REVIEW ARTICLE

ISSN (ONLINE): 3027-2998

NEXUS OF MEDICINE AND LABORATORY SCIENCE JOURNAL

ADDRESSING THE GLOBAL HEALTH BURDEN OF SNAKEBITE ENVENOMATION

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Received: 5th April, 2024
Accepted: 26th April, 2024
Published: 30th April, 2024
Available on: https//nmlsj.org/
Publisher: ScholarlyFeed

Cite as: Ikpeama RA, Ogbonnie ES, Bruce I, Lawson SD, Ezenwaka CO. Addressing the global health burden of snakebite envenomation. Nexus Med. Lab. Sci. 2024; 1(2): 18-28

Abstract

Snakebite envenomation, a Neglected Tropical Disease, affects millions annually, causing fatalities mainly in rural areas. Snakes employ constriction or venomous bites to subdue prey. Between 4.5 to 5.4 million snakebites occur yearly, with 80,000 to 130,000 fatalities. It is most prevalent in rural, low-income areas of Africa and Asia, Australia reports few deaths despite having venomous snakes. High-risk groups for snakebite envenomation, such as rural workers and children, face elevated morbidity and mortality rates, with significant vulnerability among women, especially pregnant individuals, due to cultural and healthcare access barriers. Envenomation outcomes depend on venom composition, with clinical manifestations varying widely. Snake venom delivery systems differ among species, impacting the severity and mechanism of envenomation. Thrombocytopenia is common in severe cases, influenced by venom type and quantity. Various snake venoms contain cytotoxic, neurotoxic, hemotoxic, and myotoxic components, each with distinct pathophysiological effects on victims. To conclude this review snakebite envenomation presents significant global health challenges, necessitating improved epidemiological data collection, antivenom accessibility, and public health interventions therefore it is recommended that for prevention and management, there should be enhanced Epidemiological Surveillance, Increased Access to Antivenom, Public Health Education, Training of Healthcare Providers, Research and Development, Community Engagement, Regulatory Measures and International Collaboration.

***Keywords**: Antivenom, Envenomation, Neglected tropical diseases,, Snakebite.*

1.1 Introduction

Snake venom is a glandular secretion used by snakes for various purposes, including immobilizing and digesting their prey, as well as for defensive and survival measures [1]. It is a lethal mixture composed of various substances such as amino acids, nucleic acids, carbohydrates, lipids, proteins, and peptides [2]. Snakebite envenomation, caused by toxins in the bite of a venomous snake, is a potentially life-threatening disease. It can also occur when venom is sprayed into the eyes by certain species of snakes as a defense measure [1]. Snake envenomation is a significant health problem, particularly affecting the poorest populations in rural areas. The availability of antivenoms is crucial, and efforts have been made to address the challenges related to the production, accessibility, and use of antivenoms, especially in regions with high incident and burden of snakebites such as Africa [3]. The first challenge, now, is to specify the requirements for antivenom at an operational, local level. In order to do this, it is essential to organize the collection of epidemiological data, which will enable seasonal anticipation of snakebite number and location. The only continent where this objective can be considered achieved is America. In Africa especially, as in many parts of Asia, most snakebite victims go to traditional healers, rather than to health centers, to receive treatment. This happens because the cost of medical care is out of proportion to the average income of a family of farmers. The result of this situation is inappropriate delay in administration of antivenom, which ultimately increases the rate of complications and the cost to society. The third challenge is to improve the accessibility of antivenoms. An antivenom is a complex biological product that is neither a drug nor a vaccine [4]. Despite decades of concern over the impact of SBE in low-middle-income countries (LMICs), a lack of any clear mandate from member states has made it difficult for WHO to take substantial action [5]. Indeed, it wasn't until 2015 when alarm over the possible therapeutic vacuum in Africa, caused by Sanofi-Pasteur's decision to cease production of their FAV-Afrique antivenom, galvanized renewed calls for urgent action. In 2017, after intense advocacy by concerned stakeholders including Médecins Sans Frontières [6], the Global Snakebite Initiative [7], Health Action International, and a detailed submission by more than 20 countries, WHO listed SBE as a priority neglected tropical disease (NTD) [3]. In May 2018, the 71st World Health Assembly adopted a robust resolution (WHA71.5) on SBE, providing WHO with a strong mandate to take action [8]

