The snakebite problem and antivenom crisis from a health-economic perspective

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A B S T R A C T

The scourge of snakebite has been well documented but largely ignored by the global health community for several decades, especially the role that economics has played in causing and exacerbating this crisis. Every year millions of people in low and middle-income countries face death, disability and disadvantage from snakebite envenoming (SBE) without access to appropriate treatment. Health-economic factors pervade every aspect of this neglected problem. A multitude of financial and commercial factors helped to cause, and now perpetuate, shortages of high quality, affordable and region-appropriate antivenom in areas where they are most needed. Alongside the death, physical disability and psychological anguish from SBE is a debilitating financial toll, which includes both direct costs of treatment and indirect costs from lost income. SBE is a problem that disproportionately affects poor, rural and agrarian communities, with most victims being young and industrious subsistence workers. The burden of envenoming is often felt by families and communities that can least afford it, and negatively impacts local and national productivity. The lack of long-term investment in health systems to properly manage SBE has led to insufficient funding for antivenom development, procurement, quality control and distribution, despite highly favourable cost effectiveness of some antivenoms. This has contributed to market failures that have seen antivenom output fall and become inaccessible to most victims. Solutions to these problems exist and are achievable, however the challenge for advocates is to appreciate the importance of health-economics and ensure that strategies to redress the economic causes and consequences of SBE are themselves cost-effective and financially sustainable.

1. Introduction

To fully comprehend the damage caused by snakebite - one of the world's "newest" yet most neglected tropical diseases - and to better understand many of the factors that perpetuate this sorry saga, one must trace the economic forces woven throughout the story. And the narrative is nothing short of a tragedy: a decades-long significant and neglected problem, exacting a physical, psychological and socioeconomic toll that surpasses many better known global health crises, for which safe, efficacious and cost-effective treatments exist, but are unavailable in sufficient quantities at affordable prices and often mixed amongst inappropriate products.

Financial and commercial factors are central to the many challenges that have contributed to this crisis, and considerable adverse economic consequences also arise for individual victims, their families and communities. The flow-on economic effects of high treatment costs, reduced productivity and lost income impact families and whole communities, sometimes leaving them destitute. The chronic under-resourcing of snakebite is both a cause and effect of the neglect that has come to characterise this problem, perpetuating an unwanted cycle that results in thousands of preventable deaths, millions of cases of disability and countless communities enduring financial stress. Any way one looks at this crisis, there are compelling arguments in favour of immediately ending the neglect.

Snakebite's re-classification as a Neglected Tropical Disease by the World Health Organisation in 2017 hopes to do exactly that, officially ranking it amongst the most significant global health challenges facing some of the poorest communities in the world. This is only the first step towards shining a brighter light on this neglected problem and attracting the much-needed resources to build a better system for managing SBE and saving lives. Understanding the importance of economic factors implicated in this tragedy will ensure that new sources of funding have maximum impact by targeting cost-effective strategies to make treatment more affordable, improve the availability and quality
of antivenom, and better support communities most affected. This will alleviate physical suffering and reduce economic hardship, boosting individual and national productivity along the way.

2. The burden of snakebite

Snakebite envenoming (SBE) is a major cause of morbidity, mortality and economic hardship in many communities in the developing world. It adversely impacts local and national productivity, with disability ratings that surpass many other better-known neglected tropical diseases.

2.1. Mortality and morbidity

A recent global appraisal estimates there were at least 1.8 million SBEs cause 81,000 deaths annually throughout the world (Gutiérrez et al., 2017), with most bites occurring in regional and rural centres. Victims are typically young, productive members of subsistence communities. Deaths from SBE occur largely in Asia and sub-Saharan Africa (sSA), estimated at nearly 70% and 25% respectively (Gutiérrez et al., 2017). In addition to mortality, a significant proportion of SBE survivors develop complications leading to chronic, often lifelong disability or disfigurement such as amputations, blindness, chronic infections, malignant ulcers, chronic fatigue and maternal or foetal loss. Life-changing morbidity in low-income countries throughout Asia and sSA ranges between 20% and 66%. It has been estimated that at least 6000 amputations occur each year following SBE in sSA (Chippaux 2011). Globally, these figures translate to more than half a million people each year suffering permanent or long-term sequelae from snakebite.

Alongside the obvious physical disability from SBE, psychological complications can also be debilitating for victims. Psychiatric manifestations after SBE include depression, post-traumatic stress disorder and impaired functioning, and can impact victims acutely and chronically. A comparative controlled study from Sri Lanka found that 54% of SBE victims met the criteria for a depressive disorder up to 48 months after being bitten, and 27% claimed a negative change in their employment, with more than 10% no longer able to work at all (Williams et al., 2011). Past experiences with snakebite create fear among communities and can limit certain behaviours and activities. Reported rates of post-traumatic stress disorder after snakebite range from 8% to 21.6% (Williams et al., 2011; Khosrojerdi and Amini, 2013).

