Presentation and management of snakebite envenomation in the uMkhanyakude district of KwaZulu-Natal (Mosvold Hospital)

by

Matamba Jean Benoit Kabeya
MPhil student University of Cape Town
KBYJEA001

This thesis is submitted in partial fulfilment of the requirements for the degree Masters Philosophie, Emergency Medicine: Critical Care in the faculty of Health Sciences at the University of Cape Town.

Supervisors: A/Professor Peter Hodkinson, University of Cape Town
Dr Darryl Wood

September 2023

Declaration

I, Matamba Jean Benoit Kabeya, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I authorise the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I further declare the following:

1. I know that plagiarism is a serious form of academic dishonesty.
2. I have read the document about avoiding plagiarism, am familiar with its content and have avoided all forms of plagiarism mentioned therein.
3. Where I have used the words of others, I have indicated this by the use of quotation marks.
4. I have referenced all quotations and properly acknowledged ideas borrowed from others.
5. I have not and shall not allow others to plagiarise my work.
6. I declare that this is my own work.
7. I am attaching the summary of the Turnitin match overview.

Signed by candidate

Signature: ……………………………… Date: 11 September 2023

Acknowledgements

I am forever thankful to Professors Peter Hodkinson and Darryl Wood, my supervisors, for their invaluable assistance and guidance throughout my studies. I am also grateful to the Mosvold Hospital staff who contributed to this research project, as well as my loved ones: Cathy, Hadassah, Kayla, Lucie, Lydie, Hyacinthe, and Erick, for their unwavering encouragement and efforts.

Contents

Abbreviations

ACP – Antivenin Crotalidae polyvalent

AKI – Acute kidney injury

CroFab -Crotalidae polyvalent immune fragment antigen binding

EC – Emergency care

Hb – Haemoglobin

HIC – High income country

HIV – Human Immunodeficiency Virus

IgE – Immunoglobulin E

IgG – Immunoglobulin G

IMCP – Intramuscular compartment pressure

INR - International Normalised Ratio

KZN – KwaZulu-Natal

LMIC – Low to middle-income country

PANAF – Pan-Africa antivenom

PPS – Painful progressive swelling

PW – Progressive weakness

SA – South Africa

SAIMR – South African Institute for Medical Research

SAIMR AV – South African Institute for Medical Research antivenom

SASS - South African Snakebite Symposium

SSS – Snakebite Severity Score

Tab - Table

TEG/ROTEM – Thromboelastography / Rotational thromboelastometry

UCT – University of Cape Town

WBCT – Whole blood clotting test

WHO - World Health Organization

ZSS - Zululand snakebite severity score

List of tables

List of figures

Part A: LITERATURE REVIEW

Introduction

1.1 Objectives of the literature review.

I. To identify the current state of research into snakebites globally, mainly in low to middle-income countries (LMIC) and particularly in South Africa.

II. To discuss the current management controversies. Which will include:

Clinical presentations;

Indications for antivenom;

Complications and availability of antivenom;

Adjunct treatment of snakebite patients.

1.2 Literature search strategy

PubMed, Ebsco, Scopus and Google Scholar are databases used via UCT online library as primary research. The keys words used were:

- Snakebite envenomation in South Africa;
- Snakebite management in LMIC;
- Snakebite outcome;
- Antivenom snakebite.

The literature review research covered the period 1960 to April 2023.

1.3 Inclusion and exclusion criteria

Articles written in English covering this literature review's objectives were included, especially those written in the past 30 years.

1.4 Quality criteria

The principal investigator reviewed numerous articles by reading the abstracts and titles and including those deemed relevant. Systematic reviews followed by randomised controlled trial articles were privileged. Some case reports, and guidelines were also included.

Background

The World Health Organization (WHO)(1) reports that between 81,000 to 138,000 deaths occur annually due to snakebites, while over 400,000 individuals are bitten by snakes every year. The WHO aims to halve the number of deaths by 2030 and has classified the condition as a neglected sickness since 2009. In 2017, the WHO elevated it to Category A to prioritise it in the list of neglected sicknesses(1).