2.1 Epidemiology

The continent with the lowest occurrence of snake envenomation is Europe, and the highest occurrences are in Africa and Asia [9]. In Australia, deaths from envenomation are infrequent, despite the presence of many highly venomous snakes [10]. Snakebites and death from envenomation are most frequent in rural, low-income regions, where health care often cannot be accessed quickly and antivenom and intensive supportive care might not be available. Among patients who survive, delayed or inadequate care can lead to permanent disability (e.g., amputations and blindness). However, snake envenomation occurs in both tropical and temperate climates and on all continents except Antarctica. Worldwide, the estimated number of annual deaths due to snake envenomation (80,000 to 130,000) is similar to the estimate for drug-resistant tuberculosis and for multiple myeloma [11]. Snakebite envenoming (SBE) affects as many as 2.7 million people every year, most of whom live in some of the world's most remote, poorly developed, and politically marginalized tropical communities [7]. With annual mortality of 81,000 to 138,000 and 400,000 surviving victims suffering permanent physical and psychological disabilities, SBE is a disease in urgent need of attention [12]. Snakebite envenomation (SBE) lacks adequate public health attention and funding.

Understanding its epidemiology is vital for prevention and management. WHO launched a program in 2019 to halve snakebite-related deaths and disabilities by 2030, focusing on prevention, treatment, and healthcare access [13].

3.1 Risk factors

High-risk groups for snakebite envenomation include rural workers, fishermen, and hunters, especially children. Morbidity and mortality rates are highest among the young, with children facing greater risk. Additionally, cultural barriers and limited healthcare access disproportionately affect women, particularly pregnant women, making them more vulnerable [14]. Bites most commonly involve the extremities. Unprovoked bites are more likely to involve females and the lower extremities. Provoked bites are more likely to involve males and the upper extremities. The intentionality of the interaction does not appear to be associated with the likelihood or severity of envenomation [14].

4.1 Pathophysiology of Venomous Snakebites

Not all bites by venomous snakes involve envenomation; “dry” bites occur in 2 to 50% of cases. When envenomation does occur, the clinical effects depend on the toxins in the venom. Most venom components appear to bind to multiple physiologic receptors and attempts to classify venom as toxic to a specific system (neurotoxins, cytotoxins, myotoxins and hemotoxin) are misleading and can lead to errors in clinical judgment [15].

4.1.1 Venom Delivery Systems of Snakes

Snake venom is delivered via venom glands or, in colubrids, Duvernoy’s glands, lacking large venom reservoirs. Venom glands connect to tubular fangs through a duct. In Viperidae, Elapidae, and Atractaspidinae, muscles around the glands propel venom through openings near fang tips. Colubridae use grooved fangs for low-pressure venom delivery [16]

4.1.2 Venom-Induced Consumption Coagulopathy

Procoagulant toxins in snake venoms promote consumption coagulopathy, which causes the depletion of factors in the clotting cascade and may result in either spontaneous or uncontrolled bleeding. Venoms of different types of snakes vary in the extent to which they affect clotting factors [17]. Toxins in snake venom that promote consumption coagulopathy are categorized according to where they act on the clotting cascade. Some of the most relevant procoagulant toxins, such as metalloproteinases, are activators of prothrombin, factor V, factor X, or thrombinlike enzymes (fibrinogenases) [17]. Thrombotic microangiopathy, which may accompany venominduced consumption coagulopathy, is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury [16].

4.1.3 Thrombosis

Snake envenomation can result in myocardial infarction, stroke, or other thrombotic effects. Twenty-two cases of myocardial infarction after snake envenomation have been reported [18]. Proposed mechanisms of myocardial infarction include hypovolemia, anaphylactic shock, coronary thrombosis from procoagulant factors, a direct effect of venom on cardiomyocytes, decreased oxygen carrying capacity, vasoconstriction, myocardial necrosis and hemorrhage, and microvascular thrombin deposition. Strokes may be either hemorrhagic or ischemic, but ischemic strokes are more prevalent [19].

4.1.4 Thrombocytopenia or Altered Platelet Function

In severe Crotalinae envenomation, thrombocytopenia often occurs, either alone or with other coagulopathies. Platelet consumption exacerbates complications. This phenomenon seems linked to venom composition and quantity [20]. Mechanisms for thrombocytopenia remain unclear but may involve platelet aggregation, sequestration, or reduced production, leading to spontaneous or uncontrolled hemorrhage [20]. In addition,

platelets may be inhibited or activated by various venom components (metalloproteinases and lectins), resulting in normal platelet counts but platelet dysfunction [21].