2.2. Socioeconomic impacts

Socioeconomic adversity is a common and under-appreciated feature of SBE around the world, impacting not just individual victims, but families and communities as well. In some parts of rural India where snakebites occur frequently, treatment and hospital costs have been reported at 50–70 times higher than the monthly household income of 5000 rupees (US$78), with the most extreme cases involving costs equivalent to 12-years salary (Vaiyapuri et al., 2013). This puts many SBE victims in impossible financial situations and entrenches a cycle of poverty and desperation. The lack of financial support for patients and a paucity of funding for healthcare infrastructure leaves victims economically vulnerable and forces the sale of valuable items, livestock, vehicles and land. Worst affected families sometimes send children to work to augment income, thus forgoing an education and opportunity for self-advancement. It is common for post-discharge convalescence to take between 1 and 6 months, placing further strain on families and communities supporting SBE victims who may be unable to properly contribute.

During a research visit to Kaltungo Hospital in Nigeria, a country severely affected by *Echis ocellatus* (West African Carpet Viper) envenoming, the authors interviewed seven current inpatients being treated for SBE who described the significant socioeconomic impacts that result from being bitten by a snake. These patients ranged in age from 4 years to 65 years, and included 4 farmers, 2 rat catchers/hunters and an infant. Patients had travelled an average of 6 h to reach hospital (range 3–12 h) and most had travelled with either 3 or 4 family members for support. Although the patients had been hospitalized for between 1 and 6 days each, they and their carers had been away from their usual daily activities for between 2 and 9 days due to initial consultations with local healers and time taken to arrange travel to the hospital. Modes of transportation to hospital included walking, motorcycle, taxi or family motorcar, and cost between N350 – N7000 (average N3900; equivalent to USD30 at that time). One family indicated that it would take them a whole year to pay off the debt incurred to travel to hospital for treatment. Antivenom treatment was provided at Kaltungo Hospital to these patients for no cost as part of a clinical trial, however those interviewed reported from previous experiences treating other family members who had previously suffered SBE that antivenom treatment can cost between N10,000 – N15,000, in addition to transport and other hospital costs. The families of patients interviewed reported having to sell goats, chickens, cows and farm produce to pay for these costs.

2.3. Impact of snakebite on productivity and national economic indices

Attempts have been made to assess the economic burden that is inflicted by snakebite on national-level economic indices. Snakebite is a major occupational and seasonal problem in agrarian communities involved with subsistence agriculture. Farmers, herders and artisans are at greatest risk of SBE when undertaking their duties during biting seasons. Consequently, mortality from snakebite has been found to be higher in countries with greater proportions of citizens engaged in agricultural labour force, low Human Development Index (HDI), low Gross Development Product (GDP) and with low healthcare expenditure (Harrison et al., 2009). The resulting death and disability from SBE leads to lost work-days, reduced income and financial instability for the family unit. The costs of treatment and supporting victims can affect the wider community and often perpetuates a cycle of deprivation and poverty.

While it has been demonstrated that SBE related death and disability disproportionately affects low-income and agrarian communities, the negative impact that snakebite has on a country’s overall productivity, such as gross domestic product (GDP), has not been formally evaluated. However when the overall incidence, mortality and disability rates are combined with the known relationship to occupations that are significant contributors to GDP and national income, the potential for significant adverse effects on the workforce and overall national accounts become clear. In Nigeria, for example, farming, forestry and fishing account for over 30% of the Nigerian workforce, and agriculture constitutes 40% to the country’s GDP [Nigerian National Bureau of Statistics: http://www.nigerianstat.gov.ng]. Other important industries that operate in rural areas, such as mining and resource exploration, also have to contend with the threat of snakebite for their workers. Multinational mining companies that operate in areas where snakes are prevalent commonly educate their workers about prevention and first-aid for SBE, and many have introduced additional protective clothing and deterrents.

2.4. Quantifying the burden of snakebite

Calculating the overall burden of SBE using universal metrics comprising both morbidity and mortality, such as Disability Adjusted Life Years (DALYs), is difficult due to the heterogeneity of snakebite victims, the wide range of possible outcomes and incomplete epidemiological data in some countries. However, quantifying DALYs on a region-by-region basis is possible, for example in West-Africa it has been shown that the burden from SBE would be at least 320,000 DALYs, which is higher than that for many other traditional Neglected Tropical Diseases, e.g., dengue, onchocerciasis and trypanosomiasis (Habib...
Antivenom is currently the only effective treatment for severe envenomation and it is in critically short supply in many developing countries. High quality and safe antivenoms against the most medically important snakes do exist, but are often unavailable or unaffordable to most SBE patients in low and middle-income countries. Despite the World Health Organisation’s recent recognition of SBE as a significant neglected tropical disease (NTD) there remains an enormous amount of work to be done, requiring unprecedented collaboration from major stakeholders, to meaningfully address the crisis in antivenom quality and availability. The snakebite community eagerly await the WHO roadmap towards improving antivenom quality, affordability and the overall plight of snakebite victims.

3. Antivenom crisis

Antivenom is currently the only effective treatment for severe envenomation and it is in critically short supply in many developing countries. High quality and safe antivenoms against the most medically important snakes do exist, but are often unavailable or unaffordable to most SBE patients in low and middle-income countries. Despite the World Health Organisation’s recent recognition of SBE as a significant neglected tropical disease (NTD) there remains an enormous amount of work to be done, requiring unprecedented collaboration from major stakeholders, to meaningfully address the crisis in antivenom quality and availability. The snakebite community eagerly await the WHO roadmap towards improving antivenom quality, affordability and the overall plight of snakebite victims.