Literature reports that the main focus for snakebites should be to prevent them from happening, and the cornerstone of treatment, to prevent mortality and morbidity, is in many cases use of an antivenom(1, 2, 3, 4). The availability of antivenoms remains a challenge for many population groups, especially in low- or middle-income countries such as Africa, Asia, and Latin America(1). In those countries, it is still a challenge to have appropriate treatment available, as most snakebites occur in rural areas far from medical facilities, and sometimes victims do not have any choice but to seek attention from sources of traditional medicine(1, 2).

Snakes are found on all the continents, except in Antarctica. They are primarily found in areas with a tropical, semi-tropical, or temperate climate. Snakes use the hot and humid weather to move around(4). When it is cold, they have minimal mobility, which is why there is a high incidence of snakebites during the hot season, and in temperate countries, the incidence of snakebites is low(4). However, not all snakes that bite are dangerous to humans. Furthermore, while biting, venom is not always transmitted to the victim; this condition is reported as a dry bite(4).

There has been some important research on snakebite by a small number of authors in South Africa, and from elsewhere pertinent to the Southern African. These contributions are highlighted in Table 1.

Table 1. Summary of research on snakebites in South Africa and Africa

Authors	Research years and contributions
1. Blaylock (3, 5, 6, 7, 8, 9, 10, 11, 12)	has produced written work that delves into clinical presentations, first-aid management, and a syndromic approach to snake bites, from 1982 to 2005, and has provided helpful guidelines for managing snake bites, that are relevant to this day in South Africa.
2. Chippaux (13, 14, 15, 16, 17, 18, 19)	emphasized the significance of snakebites in rural areas and the injuries sustained by young people in LMIC and America, in 2011. In 2019, he expressed concern about the inefficacy of most antivenom available in Africa, except for the SAIMR, and the need to produce appropriate snake antivenom in Africa for African victims.
3. Christensen (20)	in 1960, presented a study on the production of snake antivenom in South Africa, highlighting the efforts of the South African Institute for Medical Research (SAIMR) to combat ten species of local snakes.
4. Hawgood (21)	in 2001, underscored the significance of improving snake antivenom production to mitigate potential adverse effects.
5. Molander (22, 23, 24, 25, 26)	in 2015, studied traditional plants in sub-Saharan Africa used in snakebite treatment, but the results were not as impressive as hoped.
6. Muller (27)	in 2012, penned a piece on the effective management of snakebite, focusing on the various snake species prevalent in Southern Africa and especially the Western Cape.
7. Okumu (28, 29)	conducted research on snakebites in Kenya in 2019 and 2022, identifying a shortage of snake antivenoms as a significant problem.
8. Pantanowitz (30, 31)	between 1996 and 1998, wrote about the advancements in snake antivenom development in South Africa and how it helped in treating pregnant victims of snakebite.

9. Pattinson (32)	conducted a study of managing snakebites, focusing on Pietermaritzburg, KwaZulu-Natal in 2017.
10. Warrel (33, 34, 35)	in 1974, compared the SAIMR antivenom to a West African antivenom and stressed the importance of snakebite in Africa in 1993, in 2023, he provided an updated report on snakebites in low to middle-income countries.
11. Wood (2, 36, 37, 38, 39, 40)	delved into the burden of snakebites in KwaZulu-Natal, highlighting that uMkhanyakude had the highest utilisation rate of snake antivenom in 2016. Wood's research further revealed that cytotoxic bites were the most commonly encountered cases at Ngwelezana Hospital in northern KwaZulu-Natal. He also proposed the Zululand Severity Score to evaluate the need of antivenom on the snakebite victim. He found that fasciotomy should not be employed as a standard measure, while ultrasound could benefit patients suspected of having compartment syndrome post snakebite.