5.1 Types of snake venom

5.1.1 Cytotoxic venom

Snake venom contains enzymes like hyaluronidase, collagenase, proteinases, and phospholipases, causing local tissue injury, inflammation, pain, and edema. Edema may spread, leading to bullae and dermo-necrosis. Ecchymosis may result from increased vascular permeability or systemic coagulopathies. Metalloproteinases damage the extracellular matrix, releasing peptides with varied tissue effects, from destruction to repair. Additionally, they may cause microvascular damage, resulting in hemorrhage. [22], skeletal-muscle necrosis and lack of muscle restoration [23], blistering, and dermo-necrosis [24], as well as inflammatory mediators that account for pain, swelling, and leukocyte infiltration. Although elevated compartmental tissue pressure (due to edema in a space bounded by a rigid fascia) or elevated subcutaneous tissue pressure (due to swelling exceeding the elastic limits of the skin) may occur, the direct effects of venom can mimic the symptoms and signs of true compartment syndrome, and pressures may be normal [25]. In snake envenomation, injury to the lymphatic system plays a role in the development of edema. The lymphatic system is also involved in systemic absorption of venom toxins from tissues. In addition, some venom components are neutralized in the lymphatics, although the process is slow and incomplete [26].

5.1.2 Neurotoxic venom

5.1.2.1 Fasciculins

These toxins attack cholinergic neurons (those that use ACh as a transmitter) by destroying acetylcholinesterase (AChE). ACh, therefore, cannot be broken down and stays in the receptor. This causes tetany (involuntary muscle contraction), which can lead to death. The toxins have been called fasciculins since after injection into mice, they cause severe, generalized and long-lasting (5-7 h) fasciculations (rapid muscle contractions). Examples are mostly found in the venom of mambas (*Dendroaspis spp*) and some rattlesnakes (*Crotalus spp*) [27]

5.1.2.2 Dendrotoxins

Dendrotoxins inhibit neurotransmissions by blocking the exchange of positive and negative ions across the neuronal membrane lead to no nerve impulse, thereby paralyzing the nerves as found in mambas.

5.1.2.3 α-neurotoxins

Alpha-neurotoxins are a large group; over 100 postsynaptic neurotoxins having been identified and sequenced [27] α-neurotoxins attack the Nicotinic acetylcholine receptors of cholinergic neurons. They mimic the shape of the acetylcholine molecule, and so fit into the receptors, where they block the ACh flow, leading to a feeling of numbness and paralysis. Examples include king cobra (*Ophiophagus hannah*) (known as hannahtoxin containing α-neurotoxins) [28], sea snakes (Hydrophiinae) (known as erabutoxin), many-banded krait (*Bungarus multicinctus*) (known as α-bungarotoxin), and cobras (*Naja spp*) (known as cobratoxin)

5.1.3 Cytotoxic venom

Cytotoxic venom is a type of venom that contains toxins capable of damaging or destroying cells. These toxins typically target and disrupt cell membranes, leading to cell death. Cytotoxic venoms are often found in certain species of snakes, such as vipers and some types of cobras [27]. When a victim is injected with cytotoxic venom, it can cause local tissue damage, including swelling, pain, blistering, and necrosis (tissue death). In severe cases, it can cause extensive tissue damage and even limb loss if treatment is not received quickly and effectively [28].

5.1.3.1 Phospholipases

Phospholipase is an enzyme that transforms the phospholipid molecule into a lysophospholipid (soap) → the new molecule attracts and binds fat and ruptures cell

membranes. Phospholipase A2 is one specific type of phospholipases found in snake venom [29]. Example is found in Okinawan habu (*Trimeresurus flavoviridis*)

5.1.3.2 Cardiotoxins

Cardiotoxins are components that are specifically toxic to the heart. They bind to particular sites on the surface of muscle cells and cause depolarisation → the toxin prevents muscle contraction. These toxins may cause the heart to beat irregularly or stop beating, causing death. An example is the three fingered cardiotoxin III from Chinese cobra, an example of the short three-fingered family [29]. Examples of snakes that produce venom are mambas and some *Naja* species

5.1.4 Hemotoxins

Hemotoxins cause hemolysis, the destruction of red blood cells (erythrocytes), or induce blood coagulation (clotting, e.g. mucrocetin). A common family of hemotoxins includes snake venom metalloproteinases such as mucrolysin [29]. Examples are found in most vipers and many cobra species. The tropical rattlesnake *Crotalus durissus* produces convulxin, a coagulant [30]

5.1.4.1 Myotoxins

Myotoxins are small, basic peptides found in rattlesnake [31] and lizard (e.g. Mexican beaded lizard) [32] venoms. This involves a non-enzymatic mechanism that leads to severe skeletal muscle necrosis. These peptides act very quickly, causing instantaneous paralysis to prevent prey from escaping and eventually death due to diaphragmatic paralysis. The first myotoxin to be identified and isolated was crotamine, discovered in the 1950s by Brazilian scientist José Moura Gonçalves from the venom of tropical South American rattlesnake *Crotalus durissus terrificus*. Its biological actions, molecular structure and gene responsible for its synthesis were all elucidated in the last two decades [31].