3.1. Antivenom quality and availability

The sad reality is that most hospitals in areas where snakebites are common do not have enough stores of reliable antivenom available to treat their patients, even when patients are prepared to pay many months worth of income to acquire it. In these cases, best supportive care is offered to mitigate the toxic effects of the snake venom, resulting in dramatically higher mortality and morbidity. The loss of access to effective antivenoms has resulted in a 2–10× increase in the mortality rate in some areas (Habib and Warrell, 2013; Visser et al., 2008).

Considering that antivenom has been in use for over 100 years, there have been surprisingly few clinical trials completed to assess its effectiveness; antivenom is not routinely tested in placebo-controlled phase 3 or 4 studies. Most antivenom dossiers comprise data from preclinical, phase 1 and phase 2 studies of variable quality, many never having been recorded in a clinical trials register (Aliriol et al., 2015). However, clinicians experienced with using appropriate antivenoms are aware of its potentially dramatic response as an antidote to snake venom, often showing clinical signs of neutralizing toxic venom constituents within hours of administration. Most evidence supporting antivenom efficacy is based on observational before-and-after studies, or studies comparing appropriate versus geographically inappropriate antivenoms. Furthermore, most of the observed evidence has involved SBE with coagulopathic and haemostatic manifestations (Habib and Warrell, 2013). There is limited data on the effectiveness of antivenoms for reversing neurotoxicity, and some authorities believe antibodies are unable to reverse envenoming from presynaptic neurotoxins.

It is well known that antivenom efficacy can be highly variable, and largely depends on the concentration of specific antibodies against the target snake venom. The highest potency antivenoms currently marketed can effectively reverse envenoming after administration of 1–2 ampoules of specific antivenom (Abubakar et al., 2010). However, low potency antivenoms, which are also usually far less expensive per ampoule, sometimes require > 20 ampoule to show clinical effectiveness (Das et al., 2015). Completely ineffective or counterfeit antivenoms are also sometimes inappropriately marketed in regions containing snake species with venom unrelated to the specific antivenom (Warrell, 2008). These ineffective antivenoms are a major source of harm, waste and confusion as they absorb the limited financial capabilities of health systems and erode the reputation of what should be life-saving and highly-effective medicine.

Although the safety profiles of antivenom have improved markedly since Albert Calmette first infused hyperimmune horse serum to treat SBE in 1894, existing antivenoms are still derived from heterologous animal serum rich in polyclonal immunoglobulins. Animal antiserum are associated with early adverse reactions (EAR) and late serum reactions. Modern production and purification processes have seen the risk of EAR drop significantly, and have been measured at between 5% and 57%, with life threatening anaphylaxis in ~1% (Meyer et al., 1997, Abubakar et al., 2010, de Silva et al., 2016, Williams et al., 2007).

3.2. Antivenom costs

The cost of antivenom for most SBE victims is an obvious economic roadblock to finding an effective and durable solution for this crisis. Affordability will always be a challenge in communities where the daily wage is very low and people live a subsistence lifestyle. According to Vaiyapuri et al. (2013) the Indian labour bureau calculated the average daily wage in India for agricultural occupations in 2007–2008 was Rs76 for a man and Rs54 for a woman (Vaiyapuri et al., 2013), yet the median cost of an effective dose of antivenom in that region was between R1000-5000. In Africa it has been suggested that antivenoms costing more than £3 per treatment may be unaffordable (Theakston and Warrell, 2000). The cost of a vial of antivenom in sA has been reported to be between $18 - $135, however when the number of vials needed for an effective treatment was factored, the antivenom treatment costs rose to $60-$640 (Brown, 2012), which is above the suggested threshold and out of reach of most victims.

Compounding the difficulty is the variance in potency and overall quality of some antivenoms. Purchasing a product that has a low price per vial may seem appealing, but if the treatment regimen for that particular antivenom requires > 20 vials, the overall cost of treatment can skyrocket.

Global and collaborative efforts are underway to reduce the unit cost of antivenom, with estimates that costs could fall to US$30 - $42 per vial (AntivenomAID, a product development partnership, unpublished data, 2012). Whilst this cost per vial is significantly lower, it will still be out of reach for most SBE victims living in rural areas of India, Africa, Asia and South America. However, in the quantities needed to meet the potential demand, economies of scale make these rates affordable for donor bodies and international health funds to consider funding large-scale procurement. Furthermore, at these levels, the overall cost per DALY saved is more cost-effective than many other higher profile global health challenges.

3.3. Mismatched antivenom supply, market demand and clinical need

Significant global deficiencies in antivenom supply currently exist, in both quantity and quality. The amount of effective antivenom available to treat SBE patients in some low and middle-income countries is estimated to range from < 5% to 20% of the required need (Brown, 2012; Chippaux and Habib, 2015). The annual incidence of SBE in Africa has been estimated to be at least 435,000 (Chippaux and Habib, 2015; Gutiérrez et al., 2017) but the combined availability of antivenom in Africa is around only 80,000 treatments (Brown, 2012). Variable potency and inappropriate marketing of some antivenoms mean that a number of effective treatments is far less. The total global supply is estimated to be ~600,000 treatments, although the effectiveness of some of these antivenoms is uncertain. This constitutes less than one-third of the estimated 1.8 million SBEs that occur annually; a deficiency that probably results in more than 100,000 avoidable deaths (Brown, 2012, Gutiérrez et al., 2017).