Description of major venomous snake families and bites

Five families of snakes are found worldwide: the Colubridae, the Elapidae, the Viperidae, the Atractaspididae, and the Hydrophiidae (Table 2) (4, 41). They differ mainly based on the location of their venom gland(4, 41).

Table 2. Snake families.

Snake family	Specificities	Locations	Examples
1.The Colubridae (4, 27, 41)	has a venomous gland at the back of their upper jaw. Their fangs are also positioned far back in their mouth, which results in dry bites as they take some time to inject their venom.	Found worldwide	Boomslang
2.The Elapidae (4, 27, 41)	have a venomous gland in front of their upper jaw. They also have relatively short, fixed front fangs. For instance, the mamba has fangs mounted at the very front of the maxilla and can rotate with the pre-frontal bone.	South America and the southern United States, Africa, Southern Asia, Australia and the Pacific islands	Mambas, cobras, and coral snakes
3.The Viperidae (4, 27, 41) Viperidae are categorised into two: true vipers and rattlesnakes (Crotalinae).	have long, curved, and fully erectile fangs folded down against the upper jaw in a mucous membrane sheath when the snake is not striking. If bitten by this species, one may experience	Africa, Asia, America, and Europe	Puff adder

	superficial local tissue injury as their venom can disturb the haemostasis pattern, causing a bleeding tendency in victims. Additionally, some cases of neurotoxicity have also been reported.		
4.The Atractaspididae, also named mole vipers or stiletto snakes (4, 27, 41)	is the only snake that can still bite even when its head is held. They have additional fangs that face backwards. Called side stabbing snake. A bite by a stiletto does not respond to SAIMR antivenom and has a cytotoxic effect.	Primarily found in Africa. They are common in the north of KwaZulu-Natal in South Africa.	Stiletto
5.The Hydrophiidae (4, 27, 41)	have short fangs, resulting in a painless bite. They typically inhabit rivers.	Uncommon in Africa	Sea snake

Why snakes bite

As Darinka et al.(42) explain, snakes bite for two main reasons. Firstly, while hunting for food, as they typically prey on lizards, insects, and some green plants. Snakes inject a considerable amount of venom into their prey to incapacitate them. This behaviour is typical among Mozambican spitting cobras (Naja Mossambica), known as "M'fezi" in KwaZulu-Natal. These snakes are often found indoors, and the people whom they bite often require antivenom to treat the bite(2, 7). The second reason for a snake to bite is self-defence. The snake is forced to bite to defend itself (42). In such cases, it is quick to bite, so that it can get away from the danger. This condition is seen when a snake bites a person in a field (for example in a sugarcane field) while they are working, hunting, herding, or walking in the dark. Much of the time, these self-defence bites are a dry bite or not very dangerous(42). This can also be seen when a patient is the victim of a snake spitting venom into their eyes (43, 44). The two mechanisms are often visible in emerging economies where people work or hunt in poor conditions, not wearing shoes or protective boots, gloves, or glasses. (45). Meanwhile, in high income countries, snakebites more often happen to victims who have snakes as pets, or in zoos, among snake handlers and herpetologists who are accidentally bitten by their snakes. It remains a big problem in these high-income countries(46, 47, 48).

Snakebites and accessing care or traditional care.

After a bite occurs, according to where the patient is located, they consult a healthcare facility, or first-aid is given at the scene, and in high-income countries, the patient is usually rushed to a hospital. Much of the time in LMIC, the patient first seeks care from a traditional healer, delaying the time to reach a hospital. In addition, in rural areas in LMIC, hospitals are often located far from the places where the injuries take place(49, 50, 51). Newman(50) and Nann(51) have reported that in cases of bites, individuals may attribute the cause to an evil spirit and thus seek treatment from traditional healers. These practitioners may use scarification or tattooing at the site of the bite, which can exacerbate swelling or even result in the transmission of diseases such as HIV or Hepatitis B(1). Aspiration and tourniquets may also be employed. In certain instances, patients may receive a concoction to be taken orally or applied directly to the bite area, leading to further complications and the onset of local infections(1). In a study performed at Hlabisa hospital, in the north of KwaZulu-Natal in South Africa, Newman et al.(50) showed that almost 90 % of victims of snakebite used some traditional medicine before coming to or in hospital. In Myanmar, qualitative research carried out by Eliza et al. (49) demonstrated that this may be due to the belief that snakebites are caused by an evil spirit; the affordability and availability of traditional healers may be the reason that they are consulted first. Collaboration between traditional healers and modern medicine may be helpful, as the former can be trained to recognise a life-threatening condition and should be able to refer the patient to a hospital, if needed (49, 50, 51).