6.1 Diagnosis

A snakebite or envenomation may not be recognized because of factors pertaining to the patient or the bite. Only one fang may have achieved penetration, the punctures may be obscured by edema, or an abrasion may be the only finding [33]. Although venom does not cross intact skin or mucous membranes or usually cause injury if swallowed, it may cause ophthalmic injury [34]. Snake size may correlate with fang distance and venom volume, but venom injected varies. Toxicity depends on venom composition influenced by genetic and epigenetic factors. Diagnosing children is challenging due to limited history; symptoms like coagulopathy, neuropathy, or abdominal pain may hint at envenomation. [34]. In Australia, venom detection kits consisting of enzyme immunoassays [35] are available for identifying a snake envenomation and the species of snake. In global areas lacking bite observation, wound appearance and clinical course aid diagnosis. Specific antivenoms may be necessary, but overlap between species can complicate identification, leading to improper management with potentially available antivenoms [36]. Nonnative, captive snakes may pose challenges to species identification and case management. The pre-hospital application of ineffective and possibly harmful therapies, plus any delay in obtaining competent and definitive care, may also complicate both diagnosis and management [36].

7.1 Mechanism of action

7.1.1 Mechanics of biting

Several genera, including Asian coral snakes (Calliophis), burrowing asps (Atractaspis), and night adders (Causus), are remarkable for having exceptionally long venom glands, extending along each side of the body, in some cases extending posterially as far as the heart. Instead of the muscles of the temporal region serving to press out the venom into the duct, this action is performed by those of the side of the body [37]. Venomous snakes exhibit diverse biting behaviors. Viperids usually strike quickly, injecting venom upon penetration, while some (e.g., Lachesis) bite and hold during feeding. Proteroglyph or opisthoglyph snakes may bite firmly or chew.

Fang length variations reflect evolutionary differences in striking strategies [38]. Additionally, it has been shown that the fangs of different species of venomous snakes have different sizes and shapes depending on the biomechanical properties of the snake's prey [37].

7.1.2 Mechanics of spitting

Spitting cobras, like those from the genera *Naja* and *Hemachatus*, can eject venom up to 8 ft when threatened. Their fangs are specialized for spitting, with a 90° bend in the channel. While spitting is defensive, a direct hit can cause temporary blindness. Promptly washing away the venom with water can prevent serious effects, but untreated exposure may lead to permanent blindness or envenomation through open wounds [39]. For instance, phospholipases type A2 (PLA2s) from the Tunisian vipers *Cerastes cerastes* and *Macrovipera lebetina* have been found to have antitumor activity [40]. Anticancer activity has been also reported for other compounds in snake venom [41] [42]. PLA2s hydrolyze phospholipids, thus could act on bacterial cell surfaces, providing novel antimicrobial (antibiotic) activities [43]. The analgesic (pain-killing) activity of many snake venom proteins has been long known [44] [45]. The main challenge, however, is how to deliver protein to the nerve cells: proteins usually are not applicable as pills.

8.1 Use of snake venom to treat diseases

Given that snake venom contains many biologically active ingredients, some may be useful to treat disease [39]. For instance, phospholipases type A2 (PLA2s) from the Tunisian vipers *Cerastes cerastes* and *Macrovipera lebetina* have been found to have antitumor activity [40]. Anticancer activity has been also reported for other compounds in snake venom [41] [42]. PLA2s hydrolyze phospholipids, thus could act on bacterial cell surfaces, providing novel antimicrobial (antibiotic) activities [43].

9.1 Immunity

9.1.1 Among snakes

The question of whether snakes are immune to their own venom remains debated. An example exists of a cobra self-envenoming, causing a large abscess but surviving. Certain non-venomous species, like kingsnakes and mussuranas, are immune to venomous snakes they prey on. Some rat snakes and king snakes are resistant to rattlesnake venom. The king cobra is reportedly immune to other cobras' venom. [46]

9.1.2 Among other animals

The hedgehog (Erinaceidae), the mongoose (Herpestidae), the honey badger (*Mellivora capensis*) and the opossum are known to be immune to a dose of snake venom. Recently, the honey badger and domestic pig were found to have convergently evolved amino-acid replacements in their nicotinic acetylcholine receptor, which are known to confer resistance to alpha-neurotoxins in hedgehogs [46]. Whether the pig may be considered immune is still uncertain, though early studies show endogenous resistance in pigs tested against neurotoxins [47]. Though the pig's subcutaneous layer of fat may protect it against snake venom, most venoms pass easily through vascular fat layers, making this unlikely to contribute to its ability to resist venoms. The garden dormouse (*Eliomys quercinus*) has recently been added to the list of animals refractory to viper venom. Some populations of California ground squirrel (*Otospermophilus beecheyi*) are at least partially immune to rattlesnake venom as adults [47].