Reliable sources of antivenom have dwindled as some manufacturers have ceased production and regulatory agencies have failed to properly monitor the quality of new antivenoms. This failure of the antivenom market is in part due to a lack of financial investment from government and non-government entities to maintain oversight and support a robust, sustainable and competitive antivenom industry.
Despite the very high clinical need for antivenom, insufficient funding for procurement deprives the market of financial stimulus required to increase output or improve quality. Exacerbating the problem are the relative narrow profit margins associated with producing antivenom, the presence of inferior antivenom mixed amongst high quality products, inadequate distribution networks, lack of proper training for healthcare personnel, and the preference for unproven traditional healing methods in some areas.

These factors mean that the market demand for antivenom is paradoxically low, in contradiction to the high incidence and burden of SBE. Tragically, some reputable producers struggle to sell the antivenom that they do produce (Brown, 2012), and many manufacturers report having unutilized production capacity that they would be willing to convert into increased output if they had greater confidence that there would be a market for their product. This discourages producers from making speculative investments into a small and inconsistent market, which drives the vicious cycle that is responsible for the current antivenom crisis. This also ensures that major pharmaceutical companies will vacate the antivenom manufacturing spaces, and production for low and middle-income countries will predominantly be undertaken by public, not-for-profit or small commercial companies.

3.4. Overview of manufacturers

In South America most antivenom production facilities are operating within non-profit public sector or research facility frameworks with manufacturers catering to their country’s requirements (e.g. Instituto Butantan in Brazil and Instituto Clodomiro Picado in Costa Rica). There are few such public sector production facilities in the Asia–Pacific region (e.g., Thailand) with most being private companies operating on a commercial business model such as in Australia (e.g., CSL and India (eg VINS, Bharat, Serum Institute of India). The main facilities in North America operate on a commercial basis in Mexico and USA (Bioclon, BTG), as do antivenom manufacturers in Europe (Micropharm and Inosan). There are few antivenom production facilities in Africa: there is the Vacsera in Egypt and the South African Vaccine Producers (SAVP) previously known as the South African Institute for Medical Research (SAIMR), both of which receive government funding. Sanofi had antivenom facilities in Africa and Europe, but has recently ceased production of antivenom and have now out-licensed their antivenom portfolio to another commercial producer. The World Health Organization (WHO) has a database reporting on antivenoms and known producers by snake species and regions [available at http://apps.who.int/bloodproducts/snakeantivenoms/d database/]. A comprehensive list of antivenoms, known producers and especially those registered in clinical trials was also reported by Alirol et al. (2015).

4. The economics around antivenom production

4.1. Current investments on antivenom (snakebite)

The global AV market in 2016 was valued at USD$1.1 billion, and has been forecast to grow to just under USD$1.5 billion by 2021 (Market Data Forecast, December 2016). The greatest proportion of this comprises antivenoms for wealthy markets in USA, Australia and Europe, and also includes other antivenoms against spiders and scorpions. There is also enormous variability of antivenom markets around the world, and government or health insurer subsidies for antivenom procurement in some high-income countries further distorts the market potential. In some developed countries, the cost of an ampoule of antivenom ranges between $1200 and $2,400, with the cost of an effective course of AV sometimes exceeding USD$20,000. By comparison, the sSA snake antivenom market was calculated to be around $10 million in 2011 (Brown, 2012), and revenues from antivenom manufactured for use in all low and middle income countries comprise less than 10% of the total AV market, despite these countries accounting for > 90% of the envenomings. Even if the value of the antivenom market in sSA tripled by 2020, it would still constitute less than 2% of the global total and be dwarfed by the funds available for many other neglected tropical diseases in sSA.

4.2. Cost-effectiveness of antivenoms

Antivenom has been shown to be a highly cost-effective treatment for SBE in several published works. A preliminary study found that high quality antivenom could be one of the most cost-effective public health interventions, if potency and cost of manufacturing are optimised (Brown and Landon, 2010). This study investigated the benefits of monospecific antivenom against Echis ocellatus, and calculated a potential cost of $10 per DALY saved with antivenom, owing to its high potency and low volume required to achieve efficacy. This highly favourable finding likely relates to the relative simplicity of the target venom constituents and higher potency that can be achieved with a monospecific product; similar assessments using the more ubiquitous poly-specific antivenoms have yielded higher costs/DALYs saved due to their inherent complexity and heterogeneity of their target venoms. A similar study of all antivenoms available in Nigeria found an average cost/DALY saved of $99.60 (discounted) and $57 (undiscounted), with a clear relationship between lower costs and more efficacious products directed against Echis ocellatus (Habib et al., 2015b). A related study examining effective antivenom across 16 countries in West Africa (WA) found available antivenoms yielded a cost/DALY averted of between $83 (95% Confidence Interval: $36-$240) for Benin Republic and $281 ($159-$457) for Sierra-Leone. The cost/death averted ranged from $1997 in Guinea Bissau to $6205 for Liberia and Sierra Leone, with an incremental cost effective ratio (CER) of $1997 and $6205. (Hamza et al., 2016). In another small study, antivenoms from Pakistan were compared to those imported from India and were found to be more effective and less expensive, suggesting more favourable cost effectiveness (Qureshi et al., 2013).