The WHO(1) recommends that in case of a snakebite, one should immobilise or decrease the movement of the affected limb with an arm sling or bandage, in order to bring the patient to the closest health facility as soon as possible. The use of bandages remains controversial as they are helpful for a snakebite causing a neurotoxic effect, and valuable when well applied(4), which is often not the case, leading the WHO(1) to not encourage the use of these as a first aid, but instead to recommend immobilisation, for example, with an arm sling at heart level. At the hospital, it is always challenging to know which snake was involved as sometimes the victim saw the snake but did not manage to bring it with them or take a picture of it. Moreover, the patient cannot always describe the snake responsible for the bite. Even if it is recommended to bring the snake, if killed, to the hospital, it is often not preferable because it can still bite more victims in the process(1, 4).

It is difficult for a healthcare worker at a hospital to recognise which snake was the culprit, unless in a high-income country where a toxicologist is available for snakebite management(41). In countries such as Australia, a specific kit is used for bedside investigation to identify which snake is responsible. Body fluid can be used from around the bite, blood, or urine, to identify the snake, and indirectly assist to find the available and appropriate antivenom(4). In other areas, such as Europe and North America, a database is used to recognise the snake(42, 52). In the United States, a medical toxicologist is always involved in treating snakebites(41, 52).

Managing snakebites in hospital: Initial assessment and scoring

In assessing a snakebite victim, there are various considerations for the clinician, including the local context and prevalence of specific snakes; having any means of identifying the snake responsible; and the clinical presentation of the patient. Wood et al.(38) have developed a tool for objectively assessing snakebites and aiding subsequent clinical decision making. A snakebite severity score (SSS) is used to determine which patients require antivenom for snakebites(53). This score ranges from 0 to 23 and considers various factors such as clinical assessment; pulmonary symptoms; cardiovascular system; local wound or swelling; gastrointestinal systems; haematologic symptoms; and central nervous system(53). The SSS categorises envenomation in multiple ways. The first way is by minimal, moderate, or severe. The second way is by grade, ranging from 0 to 4. Grade 1 is considered minimal envenomation, grade 2 is moderate envenomation, grade 3 is severe envenomation, and grade 4 is very severe(53).
In South Africa, a syndromic approach is used as no bedside tests or point-of-care investigations are available to identify the involved snake from a database(3, 54)

The syndromic approach

Blaylock (3) suggested a syndromic approach consisting of six different syndromes, including: painful progressive swelling (PPS); progressive weakness (PW); bleeding; mixed painful progressive swelling and bleeding; mixed painful progressive swelling and progressive weakness; and mild to moderate swelling, as shown in Table 3.

A bleeding syndrome can occur in various body parts, such as mucous membranes, bite sites, the gastrointestinal system, skin, or other organs(3). To diagnose this syndrome, a 20-minute whole blood clotting test (WBCT) is used as a bedside exam, which is positive if the blood fails to clot after 20 minutes without an anticoagulant reagent (55) . Snakes effect and use bleeding by damaging capillaries, having a vasoactive effect, and consuming all the coagulation factors. A specific monovalent antivenom is required for this syndrome, usually caused by the Boomslang. Patients with progressive weakness syndrome might need supportive respiratory management if SAIMR AV is not given, early, because the snake venom can block the pre-and post-synaptic pathways, affecting the neuromuscular junction(3).

