

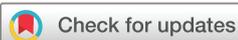
Snakebites and COVID-19: two crises, one research and development opportunity

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As the world battles COVID-19, other long-standing global health challenges continue to cause illness, suffering and death. Among them is the neglected crisis of snakebite envenoming (SBE): in the year after the COVID-19 pandemic was declared, an estimated 2.7 million SBE led to over 100 000 deaths and 400 000 long-term disabilities in the poorest and most rural communities of Asia, Africa and Latin America.¹ Yet the tools used to combat SBE remain woefully inadequate and underexplored, with the most commonly-used antivenom treatments still based on 19th-century technologies.

An oft-heard concern during the COVID-19 crisis is that shifts in research and development (R&D) spending may reduce support for neglected tropical diseases (NTDs) like SBE. Indeed, in April 2020 the WHO issued interim guidance to postpone NTD programmes and activities because of the pandemic.² The direct and indirect impacts of COVID-19 will likely endure for years.

Yet at the same time, long-term opportunities for SBE have also emerged. Notwithstanding major differences in nature, magnitude and global visibility of these two public health crises, experience gained with COVID-19 can be successfully applied to NTDs, and SBE specifically. In this article, we briefly recap the challenging status of current SBE tools and identify key lessons and recommendations from COVID-19 that could help refocus funding and accelerate progression of novel SBE candidates in the R&D pipeline. Our aim is to highlight the enormous promise of finally bringing 21st-century technologies and approaches to the age-old problem of SBE.

THE SBE STATUS QUO

SBE poses major unmet medical needs for both diagnosis and treatment, including a

Summary box

- ▶ Despite inherent differences, Snakebite Envenoming and COVID-19 have much in common in terms of research and development (R&D) challenges and opportunities.
- ▶ Both crises require a diversified portfolio of R&D solutions, ranging from diagnostics to treatments, that can effectively work and be accessible in different resource settings.
- ▶ Collaborative clinical research and streamlined regulatory pathways are critical to accelerate these candidates in the R&D pipeline.
- ▶ Transformative progress is possible with a concerted approach that aligns strong political will, coordinated financing and the needs of the most marginalised communities.

reliance on antivenoms as the cornerstone of treatment. While antivenoms save lives and prevent sequelae, they also present myriad challenges (see [box 1](#)). These range from not knowing for many patients what snake species was involved (key information for selecting which serum to use) to the limited manufacturing capacity in high-burden regions—exacerbated by the complicated, expensive method needed to produce antivenoms. Additional, post-manufacturing challenges include a lack of clinical testing or proper quality control for many circulating products as well as difficulties ensuring availability and access, not least the need for an effective cold chain management system to distribute and store most available products.

There is clearly an urgent need for a range of solutions, from better-designed, quality-assured conventional antivenoms to novel diagnostics and therapeutics and robust, efficient clinical testing approaches—all tailored to the needs of patients in low-resource settings.

Box 1 Challenges with using antivenoms in snakebite envenoming treatment

- ▶ Still uses early 1900's complex production process that cannot be fully standardised (isolation from hyperimmune plasma of immunised animals, usually horses). Technical innovations such as IgG and (Fab')₂ purification have been introduced but not uniformly adopted across manufacturers.¹¹
- ▶ Usually specific for one or few snake species, but products are often used in settings where they do not target all medically important species.
- ▶ Unknown efficacy and safety profiles for many products, few of which have been evaluated in robust clinical trials.⁷
- ▶ Insufficient quality control based on WHO guidelines, leading to many ineffective products in circulation.¹
- ▶ Supply shortages that lead to severely limited access, especially in sub-Saharan Africa.¹
- ▶ High prices, leading to potentially catastrophic cost when victims need to pay out of pocket.¹²

KEY COVID-19 LESSONS FOR CLOSING THE SBE R&D GAP

Need for a robust portfolio of candidate products

COVID-19 and SBE management and control each require a wide variety of tools, and therefore an R&D pipeline with candidates based on a variety of strategies—since inevitably some products will fail. As of December 2020, the global pipeline for COVID-19 candidates contained over 1000 potential new vaccines, therapeutics and diagnostics.³ Although we lack a complete picture of the SBE product pipeline, recent data indicate that half of R&D funding between 2007 and 2018 focused on basic research, with the remaining minimal, fluctuating resources divided across biologics, drugs and, to a very limited extent, drugs and diagnostics.⁴

The result is that, despite their limitations, antivenoms remain the only tool available in low-resource settings, while promising next-generation therapeutic and

diagnostic approaches based on newer strategies languish in the pipeline (see table 1).

Impact of innovative pathways for research and regulatory approval

Innovating clinical research and streamlining regulatory approaches have been crucial to accelerating the progress of COVID-19 candidate products. Some of the most successful COVID-19 clinical trials, designed to produce definitive, actionable results, have been large, multisite, multicountry and/or consortium-based trials using a platform-based approach to facilitate integration and standardisation⁵—for example, the UK-based Recovery trial of treatment for hospitalised patients.⁶ In many cases, regulatory pathways were also streamlined and fast-tracked without compromising the robustness of the respective assessments. Given the scarcity of rigorous clinical studies on efficacy or safety of antivenoms,⁷ similar collaborative approaches will be essential to efficiently advance appropriate products through the R&D pipeline and ensure accelerated review and approval.