Antivenoms ultimately owe their superior cost/DALY averted to its potentially curative effects and relatively short treatment regimens. In all of the above reported cost-effectiveness valuations, the base-case cost/DALY averted fell below the commonly accepted threshold of one time per capita GDP, suggesting that AV is highly cost-effective for the treatment of snakebite in all the 16 WA countries and represents excellent value by global health standards (Habib et al., 2015b; Hamza et al., 2016). Furthermore it was found that the cost per DALY saved with antivenom was similar or less than that reported for many other tropical illnesses, making it deserving of global health investment funds. Interestingly the cost per DALY averted was also clearly related to the initial cost of antivenom acquisition and the availability of a simple affordable discriminatory test to confirm envenoming had occurred prior to administration of antivenom, thus minimising inappropriate use of antivenom.

4.3. Globalisation and antivenom

Most antivenom suppliers are located in industrialized and middle-income countries. Some of the largest manufacturers of reliable, high quality antivenom against snakebites occurring in rural tropical areas have been Sanofi-Aventis (earlier called Pasteur Laboratories) in France, Commonwealth Serum Laboratories (CSL) in Australia and Behringwerke in Germany. Of these, only CSL continues to manufacture antivenoms, although Sanofi has recently out-licensed their antivenom program. A common objective of antivenom producers in industrialized countries was initially to support delivery of healthcare to indigenous populations, in which their citizens served as colonial administrators and supervisors of other colonial enterprises (e.g., agriculture, plantations, military, trade and commerce, transportation, etc). But the clinical demand for antivenom in the developing world has always
exceeded the supply chain, even during the colonial era. With political and administrative independence in these third world countries, and a diminished capacity to pay for antivenom, manufacturers in the industrialized countries gradually reduced their output and many stopped production (e.g., Behringwerke). Domestic sources of antivenom production and regulation in affected countries, especially in Africa, never developed adequately to meet demand. Population explosions and the inevitable increased risk of encounters between humans and snakes has seen the number of SBE rise and the need for antivenom far surpass the global supply.

Globalization and relaxed trade barriers over recent decades have also failed to stimulate commercialisation to fill the gap. It has been reported that prior to Sanofi’s withdrawal in 2016, its annual production of FAV Afrique antivenom was ~10,000 treatment doses, even though it was clinically proven to be effective against envenoming from ten of Africa’s most medically important snakes, including four of the most feared snakes - carpet viper, cobra, puff adder and black mamba. At its peak, this product was used widely throughout the African continent, and could still be used to treat many hundreds of thousands of patients today if there existed a more reliable marketplace. But its transnational relevance did not spare FAV Afrique from the economic forces that diminished its utilisation and viability. Unfortunately, the promotion of global trade has opened opportunities for unscrupulous producers to market antivenom to inappropriate areas. The threats of fake and ineffective antivenoms are well-known, and the results from their integration into clinical use can be devastating (Warrell, 2008). A recent study found that many antivenoms marketed in Kenya lacked efficacy against snake species from that country (Harrison et al., 2017), and doubts have been raised regarding the effectiveness and specificity of some antivenoms in West Africa and India (Visser et al., 2008; Rogalski et al. 2017).

4.4. Antivenom production processes

Compared to many other modern medicines, the profit margins are narrow for most antivenom sold in low and middle-income countries. The efficiency of production, recovery and refinement of antibodies within animal antiserum will impact significantly on the potency and overall costs of the finished product. As a drug that works by neutralizing circulating venom constituents, the concentration of the specific antibodies within the antiserum determines the potency of the finished product and the amount required to achieve an effective dose. The final antibody titre attained, the proportion of specific antibodies and the efficiency of refinement and packaging of the finished product can vary widely, which leads to significant differences in cost of goods between different manufacturers. These endpoints are heavily influenced by the specific steps taken throughout the immunization, bleeding and purification processes.

Current antivenom production methods require four major components: 1) provision of appropriate and high-quality venom, sourced either from a herpetarium or commercial procurement; 2) availability and maintenance of animals (either horses, sheep, camels, etc) for venom immunization and subsequent active hyperimmune plasma collection; 3) processing plant where plasma is treated, active antivenom immunization and subsequent active hyperimmune plasma; and 4) formulation and packaging. Each component contributes to the overall cost of manufacturing antivenom, and even small improvements within each element can reduce the overall price per vial.

5. Improving antivenom effectiveness and cost-effectiveness

The holy-grail of antivenom manufacturing is to produce highly efficacious, broadly applicable, safe and inexpensive antivenoms that are affordable and accessible to victims in low-socioeconomic endemic areas. It is currently possible to produce antivenom that achieves a number of these parameters, but a product that openly satisfies all of these criteria have remained frustratingly elusive. The most cost-effective antivenom treatments are either monospecific or polyspecific with only regional applicability. Conversely, the lowest cost antivenoms per vial also tend to be the least effective. The safest and most effective polyspecific antivenoms, manufactured using processes and facilities accredited to minimum standards acceptable to regulators in high-income countries such as the European Medicines Agency or the US Food and Drug Administration, are among the most expensive, making them unaffordable without substantial subsidisation. The strategies for overcoming these challenges will require unprecedented co-operation and collaboration between manufacturers, governments, regulatory bodies, healthcare workers and non-government organisations. A framework conducive to this would ultimately benefit all producers as it would allow for resources and expertise to be pooled, and certain costs of manufacturing to be shared, such as quality control testing and regulatory oversight.

