Stakeholder consultation on Snakebite Envenoming in Africa: R&D, Innovation and Financing
Since 2019, Policy Cures Research (PCR) has partnered with Wellcome to deliver critical data and analysis on the state of the snakebite envenoming (SBE) R&D landscape. Given the extensive burden of snakebite envenoming on the African continent and the ongoing antivenom crisis it is clear that there is an especially strong need to address this region and look at ways to integrate R&D and access perspectives. In partnership with Market Access Africa (MAA), PCR convened an expert stakeholder consultation on 14 June 2023, following the WHO Global Neglected Tropical Disease (NTD) Programme Partners’ meeting, to represent the broad range of disciplines and knowledge relevant to discuss R&D, innovation and financing for SBE in Africa. The consultation contributed cross-sectoral perspectives to ongoing efforts to develop an African SBE Plan and make a series of initial recommendations for next steps that the community can leverage upon. PCR and MAA wish to thank all participants for their valuable input and contributions to the discussion.

**Key points of convergence during the meeting:**

- There is an established list of therapeutics, diagnostics, and an emerging consensus for a coordinated vision on SBE R&D in Africa, including moving towards a portfolio approach, the need for prioritisation of research and a specific SBE R&D agenda.

- Partnerships and collaboration are essential to address challenges and prioritise research areas in SBE, despite the lack of clarity on realistic R&D capacity in Africa.

- There’s an increased understanding of why funders are investing in SBE R&D, though further exploration is needed to attract potential new funders and new funding.

- There’s an opportunity to design governance structures and mechanisms to effectively coordinate among researchers, funders, and to set a common R&D agenda at this critical juncture.

**Next Steps:**

- Plan a subsequent meeting to start to ideate a suitable governance structure to facilitate coordination among researchers and funders. With a defined governance structure, work collectively towards establishing a common R&D agenda and prioritisation framework.

- Present the outcomes of this consultation, and the subsequent session focusing on Access led by Market Access Africa, at an event co-hosted by Policy Cures Research, the Geneva Health Forum, the University of Geneva and Médecins Sans Frontières in Geneva on September 19 2023. The September event aims to introduce SBE to new actors and traditional NTD organisations to accelerate convergence on R&D and engage new actors.

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**Aim:** Validate the SBE R&D landscape in Africa for therapeutics and diagnostics and discuss pertinent next steps to clarify the R&D agenda. A list of therapeutics and diagnostics applicable for Africa was shared with the group in advance of the meeting (see Annexe II).

- **For therapeutics,** 37 candidates were in the pipeline and 18 products available on the market targeting African snake species. The pipeline was evenly split between biologics and drugs, with a focus on animal/plasma derived products and repurposed drugs. In Africa, challenges for therapeutics include: vast majority of candidates remain in early-stages of development, a lack of endogenous research, the availability and quality of pre-clinical and clinical data varies significantly for products on the market and limited manufacturing capacity.

- **For diagnostics,** only 6 studies targeting African snake species were identified, almost all are ELISA-based tests. Diagnostic R&D is under-researched and underfunded across NTDs, including SBE. Benefits of prioritising diagnostic R&D include improved patient care, epidemiology and antivenom development. Challenges of diagnostic R&D include technical aspects like ensuring affordability, sensitivity, and specificity as well as robustness when using real patient samples. There are also implementation challenges for deploying diagnostics in the field.

**Discussion:** The discussion underscored a desire to design a portfolio approach to innovation with a high-level view that allows to avoid duplication between product developers. Examples mentioned include Access to COVID-19 Tools (ACT) Accelerator and the Global AMR R&D hub. A key aspect of a prioritisation framework should be affordability, the objective should be getting out a product, or a combination of products, which is more affordable and cost-effective than existing products.

Snakebite remains an emergency in urgent need of treatments, and with an immature pipeline. We need to incorporate a temporal element to our portfolio or coordination approach – what is the minimum need in the short-term and what is the ideal that we want in the long-term. Another facet of coordination for the R&D agenda is the development of combination treatments and how to prioritize and evaluate them. Early collaboration between developers, regulators and communities will be needed and can be slotted into the portfolio approach as we have seen with other diseases.

The concept of redundancy is important to ensure that several products are available for the region and can compensate for unforeseen issues which impact manufacturing capacity. We should look to identify key actor archetypes in the R&D and manufacturing ecosystem of other regions like Central and South America and find counterparts in Africa to address the asymmetry in research and manufacturing power.