9.1.3 Among humans

The acquisition of human immunity against snake venom is ancient (from around 60 CE, Psylli tribe). Research into development of vaccines that will lead to immunity is ongoing. Bill Haast, owner and director of the Miami Serpentarium, injected himself with snake venom during most of his adult life, in an effort to build up an immunity to a broad array of venomous snakes, in a practice known as mithridatism. Haast lived to age 100, and

survived a reported 172 snake bites. He donated his blood to be used in treating snake-bite patients when a suitable antivenom was not available. More than 20 so-treated individuals recovered [48].

10.1 Treatment

The World Health Organization estimates that 80% of the world's population depends on traditional medicine for their primary health-care needs [49].

10.1.1 Methods of traditional treatments of snakebites

In Trinidad and Tobago, snakebite treatments are made into tinctures using alcohol or olive oil and stored in rum flasks called snake bottles, containing various plants and insects. Ingredients include monkey ladder vine, mat root, cat's claw, tobacco, snake bush, obie seed, wild gri gri root, and caterpillars [15]. Emergency snake medicines are obtained by chewing a three-inch piece of the root of bois canôt (*Cecropia peltata*) and administering this chewed-root solution to the bitten subject (usually a hunting dog). This is a common native plant of Latin America and the Caribbean, which makes it appropriate as an emergency remedy. Another native plant used is mardi gras (*Renealmia alpinia*) (berries), which are crushed together with the juice of wild cane (*Costus scaber*) and given to the bitten. Quick fixes have included applying chewed tobacco from cigarettes, cigars, or pipes [50]. Formerly, making cuts or sucking out venom was considered, but is now discouraged due to self-envenomation risks. Suction cups from snake bite kits are rarely beneficial [49].

10.1.2 Sero-therapy

Sero-therapy with antivenom is a crucial treatment for snakebites, tracing back to 1913. However, it's intricate; immunity to one snake's venom doesn't extend to others. For instance, an Australian immune to tiger snake venom succumbed to a copperhead bite. In India, serum effective against one snake's venom may prove futile against others. Similarly, in Brazil, antivenom for lanceheads may not counter rattlesnake venom. Matching antivenom to the snake's species is vital, with polyvalent options available for most pit vipers in the Americas. Nonetheless, specific antivenoms are required for coral snake envenomation, reflecting the complexity of snakebite treatment, especially in regions like India, with diverse snake species. [49].

10.1.3 First aid

Reassure the victim. Many snake bites are from harmless snakes and even the most venomous snakes often bite without injecting harmful amounts of venom(dry bites). Usually, if the snake has injected venom, serious effects will not develop for hours or even days, allowing plenty of time for effective medical treatment. Apply pressure pad directly over the bite wound and immobilize the patient, especially their bitten limb. Remove tight rings, bracelets, anklets, bands, clothing from the bitten limb. Transport the victim to medical care ass quickly, safely and passively as possible. For pain, give acetaminophen(paracetamol), codeine phosphate or other opoids [12].

11.1 Prevention of snake bites

The Do's:

All sleeping bags, boots and clothing should be opened and shook to dislodge snakes that amy have taken refuge inside, Ground should be checked before sitting at the base of a tree, Boots, socks and long trousers should be worn when walking in undergrowth or deep sand, A flashlight should be used at night when walking, collecting fire wood or relieving yourself, especially after heavy rain, Banks of streams, rivers and lakes are common snake haunts so beware [24].

The Don'ts:

Do not disturb, approach, corner, provoke, attack or attempt to handle snakes, even if they are said to be harmless species or appear to be dead because even a severed head may bite, Do not attend snake charmers' shows because their snakes may not be under control, Do not put hands blindly down inside rucksacks, Do not poke sticks into burrows or holes because they often harbor snakes, Do not put hands up

onto branches or ledges that cannot be see [16].

Conclusion

Snakebite envenomation is a public health challenge especially in rural areas of developing countries that should be giving more attention by the government and policy makers. More awareness should be encouraged as well as the provision of anti-venom and good medical infrastructure especially in rural areas and settlements more prone to snake bites.

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