5.1. Strategies for more potent and cost-effective antivenom

Although antivenom currently ranks highly in cost-effectiveness analyses, the overall cost remains too high for a potentially life-saving medicine required predominantly in low-income countries. Thus the challenge for producers is to extract maximum efficiency from the manufacturing processes to minimise production costs, wholesale prices, and the amount of antivenom needed to achieve a clinically successful treatment. Currently many of these elements are proprietary and would require unprecedented co-operation and incentives for manufacturers to collaborate in this fashion.

Three simple strategies to improve cost-effectiveness would be to 1) improve antivenom potency; 2) decrease the cost per unit by increasing throughput and utilising better economies of scale; 3) stimulate competition and selective collaboration within the antivenom market to drive quality control and cost-efficiency standards.

5.1.1. Increased potency

One of the most important factors influencing the cost of antivenom is the level of specific antibodies present in the antiserum from which it is to be manufactured. For example, if specific antibody concentrations in animal blood can be doubled then only half the number of animals need to be immunised and the patient need receive only half the amount of foreign protein. The latter significantly reduces both the cost and risk of side-effects. Simple processes to test and optimise the humoral immune responses to various venom immunisation protocols, for example using small-scale affinity chromatography, can be incorporated into existing processes to minimise losses during the refinement phase.

Every step in the manufacturing procedure adds cost, increases losses of specific antibodies and causes some impairment, however slight, in the ability of the specific polyclonal antibodies to bind to and neutralise the various deleterious components of a snake venom. Using more efficient manufacturing techniques such as utilising intact IgG instead of Fab’2 digestion, has been found to reduce losses of specific antibodies during the multi-step refinement phase and decrease the overall costs of production by 37%-42% (Morais and Massaldi, 2006). Simplified methods for purifying intact-IgG, F(ab’)2 and Fab products using caprylic acid have been developed to improve antivenom yield whilst maintaining potency and reducing costs (Al-Abdulla et al., 2014). Adopting some of these strategies has resulted in a > 60% increase in specific antibody titres and subsequent neutralisation for one manufacturer (Landon et al. 2000).

5.1.2. Increased throughput and economies of scale

Increased throughput and better economies of scale could significantly decrease the per unit price of antivenom produced. Many production costs are fixed, with little variations regardless of the amount of antivenom produced. However, economies of scale greatly influence other aspects of the process, meaning that per unit costs of
production fall significantly when processing large antivenom volumes. In South America it has been shown that increasing throughput from 100L to 1000L of antivenom annually will lead to cost savings of around 65%–73%. Here it has been projected that the most efficiently produced antivenoms could potentially cost ~$2.4 per 10 ml vial, which is one-tenth of the cost once throughput and refinement processes are optimised (Morais and Massaldi, 2006). This study also found that the effect of doubling the titre of the specific antibodies in antisera will decrease the per unit price of antivenom by between 37 and 48%. Another projection based on antivenom production for Africa estimated that increasing the number of ampoules manufactured and filled from 2500 to 120,000 would reduce costs by 95% and could potentially result in a treatment price of < $10 per amoupe for monospecific antivenom (Landon et al., 2003). Another analysis has estimated that building and upscaling farm facilities located in West Africa from 500 to 2000 animals for producing hyperimmune serum in Africa could reduce the overall cost of a single vial of antivenom by > 60% (Landon et al., 2000). Other projections estimate that increasing the number of animals used for immunization from 100 to 5000 will reduce the cost per litre of antiserum produced by more than 90% (Landon et al., 2003). Across the many varied antivenoms manufactured globally there remains a clear inverse relationship between output and per unit price, illustrating the potential saving power that utilising economies of scale could bring to the entire industry (Brown, 2012).

5.1.3. Stimulate the antivenom market through prequalification

Prequalification is a process adopted by the World Health Organisation to assess and maintain the quality of drugs purchased by donor organisations. It imposes minimum efficacy and safety standards required for products to be placed on the list of approved medicines, providing reassurance to funding bodies that their investments are being used to purchase effective and appropriate treatments. It also generates confidence in the quality of the available medicines, for both the healthcare workers administering them and the patients who receive them. A prequalification-like process is currently in the early stages of being adapted for use with antivenoms, using internationally agreed standards with independent assessors. Such a development will contribute enormously to raising the quality of antivenom products around the world. Because only products that meet the prequalification standards will be included in the list of essential medicines that can be acquired using donor funds, manufacturers will be incentivised to submit their product dossiers for assessment and to improve their processes where possible. Significant increases in funding will be required to support the quality control and stimulation of the antivenom market through this mechanism.