**Outcomes:** We have compiled a comprehensive list of therapeutics currently available and under investigation, along with diagnostics, specifically designed for Africa. We are also closer to drawing consensus around the need for a coordinated vision of SBE R&D on the continent including portfolio approach, prioritisation and an agenda. We need to keep working together to establish concrete steps towards guiding documents like an R&D agenda and investigate suitable structures of coordination to do this.
Aim: Understand the challenges to, and capacity for, R&D in Africa, looking at the R&D pathway including: translating pre-clinical biologics research, clinical trial capacity and the WHO’s risk-benefit assessment.

- **Overview of R&D pathway**: highlighted new technologies in the pipeline, distinguishing between venom-specific and toxin-specific approaches and how we’ll need a combination of modalities, with robust pre-clinical and clinical data, to tackle the diversity of pathologies resulting from envenomings.

- **Challenges to translating pre-clinical research**: bottlenecks for translation included neutralising complex cocktails of toxic proteins, selection of appropriate pre-clinical models and endpoints to evaluate candidates, the lack of funding for later-stage research and manufacturing.

- **Clinical trial capacity**: Only one adequately powered clinical trial has been conducted in Africa and more are urgently needed to assess current products and assess future candidates. Clinical trials are hard to run globally, not just in Africa. Furthermore, we shouldn’t shy away from re-examining our assumptions of what is good practice or gold-standard for SBE.

- **WHO risk-benefit assessment**: A total of 13 products have applied for the risk-benefit assessment for sub-Saharan Africa some of which have been successful, terminated, pending GMP compliance or reapplied, with three new applications in 2023 alone.

Discussion: As in the previous session, the need for partnerships among various stakeholders and coordinated approaches to R&D (prioritisation, agenda, technical strategy) was reiterated.

On clinical trials, there is a need for continued standardisation, data integration and sustainable site resourcing to support future clinical studies, especially clinical trials for products on the market without clinical data. Clinical trial capacity is available in Africa and increasing off the back of the COVID-19 pandemic.

Understanding the role of biomarkers is key for mapping the contribution of different toxins to envenomation pathologies, which could serve as more sensitive outcome measures. Improved diagnostics capable of accurately detecting specific toxins, such as PLA2s could be potential tools for evaluating the efficacy of small molecule inhibitors. Looking to the future, guidance is needed on how to support testing for combination therapies, emphasising early engagement between sectors to streamline approval and uptake.

Despite promising developments, there are concerns about the fragile ecosystem and what that means for market entry of next-gen products and delivery of existing antivenoms, the “second valley of death” in product development. Overarching this, limited donor interest for SBE, and NTDs more broadly, is worrying.

Outcomes: Clear consensus on the need for partnership and convergence on points like research prioritisation and an R&D agenda. However, the group did not get a clear understanding of the realistic R&D capacity in African regions; there is work to be done to clarify this. Concerns on limited donor interest need to be addressed more broadly but will touched on at the September 19 2023 event in Geneva.
Aim: The aim of this session was to better understand the reasons why certain funders have entered the SBE R&D space and how this can inform engaging other potential funders, including innovative coordination and financing mechanisms.

- Key moments that brought Wellcome concretely into the SBE R&D space included the Hinxton retreat on 'Mechanism to reverse the public health neglect of tropical snakebite victims' in 2015 which brought together key stakeholders and advocates. In addition, the involvement of Kofi Annan as a high profile figure in global health bringing attention to "the biggest public health crisis you've never heard of" was important in galvanising action. Stakeholder convergence and advocacy efforts are needed to attract new actors. While the program is due to end in 2026, Wellcome expressed their intention to build partnerships with other funders for a sustained impact as part of the legacy of the program.

- Open Philanthropy aims to fill funding gaps where other funders aren’t yet active in areas that are neglected, like SBE. Their criterion focuses on high impact, transformative research, neglectedness, and tractability. In terms of the third criterion, tractability, they emphasize the probability of success and the potential for significant positive effects on people’s lives measured using a mix of quantitative approaches focusing on logistics, uptake and price. Open Philanthropy has picked up on the tractable solution in development for SBE, which is why they’ve entered this space.

Discussion: the discussion centred on collaboration and convergence among funders in the SBE R&D space. A possible funders group governance structure could include information sharing without pooling money, allowing for individual funding decisions based on collective priorities like the Global Funders Consortium for Universal Influenza Vaccine Development. It was also highlighted that a clear R&D agenda and a cohesive and coordinated research community facilitates funders’ decision-making process.