Table 3: A syndromic approach promoted by Blaylock(3)

Syndrome	Characteristics	Examples
1. Painful progressive swelling (PPS)	Rapid progression of swelling blistering discolouration Sometimes necrosis on the bite No bleeding	Mozambique Spitting Cobra, rinkhals/ night adder / stiletto snake
2. Progressive weakness (PW)	Slurred speech Struggling to swallow Mimicking intoxication Difficulty breathing Late broken neck syndrome	Black Mamba, non-spitting cobras
3. Bleeding	Negligible swelling Bleeding Incoagulable blood 20-minute whole blood clotting test (WBCT) is positive	Boomslang, Vine snakes
4. Mixed painful progressive swelling and bleeding,	Rapid progressive swelling and blistering A tendency to bleed. A reactive lymph node can be present.	Puff Adder, Gaboon Adder
5. Mixed painful progressive swelling and progressive weakness,	Rapid progression of swelling Slurred speech Struggling to swallow Mimicking intoxication Difficulty breathing	Berg Adder, Forest Cobra
6. Mild to moderate swelling	Slow progression of swelling most common in South Africa	Natal Green Snake, Green House Snake

From Blaylock RS. The identification and syndromic management of snakebite in South Africa. South African Family Practice. 2005;47(9):48-53.

In-hospital management of snakebite: General management and use of antivenom

Once the type of syndrome has been recognised, a patient may benefit from an antivenom, which is the cornerstone of snakebite treatment, and/or may benefit from analgesia, limb elevation of the affected limb or part of the body, and the administration of a tetanus antitoxin and intravenous crystalloid(1, 4). Still, the clinician must decide who gets an antivenom and who does not. When a patient presents with unstable vital signs, decreased level of consciousness, significant swelling, or bleeding tendencies, they require antivenom (3, 4). Nevertheless, in other presentations it may be unclear if the patient needs an antivenom or not. A score has been developed, such as the snakebite severity score (SSS)(53) or a Zululand severity score (ZSS) (Table 4), developed by Wood(38), that considers six criteria to decide who will benefit from antivenom or not. A score of more than four points indicates the need for antivenom, and one less than or equal to four is a reason for a patient to be observed for a minimum of 12 to 24 hours after the bite, before discharge(38).

Table 4 Zululand snakebite score

Criteria/risks predictors	Allocated score
Age of less than 14 years old	1
Delay of admission or victim presentation to a hospital of more than seven hours	1
A white blood cell count of more than $10x10^9$/L	1
A thrombocytopenia of less than $92x10^9$ /L	1
Anaemia with haemoglobin (Hb) count of less than 7.1g/dl	1
International normalised ratio (INR) of more than 1.2	1

From Wood D, Sartorius B, Hift R. Classifying snakebite in South Africa: Validating a scoring system. South African Medical Journal. 2017;107(1):46-51.

While there have been attempts to create scoring systems to help clinicians determine who needs antivenom treatment, there still needs to be a unanimous agreement. The SSS is commonly used in the United States, while the ZSS is more prevalent in the northern region of KwaZulu-Natal. In addition, the South African Snakebite Symposium 2022 (SASS) (56)has established clear guidelines for administering antivenom, which is outlined in Table 5.

Table 5 Antivenom indication from SASS 2022

- Systemic signs and symptoms or severe spreading local tissue damage.
- Signs of neurotoxicity.
- Positively identified Puff Adder, Gaboon Adder, Mozambique spitting Cobra or Rinkhals with clear signs of severe progressive cytotoxicity.
- Unidentified snakebites and evidence of severe progressive cytotoxicity envenomation; with:
    - Swelling of whole hand or foot within 1 hour;
    - Swelling to the knee or elbow in less than 6 hours (or two joints above bite in 6 hours);
    - Swelling of the whole limb in less than 12 hours;
    - Swelling progression more than 5 cm per hours;
    - Discoloration of the skin /necrosis at the bite-site;
    - Threatened airway due to swelling;
    - Clear complication as Compartment syndrome;
    - Thrombocytopenia or raised INR / abnormal TEG/ROTEM.
- Boomslang bite clearly identified.

from (Hardcastle et al.(56)) *Hardcastle T, Kajee M, Lachenicht K, van der Walt N. Approach to the diagnosis and management of snakebite envenomation in South Africa in humans: Layperson aspects and the role of emergency medical services. South African Medical Journal. 2023:10-8*.

