Cobra Antivenom (Biologicals Manufacturing Division of Research Institute for Tropical Medicine, Philippines)
- Monovalent serum against snake venom gyurza (UzbioPharm LLC, Uzbekistan)
- *Naja atra* monovalent antivenom - NaAV (Shanghai Serum Bio-technology Co Ltd, China)
- Neuro-polyvalent snake antivenom (Queen Saovabha Memorial Institute, Thailand)
- North American Equine Coral Snake Antivenin (Wyeth, USA)
- Pentavalent snake antivenom immunoglobulin (Razi Vaccine & Serum Research Institute, Iran)
- Polisera (Vetal Serum ve Biyolojik Ürünler Üretim Sanayi Tic. A.Ş, Turkey)
- PoliVal-ICP (Instituto Clodomiro Picado, Costa Rica)
- Polyvalent Anti Snake Venom Serum I.P. (King Institute of Preventative Medicine and Research, India)
- Polyvalent Anti-Snake Serum (Egyptian Organisation for Biological Products and Vaccines (VACSERA), Egypt)
- Polyvalent Antisnake Venom Serum (National Institute of Health, Pakistan)
- Polyvalent Anti-Vipers Serum (Egyptian Organisation for Biological Products and Vaccines (VACSERA), Egypt)
- Polyvalent serum against snake venoms gyurza, efa, and cobra (UzbioPharm LLC, Uzbekistan)
- Polyvalent Snake Antivenin I.P. - Asia (Haffkine Biopharmaceutical Corporation Ltd, India)
- Polyvalent Snake Antivenom - Equine (National Antivenom & Vaccine Production Center, Saudi Arabia)
- Russell's viper antivenin (Queen Saovabha Memorial Institute, Thailand)
- SAIMR Boomslang antivenom (South African Vaccine Producers, South Africa)
- SAIMR *Echis* antivenom (South African Vaccine Producers, South Africa)
- SAIMR Polyvalent Snake antivenom (South African Vaccine Producers, South Africa)
- SAV-*Naja* (Institute of Vaccines and Biological Substances, Vietnam)
- SAV-*Trimeresurus* (Institute of Vaccines and Biological Substances, VietNam)
- Seqirus Black Snake antivenom (Seqirus Pty Ltd, Australia)