With a lot of the funding in this field earmarked for basic and early-stage research, the space needs to diversify the funders base to ensure activities across the research, and programmatic, spectrum can be sustainably funded. For R&D, this especially concerns funding for late-stage clinical studies and manufacturing. The European and Developing Countries Clinical Trials Partnership (EDCTP) was highlighted a key actor in the NTD R&D ecosystem and serves a critical function for clinical trial capacity in Africa who are not yet active in SBE. The establishment of the African Pharmaceutical Technology Manufacturing Foundation was identified as another promising development for manufacturing in Africa.

Overall, the group emphasized the importance of formally bringing funders together, identifying and communicating collective priorities to funders, and implementing mechanisms to facilitate collaboration and coordination between researchers.

Outcomes: An improved understanding of the rationale behind funders entering this space, some of the key factors which have led to philanthropics investing in SBE R&D and potential pathways to facilitating funding-decisions through different levels of coordination. Taking this forward, it needs to be reviewed for application on different funder profiles and to assess the likelihood of traditional NTD funders to be interested in this space.
Conclusions

This first stakeholder consultation on R&D, innovation and access for SBE in Africa was a success in bringing together key actors to discuss and brainstorm. While many technical aspects were discussed, a key message came out across the different sessions – the need for cooperation and coordination.

We are at an inflection point and have an opportunity to begin designing governance structures that will allow us to effectively coordinate, between researchers, between funders, as well as defining a common agenda of R&D priorities. Overall, much groundwork has already been done thanks to the incredible contributions of the diverse SBE community. Now we must work together to consolidate our knowledge base, and design coordination mechanisms that are fit-for-purpose and will facilitate converging towards common goals.

The following recommendations are made based on the group’s discussions:

- Encourage SBE actors to conduct an “internal audit” of their organisation's goals and capacity to contribute towards a common SBE R&D agenda

- Encourage increased transparency between actors so the SBE R&D community can come together to critically assess the capacity of the R&D ecosystem and resources available to better visualise the needs to accelerate R&D

- Map the sector for champions based on organisational capacities and goals via timely subsequent meetings post-consultation

- Organise subsequent meetings to align and agree on a chosen governance structure for both researchers and funders to facilitate coordination and harmonization.

By establishing a governance structure comprising funders and researchers, and with a realistic understanding of the community’s capabilities and objectives, we can initiate collaborative efforts towards developing a shared research and development (R&D) agenda and defining priorities

Next steps:

- Market Access Africa is hosting a subsequent virtual stakeholder consultation focusing on access to SBE treatments in Africa in late August 2023. For more information on the meeting, please contact Dr Sonia Osi, sosilmarketaccess.africa

- Present the outcomes of these consultations at an in-person event in Geneva on 19 September 2023. The event is co-hosted by Policy Cures Research, the Geneva Health Forum, the University of Geneva and Médecins Sans Frontières for Accelerating R&D for Snakebites: Building a Common Agenda for Progress. This event aims to introduce SBE to new actors and traditional NTD organisations to accelerate convergence on R&D and engage new actors. For more information on the event, please contact Juliette Borri, jborri@policycuresresearch.org

- Plan a subsequent meeting to start to ideate a suitable governance structure to facilitate coordination among researchers and funders. With a defined governance structure, work collectively towards establishing a common R&D agenda and prioritisation framework.
Participant list

- Abdulrazaq Habib (Bayero University Kano)
- Andrés Hernández (Instituto Clodomiro Picado)
- Andrew Tuttle (Policy Cures Research)
- Anne Ljungars (Technical University of Denmark)
- Cecilie Knudsen (VenomAid)
- David Williams (World Health Organization)
- Diogo Martins (Wellcome)
- Emmanuelle Bomo (Policy Cures Research)
- Gabriel Alcoba (MSF Geneva / Hôpitaux Universitaires de Genève)
- George Omondi (Kenya Snakebite Research and Intervention Centre)
- George Phillips (Wellcome)
- Heather Young (Open Philanthropy)
- Isabela Riberio (DNDi)
- John Amuasi (African Research Network for Neglected Tropical Diseases)
- José María Gutiérrez (Instituto Clodomiro Picado)
- Julien Potet (MSF Access)
- Juliette Borri (Policy Cures Research)
- Mathew Lewin (Ophirex / California Academy of Sciences)
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- Naoual Oukkache (Institut Pasteur du Maroc)
- Nick Casewell (Liverpool School of Tropical Medicine)
- Omu Anzala (Kenya AIDS Vaccine Initiative - Institute for Clinical Research, KAVI-ICR)
- Sally Stephens (Ophirex)
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**Therapeutic candidates targeting at least one African snake species**