It has been shown that high-income countries are prompt to give antivenoms, probably because these are not likely to create many side effects as is the case in low-income countries(57, 58).

Use of antivenom: Internationally

Snake antivenoms remain the baseline of snakebite treatment(1, 4). In all countries, antivenom is given for severe envenomation, based on the snake being identified (or a typical clinical presentation) and an appropriate antivenom being available(1, 4). In high-income countries, an appropriate antivenom (FabAV=CroFab) is made available from appropriate industries; these antivenoms are made from snake venoms that are inoculated to horses or cows, then purified to produce appropriate antivenom that is often very expensive, costing up to $1000 per vial(58). Therefore, the cost is almost $8000 for eight vials of treatment to be given to a single patient(58). Many low-income countries, such as Ghana, Bangladesh and Venezuela, are still not producing antivenoms and they mostly import from other countries, such as India and Costa Rica(59, 60), making it difficult to make them available in remote areas. Also, some imported antivenom is given in sub-Saharan Africa where their efficacity is not proven(59).

South Africa imported an antivenom from the Louis Pasteur Institute in France(30, 61) until 1971. After that, the South African Institute for Medical Research (SAIMR) developed and made available polyvalent and monovalent antivenom. The polyvalent antivenom has efficacy against the ten commonly encountered toxic snake venoms in Southern Africa(30, 61): the vipers Bitis arietans (Puff Adder) and B. gabonica (Gaboon Adder); the Cobras and Rinkhals - Naja nivea (Cape Cobra), Naja mossambica (Mozambican Spitting Cobra), N. melanoleuca (Forest Cobra), N. annulifera (Snouted Cobra), and Hemachatus haemachatus (Rinkhals); and the mambas—Dendroaspis polylepis (Black Mamba), D. Jameson (Jameson's Mamba), and D. augusticeps (Green Mamba) (30, 61). The monovalent antivenom has efficacy against the Dispholidus typus (Boomslang), only(30, 61).

The antivenom is a mixture collected from an equine or bovine serum that was initially exposed to snake venom. The snakebite manufacturing process starts when a healthy snake is carefully milked, and its venom is stored in a cold chain(62). Gradually, the venom is injected into horses until they can produce immunoglobulins(62). The horses undergo either automatic or manual apheresis, with the former being a more purified serum collection(62). The serum is then purified through a series of processes, resulting in three possible final products: intact IgG, F(ab')2 fragments, or fab fragments(62). The purification process involves using either ammonium sulfate or caprylic acid, with the latter producing a product with higher purity (60%–75%) and low protein aggregate formation(62). Conversely, the former produces a product with lower purity (30%–40%) but higher protein aggregate formation(62). The high rate of side effects caused by antivenom is often attributed to the amount of protein aggregate in the antivenom(62). The SAIMR antivenom is purified using pepsin and ammonium sulfate as downstream processes, resulting in a high incidence of side effects(30). Unfortunately, this technology has not been improved upon since its development(30). In contrast, the United States has transitioned from using antivenin Crotalidae polyvalent (ACP) to Crotalidae polyvalent immune Fab (FabAV l), which has significantly reduced adverse reactions from 23%–56% to less than 5%(58). FabAV uses a depth filtration system combined with filter aids and affinity chromatography, resulting in a safer product(58).

Antivenom use in SA and side effects/ complications.