- Seqirus Brown Snake antivenom (Seqirus Pty Ltd, Australia)
 - Seqirus Death Adder antivenom (Seqirus Pty Ltd, Australia)
 - Seqirus Polyvalent antivenom (Seqirus Pty Ltd, Australia)
 - Seqirus Taipan antivenom (Seqirus Pty Ltd, Australia)
 - Seqirus Tiger Snake antivenom (Seqirus Pty Ltd, Australia)
 - Siamese cobra antivenin (Myanmar Pharmaceutical Factory, Myanmar)
 - SnaFab5 (Padra Serum Alborz, Iran)
 - SnaFab6 (Padra Serum Alborz, Iran)
 - Snake Antivenin (Polyvalent) IP (Biological E Limited, India)
 - Snake venom antiserum - Pan Africa (Premium Serums and Vaccines Pvt. Ltd., India)
 - Snake Venom Antiserum African - 10 (VINS-A) (VINS Bioproducts Ltd, India)
 - Snake Venom Antiserum Echiven Plus (VINS Bioproducts Ltd, India)
 - Snake venom antiserum I.P. (Premium Serums and Vaccines Pvt. Ltd., India)
 - Snake Venom Antitoxin - Menaven (VINS Bioproducts Ltd, India)
 - Soro Antibotrópico Pentavalente (Instituto Butantan, FUNED, Instituto Vital Brazil, CPPI, Brazil)
 - Soro Antibotrópico pentavalente e Crotálico (Instituto Butantan, FUNED, Instituto Vital Brazil, Brazil)
 - Soro Antibotrópico pentavalente e Laquélico (Instituto Butantan, FUNED, Instituto Vital Brazil, Brazil)
 - Soro Anticrotálico (Instituto Butantan, FUNED, Instituto Vital Brazil, CPPI, Brazil)
 - Soro Antielapídico Bivalente (Fundacao Ezequiel Dias & Butantan Institute, Brazil)
 - Suero Antibotrópico Polivalente (Instituto Nacional de Salud, Peru)
 - Suero Anticoral Polivalente (Instituto Nacional de Salud, Colombia)
 - Suero Anticrotálico Monovalente (Instituto Nacional de Salud, Peru)
 - Suero Antilachésico Monovalente (Instituto Nacional de Salud, Peru)
 - Suero Antiofídico (BIOTECFAR, Venezuela)
 - Suero Antiofídico Anticoral Polivalente Liofilizado (Laboratorios Biologicos PROBIOL Ltda, Colombia)
 - Suero Antiofídico Polivalente (Instituto Nacional de Salud, Colombia)
 - Suero Antiofídico Polivalente BIOL (Instituto Biologico Argentino S.A.I.C, Argentina)
 - Suero Antiofídico Polivalente Botropico/ Crotalico (Ministerio de Salud y Deportes, Instituto Nacional de Laboratorios De Salud, Bolivia)
 - Suero Antiofídico Polivalente Botropico/ Laquesico (Ministerio de Salud y Deportes, Instituto Nacional de Laboratorios De Salud, Bolivia)
 - Suero Antiofídico Polivalente Centroamericano BIOL CLB (Instituto Biologico Argentino S.A.I.C, Argentina)
 - Suero Antiofídico Polivalente Liofilizado (Laboratorios Biologicos PROBIOL Ltda, Colombia)
 - Suero Bothropico Bivalente (Instituto Nacional de Produccion de Biologicos, Argentina)
 - Suero Bothropico Tetravalente (Instituto Nacional de Produccion de Biologicos, Argentina)
 - Viekvin (Institute of Virology, Vaccine and Sera, TORLAK, Serbia)
 - Viper venom antitoxin (BIOMED Wytwornia Surowic i Szczepionek, Poland)
 - *Vipera palaestinae* Equine Antiserum (Kamada Limited, Israel)
 - ViperaTAb (MicroPharm Ltd, United Kingdom)
 - VIPERFAV (MicroPharm Ltd, United Kingdom)
- Approved – discontinued products**
- FAV-Afrique (Sanofi Pasteur, MicroPharm)
 - Favirept (MicroPharm UK, previously Sanofi-Pasteur, France)

Unclear approval pathway

- Anti-Yamakagashi Antivenom (KM Biologics Co. Ltd, Japan)
- *Bungarus candidus* Antivenom (Venom Research Unit, University of Medicine and Pharmacy Ho Chi Minh City, Vietnam)
- *Bungarus candidus* Monospecific Antivenom (Venom Research & Antivenom Production Unit, National Poison Control Center, Vietnam)
- *Calloselasma rhodostoma* - Malayan Pit Viper Antivenom (Venom Research Unit, University of Medicine and Pharmacy Ho Chi Minh City, Vietnam)
- Combipack of Snake Venom Antiserum (African- Ten) (Premium Serums and Vaccines Pvt. Ltd., India)
- *Daboia Russelii* Mono (VINS Bioproducts Ltd, India)
- *Naja kaouthia* Antivenom (Venom Research Unit, University of Medicine and Pharmacy Ho Chi Minh City, Vietnam)
- *Naja Kouthia* Mono (VINS Bioproducts Ltd, India)
- *Naja siamensis* Antivenom (Venom Research Unit, University of Medicine and Pharmacy Ho Chi Minh City, Vietnam)
- *Ophiophagus hannah* Antivenom (Venom Research Unit, University of Medicine and Pharmacy Ho Chi Minh City, Vietnam)
- Polyvalent Big Four Fab'2 antivenom (Incepta Vaccines, Bangladesh)
- SIPL-01 Polyvalent Anti-snake Venom Serum (Serum Institute, India)
- Snake Venom Antiserum - Central Africa (Premium Serums and Vaccines Pvt. Ltd., India)
- Snake Venom Antiserum Afriven (VINS Bioproducts Ltd, India)
- Snake Venom Antiserum *Echis Ocellatus* - Echiven (VINS Bioproducts Ltd, India)
- V-ASV polyvalent antivenom (Virchow Biotech, India)