Importance of diversified financing and incentives for R&D

The year 2020 has shown dramatically that with enough resources, focus and political will, significant improvements are possible far faster than with 'business-as-usual' approaches. While there are no precise numbers for worldwide spending on COVID-19 R&D in 2020, overall R&D spending in biopharma increased 23% (to US\$44 billion) from 2019, much of which was on the new disease. Over US\$9 billion in funding announcements had been made across public, philanthropic and industry partners to support candidate products as of October 2020.³ One year into the pandemic, several highly effective vaccines and many diagnostic products had already received market authorisation.

In contrast, between 2007 and 2018 global funding for SBE research totalled only US\$57 million (a mean annual

Table 1 Examples of promising products in the R&D pipeline for SBE

Product categories	Mechanism of action	Description and potential use
Small-molecule inhibitors ¹³	Inhibition of venom phospholipase A2 (sPLA ₂) enzyme Inhibition of venom metalloproteases	<ul style="list-style-type: none"> ▶ Promising rapid treatment for venom-induced neurotoxicity and cytotoxicity ▶ Can be administered quickly, before patient accesses injectable antivenoms, or as adjuvant treatment ▶ Neutralisation of broad spectrum of venoms ▶ Inhibits haemorrhagic activity of venoms ▶ Acceptable safety profile for use as anticancer drug due to antiangiogenesis properties
Monoclonal antibodies (mAbs) ¹⁴	Neutralisation of venom	<ul style="list-style-type: none"> ▶ Neutralisation of key toxins from different snake species by binding to conserved epitopes ▶ Creation of region-specific cocktails of a few antibodies tailored to local snake distribution ▶ Reduced risk of anaphylactic shock with use of humanised mAbs
Rapid diagnostic tests ¹⁵	Venom-identification kits	<ul style="list-style-type: none"> ▶ Earlier diagnosis of systemic envenomations ▶ Improved identification of offending snake species ▶ More rational use of antivenoms

R&D, research and development; SBE, snakebite envenoming.

investment of less than 5 million).⁴ According to the latest G-Finder report, funding for snakebite-related R&D totalled US\$10.29 million in 2019, equivalent to only 0.3% of all R&D investment in neglected diseases⁸—although still, an increase of over 60% (US\$3.7 m) from 2018. Much of this growth came from the UK, which provided three-quarters of all SBE global funding in 2019. Industry funding also doubled. Together, these increases drove a near-fourfold rise in funding for snakebite biologics (up US\$ 5.4 million). Still, the total R&D investment remains quite small and is currently in extreme jeopardy since the UK, as the main investor, recently announced funding cuts effective in mid-2021 of up to 90% for many NTD programmes,⁹ decreases which will severely impact ongoing SBE projects. More broadly, this chronic underfunding has slowed progress in R&D for new technologies and has limited development of solutions to ensure that safe, effective and accessible products reach the markets where they are most needed.

Imperative to address inequities and priorities from resource-limited settings

Despite the massive budgets and innovation driving COVID-19 product development, a huge imbalance remains in mid-2021 between high-income and low-income countries in availability of these tools, especially highly effective vaccines—and consequently in the severity of the pandemic. Most funding so far has strongly prioritised the needs of wealthy countries, and decisions have been made largely by people in and from these settings. Furthermore, though many innovations have been driven by public funding and/or public-interest research institutions, there are presently only very limited requirements known for transparency on R&D and manufacturing costs, or contractual requirements for equitable access. Since populations in poorer countries bear the overwhelming burden of SBE, it is crucial that R&D priorities are driven by their needs and decision-makers, and that investments include robust guarantees for access, potentially including transfer of manufacturing technologies and build-up of production capacity in high-burden regions.

CONCLUSIONS

The past year has demonstrated extraordinary global capacity for R&D mobilisation. Meanwhile, for both COVID-19 and SBE, there have been few solutions and relatively little funding for the health priorities of low-resource settings.

Still, successes with COVID-19 reveal tremendous opportunities to catalyse investments and close the R&D gap for snakebite. Reviving R&D for SBE must involve:

- ▶ A global R&D strategy which considers an end-to-end approach, from basic research to strategies for remote, marginalised communities to access successful products.
- ▶ Development of clinical trial platforms or networks to facilitate standardisation of methodologies,

integration of results, and rapid assessment of new tools for SBE management.

- ▶ Streamlining regulatory pathways to facilitate R&D, encourage innovation and speed the approval of new products given the extreme, longstanding neglect of SBE.
- ▶ A coordinated investment strategy which capitalises on available public funding and leverages greater commitment from the private sector, including biotech firms. It should clearly link R&D objectives with financial incentives that promote both innovation and equitable access to SBE interventions.

High-burden regions must be at the centre of R&D agendas, an obligation underpinning these recommendations.

A post-pandemic world may appear distant for most NTD-affected countries, given the enormous gaps in their access to new products that are gradually controlling the pandemic in high-income regions. But as NTD programmes resume the research community must harness newlygained knowledge, partnerships and collaborative approaches to accelerate progress towards the ambitious 2030 NTD targets^{1 10} and the reduction of health inequities. Each of these components will become increasingly important for success in achieving the WHO goal of reducing death and disability from SBE by 50% within a decade. That time approaches. We must stand ready to challenge the status quo and deliver transformational change.

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