- Chicken IgY (egg yolk derived) (against Bitis arietans and Crotalus durissus terrificus)
- Murine monoclonal 3FTx-specific IgGs (against Naja ashei)
- Novel anti-short-chain α-neurotoxin (ScNtx) antivenom via toxin immunization (against elapids)
- 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 pan-specific antiserum via diverse-toxin immunization (against elapids)
- Novel murine anti-haemorrhagic antivenom via DNA immunization (against Echis ocellatus)
- Novel ovine pathology-specific experimental antivenom (EAV) 1 (against VICC/haemotoxic)
- Novel ovine pathology-specific experimental antivenom (EAV) 2 (against VICC/haemotoxic)
- Broadly neutralizing antibodies (against Indian and African snakes) (Project)
- Camelid nanobodies (VHH) (against Cobra toxin) (Project)
- Camelid nanobodies (VHH) (against necrosis-inducing venom toxins (NITs)) (Project)
- Combined humanised IgG and camelid VHHs antivenom for Sub-Saharan Africa (Project)
- Human oligoclonal recombinant IgG antibodies (against Dendroaspis polylepis)
- Human scFv (against Macrovierea lebetina)
- Vipax (synthetically evolved camelid nanobody-based antivenom)
- rAnti-3FTX nAChR-binding proteins (Ls-AChBP and humanized α7-AChBP)
- BRS-P19 (Bauhinia rufescens seed extract isolate)
- Rosmarinic acid (polyphenol plant extract isolate)

**Antivenom products on African market**

- Inoserp PAN-AFRICA (INOSAN BIOPHARMA S. A., Spain)
- Snake Venom Antiserum Afriven (VINS Bioproducts Ltd, India)
- Polyvalent Anti-Vipers Serum (Egyptian Organisation for Biological Products and Vaccines (VACSERA), Egypt)
- Antivipmyn Africa (Instituto Bioclon/Laboratorios Silanes, S. A. de C. V., Mexico)
- SAIMR Polyvalent Snake antivenom (South African Vaccine Producers, South Africa)
- Snake venom antiserum - Pan Africa (Premium Serums and Vaccines Pvt. Ltd., India)
- Gamma-Vip (Institut Pasteur de Tunis, Tunisia)
- Anti Snake Venom Serum Central Africa - 6 (Biological E Limited, India)
- Polyvalent Anti-Snake Serum (Egyptian Organisation for Biological Products and Vaccines (VACSERA), Egypt)
- Combipack of Snake Venom Antiserum (African- Ten) (Premium Serums and Vaccines Pvt. Ltd., India)
- IPAVIP Antiviperin Sera (Institut Pasteur d’ Algerie, Algeria)
Annexe II

- ASNA-C (Bharat Serums and Vaccines Limited, India)
- Inoserp MENA (INOSAN BIOPHARMA S. A., Spain)
- Snake Venom Antiserum - Central Africa (Premium Serums and Vaccines Pvt. Ltd., India)
- FAV-Afrique (Sanofi Pasteur, MicroPharm)
- Anti Snake Venom Serum Pan Africa - 10 (Biological E Limited, India)
- Snake Venom Antiserum Echiven Plus (VINS Bioproducts Ltd, India)
- SAIMR Echis antivenom (South African Vaccine Producers, South Africa)
- Anti Snake Venom Serum Monovalent Echis ocellatus (Biological E Limited, India)
- EchiTAbG (MicroPharm Ltd, United Kingdom)
- Snake Venom Antiserum Echis Ocellatus - Echiven (VINS Bioproducts Ltd, India)
- SAIMR Boomslang antivenom (South African Vaccine Producers, South Africa)
- Snake Venom Antitoxin - Menaven (VINS Bioproducts Ltd, India)
- EchiTAb-plus-ICP (Instituto Clodomiro Picado, Costa Rica)
- Snake Venom Antiserum African - 10 (VINS-A) (VINS Bioproducts Ltd, India)
- Favirept (MicroPharm UK, previously Sanofi-Pasteur, France)

**Diagnostics tests targeting African snake species**

- Immuno-diffusion assay targeting *B. arietans*, *C. maculatus*, *E. carinatus*, *N. haje*, *N. melanoleuca*, *N. nigricollis* (area: Africa)
- ELISA test targeting *B. arietans*, *C. maculatus*, *E. carinatus* (area: Multiple)
- ELISA test targeting *B. arietans*, *C. maculatus*, *E. carinatus* (area: Nigeria)
- ELISA test targeting *E. pyramidum* (area: Tunisia)
- ELISA test targeting *N. haje*, *N. nigricollis*, *W. aegyptia* (area: Egypt)
- LFA test targeting *Naja spp.* (area: Asia and Africa)