Investigational SBE candidates

Biologics

Immunoglobulin products - animal plasma/serum derived

- Chicken anti-neurotoxin IgY (ANT- IgY) (egg yolk derived) (against cobra and krait)
- Chicken IgY (egg yolk derived) (against *Bitis arietans* and *Crotalus durissus terrificus*)
- Chicken IgY (egg yolk derived) (against *Bothrops alternatus*)
- Chicken IgY (egg yolk derived) (against *Bungarus multicinctus*)
- Chicken IgY (egg yolk derived) (against Cobra, Krait, Russells Viper and Saw-scaled Viper)
- Chicken IgY (egg yolk derived) (against *D. acutus*, China)
- Chicken IgY (egg yolk derived) (against *D. acutus*, Taiwan)
- Chicken IgY (egg yolk derived) (against *Daboia russelii formosensis*)
- Chicken IgY (egg yolk derived) (against *Naja naja atra*)
- Chicken IgY (egg yolk derived) (against *Oxyuranus scutellatus*)
- Chicken IgY (egg yolk derived) (against *Trimeresurus albolabris*)
- Chicken IgY (egg yolk derived) (against *Trimeresurus mucrosquamatus*)
- Chicken IgY (egg yolk derived) (against *Trimeresurus stejnegeri*)
- Combined Bothrops AV + synthetic SVSP peptides pepB and pepC
- Inoserp Europe polyvalent antivenom (against European vipers)
- Murine monoclonal 3FTx-specific IgGs (against *Naja ashei*)
- Novel anti-Crotalus *mictlantecuhtli* rabbit antiserum (against *C. mictlantecuhtli*)
- Novel anti-crotamine polyclonal antibodies (against *Crotalus molossus nigrescens*)
- Novel anti-crotamine polyclonal antibodies (against *Crotalus oreganus helleri*)

- Novel anti-crotamine polyclonal antibodies via recombinant fusion protein immunisation (against *Crotalus* spp)
- Novel anti-short-chain α -neurotoxin (ScNtx) antivenom via toxin immunisation (against elapids)
- Novel anti-short-chain α -neurotoxin D.H. rabbit antiserum via toxin immunisation (against *Micrurus diastema*)
- Novel anti-SVSP antivenom via toxin immunisation (against *Bothrops jararaca*)
- Novel bivalent snake antivenom (IgG) (against *Daboia russelii* & *Echis carinatus*) (Pakistan)
- Novel camelid IgG antivenom (against *Echis sochureki*)
- Novel equine anti-*Bitis* antivenom (against *B. arietans*)
- Novel equine anti-*Bitis* antivenom (against *B. nasicornis* and *B. rhinoceros*)
- Novel equine anti-elapid antivenom (against *N. annulifera*, *D. polylepis*, *D. angusticeps*)
- Novel equine anti-*Naja* antivenom (against *N. melanoleuca*)
- Novel equine anti-*Naja* antivenom (against *N. mossambica*)
- Novel equine blended anti-*Micrurus tener* and anti-ScNtx antibodies (against elapids)
- Novel equine F(ab')₂ antivenom via streamlined processing (against *Vipera ammodytes*)
- Novel equine pan-specific antiserum via diverse-toxin immunisation (against elapids)
- Novel equine/rabbit broad-spectrum antiserum via r3FTX toxin immunisation (against cobra spp)
- Novel F(ab')₂ antivenom (against *Daboia russelii siamensis*) (China)
- Novel freeze-dried trivalent antivenom (FDTAV) (against *Bothrops*, *Lachesis*, *Crotalus*)
- Novel ICP-AVRI-UOP Sri Lankan polyspecific antivenom
- Novel murine anti-haemorrhagic antivenom via DNA immunisation (against *Echis ocellatus*)
- Novel murine antiserum via DNA+ protein boost immunisation (against *Micrurus corallinus*)
- Novel murine antivenom via toxin/peptide immunisation (against *Deinagkistrodon acutus*)
- Novel ovine pathology-specific experimental antivenom (EAV) 1 (against VICC/haemotoxic)
- Novel ovine pathology-specific experimental antivenom (EAV) 2 (against VICC/haemotoxic)
- Novel pan-specific antivenom (against medically significant snakes of India) (Project)
- Novel PNG taipan antivenom (against *Oxyuranus scutellatus*)
- Novel polyvalent equine antivenom (against *Micrurus* spp, Argentina)
- Novel polyvalent equine antivenom (against *Micrurus* spp, Colombia)
- Novel polyvalent murine, equine and rabbit antisera (against *Micrurus* spp, Brazil)
- Novel rabbit antivenom via venom plus toxin immunisation (against *Micrurus* spp)
- Novel Sri Lankan Polyvalent Antivenom (SL PAV)
- Rabbit anti-rDisintegrin polyclonal antibodies (ARDPAs) via recombinant toxin immunisation (against *Crotalus* spp)
- Snake (*Micrurus*) North American immune F(ab')₂ Equine