The provision of increased funding for antivenom procurement, benchmarked against standardised minimum efficacy and safety requirements, will level the playing field for manufacturers and stimulate competition to drive further improvements in SBE treatment and throughput. Achieving greater potency, lower per unit production costs and increased output, within the context of a greater pool of funding, will fundamentally alter the economic drivers around SBE treatment by simultaneously increasing its profitability, affordability and availability. Restoring the viability of the antivenom market will boost confidence and promote investment in manufacturing, attract additional funds for procurement of better, even more cost-effective medicines, and create a positive cycle towards universal access of the SBE treatments.

5.2. Regulatory barriers to improving antivenoms

A major impediment to improving antivenom quality and cost-effectiveness are the high costs associated with bringing a new antivenom to market or altering a product’s formulation once licensed. Regulatory processes around product licensing can be time consuming and complex, and the supporting trials required to validate an antivenom’s safety and efficacy are expensive, especially for products with low profit margins. This provides a disincentive for manufacturers to consider ways of improving their antivenoms when technology and techniques evolve to allow for greater efficacy, better safety or lower costs to be incorporated into their products.

Given the relatively small antivenom market that currently exists in low-income countries, it is difficult for companies to build a business case for altering a product that has already been approved for marketing. Without additional funding and financial incentives to justify changing production techniques towards improving current antivenom quality, and flexible regulatory processes to more easily allow companies to demonstrate improved efficacy or safety of their modified product, many established products may become out-dated but remain legitimately marketed in many countries.

A regulatory and funding model that embraces innovation while incentivising companies to incorporate evolving technology to ensure the safest and most effective antivenoms are marketed without a commercial penalty, will help to drive quality standards and greater efficiencies. A number of established antivenoms with good clinical reputations could currently benefit from such an arrangement.

5.3. The future of antivenom

In the 122 years since antivenom was first invented, the research supporting this medicine has lagged behind many other life-saving drugs, and technical evolutions have been reactive and modest. Although an important humanitarian and social issue, death from snakebite lacks the status and assistance afforded to other international health crises in low and middle income countries, and thus suffers from a lack of research funding. Confounding the long-term trend, and coinciding with increased attention from the campaign to list SBE as a WHO Neglected Tropical Disease, the last decade has seen novel and creative research ideas for antivenom developed and tested. Most have been derived from research portfolios in other diseases, with researchers aiming to use technological evolutions in related fields to also benefit antivenoms. Many of these endeavours may well fail to achieve their objective, but some could deliver better, safer and less-expensive antivenoms for all victims.

Current antivenoms are mostly polyclonal immunoglobulins (IgG) of animal sera origin, containing heterologous serum that is fractionated into either pepsin digested Fab, papain digested Fab or whole IgG. Antivenomics, based upon the science of proteomics to identify which elements within snake venom are the most toxic, has opened up new frontiers in the search for more effective antivenoms (Warrell et al., 2013). Proteomics can also be used to test the potency and relevance of existing antivenoms without needing to use small animal models.

The production of recombinant antivenom is also being investigated, based on oligo- or mono-clonal mixtures of humanised IgG antibodies with activity against specific venom toxin epitopes produced by cell cultivation for therapeutic use in SBE. Aside from the extra costs, a major potential disadvantage of using monoclonal antibodies is the need to target the broad, heterogeneous array of toxic constituents found in most venom types. However, in selecting venom toxin epitopes, proteomics will be used to choose the most appropriate substances based on their medical relevance (Williams et al., 2011). These could result in more specifically targeted and safer products, with reduced hypersensitivity reactions and probably more potent and efficacious antivenoms. Initial analysis based on industry data estimated the cost of treatment for a SBE with recombinant antivenom to be potentially as low as USD 60–250 for the Final Drug Product. This compares favourably to existing effective polyspecific antivenom therapies, such as the SAVP Snake Polyvalent Antivenom (reported to have a wholesale price of USD 640 per treatment for an average snakebite) and Instituto Clodomiro Picado polyspecific antivenom EchiTabPLUS (average cost
USD100-200 per treatment), and is equivalent to the most cost-effective monospecific antivenom currently produced by Micropharm, EchiTAbG (available at USD50-75 per treatment). Other non-traditional, novel production methods being applied to antivenoms include the use of nanoparticles, humanised antibodies, plant-based antivenoms and the development of universal antivenom (Mirzaei et al., 2017; Gao et al., 2016; Julve Parreño et al. 2017). Thus, it is possible that next-genera-
tion antivenoms will be more broadly applicable and cost-competitive, and even more cost-effective, than existing serum-based treatments (Laustsen et al., 2017).

6. Optimising the economics of snakebite

Whilst the challenges with snakebite are considerable, there is great hope and realistic prospects for a brighter future. A major cause for optimism has been the formal recognition of snakebite as a neglected tropical disease by the WHO, which will unlock resources from gov-
ernments and non-government organisations to help drive the eco-


nomic changes that will generate the necessary improvements across the spectrum of problems contributing to the snakebite crisis. A blue-print towards this future has been constructed and will provide a multifaceted strategy for improving treatment of SBE around the world and reducing the burden from this often-preventable affliction.

A major part of the strategy to decrease mortality and morbidity from snakebite will be to ensure that new interventions are effective, cost-effectiveness and represent attractive investments for both gov-
ernment and private funding bodies to consider. Increased funding for procurement of quality assured antivenom will renew market demand, promote further investment and provide manufacturers with a greater incentive to convert unutilized capacity to increase output.