With the side effects of SAIMR antivenom still high at 40%–60%(39, 57), this explains why the choice of antivenom given must be well studied and documented, as a patient may develop considerable side effects from a Type one reaction, anaphylaxis to a Type three reaction, or serum sickness (Table 6)(39, 57). Occasionally, individuals may have a response to horse proteins that are not triggered by IgE but instead classified as a Type 1 hypersensitivity. This can be verified by conducting a skin test or radioallergosorbent test, which will indicate the absence of IgE and the activation of complement by IgG due to the antivenom protein aggregate(62). This type of reaction is not considered an allergic reaction(62).

Table 6 Snake antivenoms reactions.

Anaphylaxis reaction	**Pyrogenic reaction**	**Serum sickness**
Minutes to 3 hours • urticaria • dry cough • fever • abdominal symptoms (diarrhoea, vomiting, colic) • life threatening (hypotension, bronchospasm, angioedema)	1 to 2 hours • more frequent • due to pyrogen contamination during production • shaking, chills, rigors • fever causing vasodilatation leading to hypotension	1 to 12 days • fever • abdominal symptoms (diarrhoea, vomiting, colic) • itching • recurrent urticaria • joints and muscles pain • lymphadenopathy

from WHO(62) *World Health Organization W, Organization WH. WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins. Geneva: WHO. 2010;134*.

The most common side effect is a pyrogenic reaction observed in most patients receiving antivenoms. It is recommended that more studies be done to improve the SAIMR AV and avoid the considerable side effects(39, 57).

The debate about using premedication prior to antivenom administration remains current. Most of the literature does not recommend using any premedication before giving antivenom or advice about

treating the side effects. At the same time, if they do occur, either adrenalin, antihistamine or steroids can be used. Wood(39) recommended that, as there is no clear consensus on the use of adrenalin, it can be used, as there is no change in the outcome, as noticed with the use of steroids or antihistamine as premedication(57). It has been noted that patients who received adrenalin premedication were still prone to developing anaphylaxis or serum sickness(63). In most SA healthcare facilities, adrenalin prophylaxis is given prior to antivenom being administered, as is still the case at Ngwelezana Hospital (a regional hospital in the North-East KwaZulu-Natal in South Africa) as stressed by Giles(64) and Buitendag(65). Lavonas et al.(66) and Malasit(63) reported that administering steroids as a premedication before antivenom led to a negative outcome. Also, in their randomised control trial study, De Silva et al.(67) in India, showed that adrenalin significantly reduced severe antivenom reactions by almost 43% in the first hour, and by 38% up to 48 hours after antivenom was given. De Silva(67) also demonstrated that hydrocortisone and promethazine did not decrease the severe antivenom reaction and that the former negated the benefit of adrenalin. The Indian antivenom used in that study often comes from horses with almost the same composition as the SAIMR AV(56). The De Silva(67) study reinforced what Wood(39) had reported earlier: giving adrenalin as premedication benefits patients requiring antivenom.
However, all studies are unanimous in that a clinician should be ready to manage anaphylaxis if it occurs when using antivenom. They recommend having available emergency drugs and equipment to use in case of anaphylaxis or serum sickness(39, 57, 67).

In the literature, a patient who developed an anaphylaxis reaction required adrenalin infusion for a few hours. Pantanowitz(30) initially reported that the SAIMR AV has a low incidence of anaphylaxis, less than 1%. However, it was rapidly demonstrated to be wrong as there was an incidence of up to 76% of anaphylaxis noted when giving antivenom, as denoted by Moran(57) in his article "High incidence of early anaphylactoid reaction to SAIMR AV". This could have been the case because no premedication was given; however, many other studies by Pattinson(32), Blaylock(3), Giles(64) and Buitendag(65) all find a hypersensitivity post-antivenom, ranging between 20% and 61% when premedication was given; premedication was essentially made up of adrenalin. Hypersensitivity post-antivenom is probably due to an insufficient purification of the SAIMR AV, which is made of pepsin-refined immunoglobulins (F[ab']2 fragment) from a horse(57), that causes release of histamines from the IgE mediation or via the activation of a complement(30, 57). A patient who receives an antivenom may later develop a serum sickness that occurs some hours or days after its administration as the body tries to eliminate the protein from its system(30, 57).