Immunoglobulin products - recombinant

- Broadly neutralizing antibodies (against Indian and African snakes) (Project)
- Broadly Neutralizing svMP-specific Human mAbs (against North American vipers) (Project)
- Camelid nanobodies (VHH and VHH-Fc) (plant expressed) (against *Naja kaouthia*/ α -cobratoxin)
- Camelid nanobodies (VHH) (against *Bothrops atrox*)
- Camelid nanobodies (VHH) (against *Bothrops jararacussu*)

- Camelid nanobodies (VHH) (against Cobra toxin) (Project)
- Camelid nanobodies (VHH) (against *Daboia russelii*)
- Camelid nanobodies (VHH) (against necrosis-inducing venom toxins (NITs)) (Project)
- Chicken scFv (egg yolk derived) (against *Bungarus multicinctus*)
- Chicken scFv (egg yolk derived) (against *D. acutus*, Taiwan)
- Chicken scFv (egg yolk derived) (against *Daboia russelii formosensis*)
- Chicken scFv (egg yolk derived) (against *Naja naja atra*)
- Chicken scFv (egg yolk derived) (against *Trimeresurus mucrosquamatus*)
- Chicken scFv (egg yolk derived) (against *Trimeresurus stejnegeri*)
- Combined humanised IgG and camelid VHHs antivenom for sub-Saharan Africa (Project)
- Human anti-kaouthiagin scFv (15, 20, and 61) (against *Naja kaouthia*)
- Human monoclonal antibodies (IgG) (broad spectrum anti-snake venom) (Project)
- Human oligoclonal recombinant IgG antibodies (against *Dendroaspis polylepis*)
- Human polyclonal scFv (against multiple Iranian snakes)
- Human recombinant IgG antibodies (against *Naja kaouthia*/α-cobratoxin)
- Human recombinant polyclonal F(ab) (against *Echis carinatus*)
- Human scFv (against *Macrovipera lebetina*)
- Human scFv (B7, C11, and E9) (against *Bothrops jararacussu* and *Crotalus durissus terrificus*)
- Human scFv (C13, C24, C39, C43, and C45) (against *Naja oxiana*)
- Human scFv (G12F3) (against *Naja oxiana*)
- Humanised murine mAbs (against venom-induced consumption coagulopathy) (Project)