The provision of increased financial support for this neglected problem will influence all economic aspects of SBE: More prevalent, affordable antivenoms that are easier to access will reduce the financial burden on victims and their families. Earlier administration of appro-
riate antivenom after SBE will reduce morbidity and shorten recovery times, thereby accelerating a return to productive endeavours for vic-
tims within their communities and mitigating potentially wide-reaching economic consequences.

Although critically important to any framework seeking to improve outcomes for snakebite victims, increased funding alone is not the sole requirement. Greater antivenom procurement and quality control needs to be matched by additional funding to improve health infrastructure, drug distribution networks, medical training for clinicians and in-
creased public awareness of the dangers of snakebite and the benefits of antivenom.

While there is an urgent need for greater output of more affordable and higher quality antivenom, minimum levels of market demand and profitability must be assured before there is commercial resurrection and increased production. It is unrealistic to expect that manufacturers will produce antivenoms that are commercially unviable or lack a fi-
nancial incentive. Similarly it is implausible for governments to commit additional funding for a product that is of uncertain quality or eco-


nomically unfavourable. A combination of greater public and private funding would likely provide a stimulus to reverse the current futile market situation and create a sustainable cycle with long-term viability that will drive innovation, balance affordability with profitability, and lead to restoration of market demand and supply. Such a scenario will see producers compete for a share of the growing market and allow free-market forces to promote long-term sustainable prices for in-
creasing numbers of high quality products.

6.1. Future perspectives

A multifaceted approach is required to solve this complex crisis, and global partnerships and strategies have been suggested (Gutiérrez et al., 2014; Williams et al., 2011), with increased funding being an essential component. New funding mechanisms and justifications for increased investment are required to convince governments and non-government organisations of the value of better funding SBE treatment strategies.

One such example is the Global Alliance for Vaccines and Immunisations (GAVI Alliance) and International Finance Facility for Immunisations (IFFIm). This program links and co-ordinates govern-
ments, vaccine manufacturers, research groups, business groups, inter-
national aid foundations, the WHO and other interested individuals and non-government organisations. Its goal is to save lives and protect health by increasing access to immunizations in low and middle-income countries. A similar model designed around treating SBE would not only drive the changes required around antivenom quality and avail-
ability, but would constitute a more cost-effective investment, with greater long-term returns, than many other global health problems.

The cost-effectiveness assessments discussed earlier, namely cost per DALY averted and cost per death averted, demonstrate that boosting antivenom funding is affordable and represents real value in terms of saving lives and preventing morbidity. Furthermore, the amount of money required to fully-fund antivenom provision to all patients requiring it would be considerably less than the money that is currently directed at other global health issues. Governments, non-
government organisations and global health foundations should be encouraged to invest in antivenom therapy and form an investment entity analogous to the IFFIm that could be used to fund antivenom procurement, maintain quality, avert suffering, increase community education, improve health infrastructure and reduce costs of treatment.

7. Conclusion

Economic forces pervade most elements of the snakebite story, in-
cluding considerable socioeconomic burdens, many of the underlying causes, and also potential strategies for reversing the decline. An ana-
lysis of the economic factors implicated in this saga illustrates a so-
bering picture: significant financial hardship faced by victims and their families in treating snakebite and living with its aftermath; the lost productivity from the physical and psychological morbidity at both a local community and national level; the collapse of the antivenom market; the degradation of reliable regulatory oversight; and the many other reasons why antivenom and the management of SBE in general have been so badly neglected. Quantifying the burden of snakebite and combining that with healthcare economic analyses of the potential cost-
effective gains from better treatment, which includes high quality and affordable antivenom, provides a convincing argument in favour of increasing funding to address the snakebite crisis. Based on overall cost of DALYs averted and lives saved, investing in better antivenoms and related healthcare infrastructure represents excellent value for global healthcare providers. The establishment of new funding mechanisms to increase antivenom procurement and implement quality control pro-
cesses, such as Prequalification, will help to re-stimulate the antivenom market and drive further improvements in potency, safety and output. Through competition and collaboration, it will become possible to in-
crease potency and decrease the cost of producing antivenom, while current and future research projects have the potential to evolve the treatment of SBE beyond exogenous antiserum-based products and into new and improved frontiers.

Is it possible that if there had been greater investment in procuring antivenom through the 1970s and 1980s that large pharmaceutical companies with high-levels of experience in manufacturing serum-based products would not have withdrawn from the market? If greater attention had been paid to solving the regulatory hurdles preventing cost-effective evolution of antivenoms alongside improved technology and manufacturing techniques, would there have been greater progress made with snakebite treatments? If investment in improved healthcare infrastructure, community education and clinical outcomes for snake-
bite envenoming was a priority 30 years ago, would there have been the decline in antivenom quality, quantity and affordability that has
characterised the industry in recent decades? The answers to these questions are speculation, however healthcare economic analyses suggest that millions of lives would have been spared the tragic consequences of SBE if snakebite had not become the neglected tropical disease that it is today.

Conflict of interests

AGH and NIB are both Directors of The Global Snakebite Initiative. AGH has no relevant financial competing interests to declare. NIB is consulting Medical Director for Micropharm Ltd. No other competing interests to declare.

Ethical statement

The authors have complied with all ethical considerations for preparing a review paper.

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References


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