- PEO-1 plantivenom (camelid VHH, plant expressed) (against *Bothrops asper*)
- scFvBaP1 (plant expressed) (against *Bothrops asper*)
- scFv-Svmp (chicken derived, plant expressed) (against *Bothrops pauloensis*)
- Vipax (synthetically evolved camelid nanobody-based antivenom)

Non-immunoglobulin products - animal/naturally derived/recombinant

- BJ46a (endogenous SVMPI) (against *Bothrops jararaca*)
- Naked DNA (Calf thymus)
- rAnti-3FTX nAChR-binding proteins (Ls-AChBP and humanized α7-AChBP)
- rBaltMIP (alpha snake blood PLA₂ inhibitor) (from *Bothrops alternatus*)
- rDM64 / DM64 protein (from opossum protein DM64)
- Recombinant endogenous snake toxin inhibitors (Project)
- rLTNF-11 peptide (from opossum protein oprin)
- rOprin-like (DM43-like) protein (from opossum protein oprin/DM43)
- rTryptase β / Tryptase β (human mast cell tryptase)
- saPLIγ (gamma snake blood PLA₂ inhibitor) (from *Sinonatrix annularis*)

Drugs

Therapeutic - natural/botanical

- 14-acetylandrographolide (Andrographis paniculata extract isolate)
- 14-deoxy-11,12 didehydroandrographolide (Andrographis paniculata extract isolate)
- 14-deoxy-11-oxoandrographolide (Andrographis paniculata extract isolate)
- 2-hydroxy-4-methoxybenzaldehyde (polyphenol plant extract isolates)
- 4',7-dihydroxy-5-methoxyflavone-8-C-β-D-glucopyranoside (Oxalis corniculata extract isolate)

- Andrograpanin (*Andrographis paniculata* extract isolate)
- Aristolochic acid (*Artistolochia* sp. extract isolate)
- Bakuchiol (plant extract isolate)
- Betulinic acid
- BRS-P19 (*Bauhinia rufescens* seed extract isolate)
- Butein (plant extract isolate)
- Caffeic acid (polyphenol plant extract isolate)
- Caftaric acid (polyphenol plant extract isolate)
- Casuarictin (*Laguncularia racemosa* extract isolate)
- Chicoric acid (polyphenol plant extract isolate)
- Chlorogenic acid (polyphenol plant extract isolate)
- Crepiside E beta glucopyranoside (*Elephantopus scaber* extract isolate)
- Fucoidan (Brown seaweed extract isolate)
- Gallic acid (polyphenol plant extract isolate)
- Go3 (Green seaweed extract isolate)
- Hesperetin (citrus extract isolate)
- Hispidulin (*Moquiniastrum floribundum*/*Aegiphila integrifolia* extract isolate)
- Ikshusterol3-O-glucoside (*Clematis gouriana* extract isolate)
- Isoandrographolide (*Andrographis paniculata* extract isolate)
- Jatromollistatin (*Jatropha mollissima* extract isolate)
- Kolaviron (flavanoid plant extract isolate)
- Lansiumamide B (*Clausena excavata* extract isolate)
- Lupeol (*Aegiphila integrifolia* extract isolate)
- Mannitol (*Aegiphila integrifolia* extract isolate)
- Mimosine (*Mimosa pudica* extract isolate)
- Myricetin (polyphenol plant extract isolate)
- Oleanolic acid
- p-Coumaric acid (polyphenol plant extract isolate)
- Pectolarigenin (*Aegiphila integrifolia* extract isolate)
- Pinostrobin (*Renealmia alpinia* extract isolate)
- Piperine (*Piper longum* L extract isolate)
- Quercetin (polyphenol plant extract isolate)
- Quercitrin (*Euphorbia hirta*/polyphenol extract isolate)
- Rosmarinic acid (polyphenol plant extract isolate)
- Rutin/Rutin succinate (polyphenol plant extract isolate)
- Scutellarin (flavanoid plant extract isolate)
- Silymarin (milk thistle extract isolate)
- Spiro [androst-5-ene-17,1'-cyclobutan]-2'-one,3-hydroxy-(3 β ,17 β)
- Stigmasterol (*Aegiphila integrifolia* extract isolate)
- Sulfated agar (Red seaweed extract isolate)
- Tannic acid (polyphenol plant extract isolate)
- Ursolic acid
- Vanillic acid (polyphenol plant extract isolate)
- Vitamin B complex
- Vitamin C (Ascorbic acid)
- Vitamin E
- Vitexin (flavanoid plant extract isolate)
- Zinc / zinc oxide (ZnO) complex (ZC)
- β -sitosterol (*Aegiphila integrifolia*/citrus extract isolate)

Therapeutic – synthetic

- 1-(2-methyl-8-naphthalen-1-yl-imidazo-[1,2- α]pyridin-3-yl)ethanone
- 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF)
- 4-benzoyl-3-hydroxyphenyl benzoate (BHB)
- Abiotic hydrogel nanoparticle (against Elapids)
- Abiotic synthetic nanoparticle TIMP-mimicking polymers (against SVMs)

- Acetylsalicylic acid (ASA)
- ADDovenom: ADDomer and ADDobody protein-based NP neutralizing superbinders (Project)
- Anti-batroxobin (SVSPs) peptides (pepC and pepB) (against *Bothrops jararaca*)
- Anti-dendrotoxin peptides (via phage display) (against *Dendroaspis polylepis*)
- Anti-myotoxin II peptides (via phage display) (against *Bothrops asper*)
- Anti-necrotic enzyme inhibitors (against necrosis-inducing venom toxins) (Project)
- Anti-PLA₂ peptides (via phase display/ on M13 phages) (against Western cottonmouth)
- Anti-α-cobratoxin peptides (via phage display) (against *Naja kaouthia*)
- Batimastat
- C60 fullerene nanoparticle
- Carbodithioates (benzyl 4-nitrobenzenecarbodithioate)
- Dexketoprofen
- Diethylene triamine pentaacetic acid (DTPA)
- Dimercaprol
- Disulfiram
- DMPS (Unithiol)
- DNA aptamers (against *Bungarus multicinctus*/α-bungarotoxin)
- DNA aptamers (against Daboxin P/*Daboia russelii*)
- DNA aptamers (against *Naja melanoleuca*)
- EDTA / CaNa₂EDTA
- Flurbiprofen
- Gold nanoparticle conjugated andrographolide (GNC-andrographolide)
- Gold nanoparticle Vitex negundo conjugated (VN-GNP)
- Gold nanoparticle-conjugated 2-hydroxy-4-methoxybenzoic acid (GNP-HMBA)
- Heparin / LMWH
- Ketoprofen
- Marimastat
- Marimastat Varespladib mixture
- Methyl-varespladib
- Morphine
- N,N,N',N'-tetrakis (2-pyridylmethyl) ethane-1,2-diamine (TPEN)
- Nafamostat
- Oral broad small molecule toxin inhibitors (Project)
- p-bromophenacyl bromide (pBPB)
- Prinomastat
- Silver nanoparticles (AgNPs)
- Sodium silicate complex (SSC)
- Suramin
- Synthetic peptides from atPLI_γ (gamma snake blood PLA₂ inhibitor) (from *Bothrops atrox*)
- Synthetic SVMPI peptides: pERW and pEKW (against *Daboia russelii siamensis*)
- Synthetic variant peptide BLG-col (from β-Lactoglobulin, Buffalo Colostrum)
- Thioesters (2-Sulfonyl Ethylacetate derived)
- Thiosemicarbazones (5A and 5B)
- Titanium dioxide nanoparticles (TiO₂-NPs)
- Varespladib
- X-Aptamers (against North American snakes) (Project)

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POLICY CURES RESEARCH

www.policycuresresearch.org

info@policycuresresearch.org

55 Brisbane Street, Surry Hills,
NSW 2010 Australia
Tel: +61 (2) 8218 2109

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