Antivenom dosage remains a significant controversy. Literature shows that up to ten vials with a minimum of four may be given, with a possible second dose being administered(3, 4, 52, 66). The dosage is not dependent on weight, explaining why a paediatric patient receives the same dose as an adult patient. The antivenom must neutralise the same dosage of venom in adult or child victims(54, 65, 68). There is a common practice of using a high dosage of antivenom in small children, with the recent study by Buitendag et al.(65) at Ngwelezana hospital in the northeast of KwaZulu-Natal, showing the importance of this in paediatric patients, as the venom neutralisation is in high concentration in small volumes(42, 65). With the body surface being less for a child, this explains the quick expansion of the venom(3, 69, 70).

Antivenom: The future

An African study looking at the efficacity of snake antivenom on the continent, showed that most antivenoms are not efficacious(59). The leading antivenom remains the SAIMR AV, but it is difficult to access, especially outside of South Africa. In Eswatini, a small country neighbouring South Africa, it is advised to use two snake antivenoms: the Panafrican Antivenom and PANAF, produced in Costa Rica and India(61). These two antivenoms would seem as effective as the SAIMR polyvalent for the venom of a Mozambican Spitting Cobra. This snake is common in Eswatini, but these two antivenoms have less efficacy against other species than the SAIMR AV, which has proven efficacy(61). There needs to be a greater quantity and production of the SAIMR AV available, as it is made mainly for the South African population, making it difficult to access in neighbouring countries, such as Eswatini or Mozambique, where the same snakes are present. Since the SAIMR AV remains expensive, it pushes these countries to look for alternatives elsewhere(61). The Indian antivenoms are sometimes used, although the quality of products remains an issue(61).

FAV is used in Ghana and some other countries, but it remains expensive and challenging to fund in rural areas, where most snakebite cases occur(71). There is still a revolution needed to provide cheap and available antivenom, but the most crucial issue is to have antivenom with fewer side effects; for that, the WHO is encouraging countries to make more types of antivenom, and they are mobilizing funds for further research on snake antivenom(1).

In vitro, recombinant antivenom is one of the future alternatives for antivenom, as demonstrated by Seifert(4); as such synthetic antivenoms will be the next generation of antivenom. They will be less expensive, and the side effects will be less frequent and pronounced than the current antivenoms. The

WHO(1) will have to invest more in this next generation of antivenoms if they want to halve the number of deaths due to snake venom by 2030. Another effective alternative in the future is using oral tablets as antivenom; research is looking at a combination of tablets to prevent the rapid progression of snake venoms, allowing more time while preparing to give antivenom. Indeed, some oral treatments, such as antiphospholipase, metalloproteinases inhibitors or some natural plants may be used to help stop the spread of the snake's toxin(4, 72). However, research is still in progress, and no tablet is available in a range of healthcare facilities worldwide(4, 72). One study estimates that expired antivenom may still be used in case of a shortage of antivenom; according to Sanchez(73), including four antivenoms, amongst which the SAIMR AV can still be used 20 years after expiration.

Nevertheless, most legislation is against using expired products, but this study shows that there is room for such a product if clinicians find themselves without other options. The use of appropriate consent may be needed in such cases. The antivenom market must be well replenished worldwide, as most companies find it challenging to produce antivenom as it is not lucrative. For example, one of the big companies producing Fav-Africa had to stop its production as it was not lucrative enough for them(74). Meanwhile, the WHO is trying to inject more money into antivenom production(1).

Outcomes of snakebites

Most patients who do not receive antivenom are either discharged on the same day, especially if the snake is known to be non-venomous, especially in a region where snakebite is treated with a medical toxicologist(41, 66). This occurs as well in some other cases, such as in the southern African setting, which may have the good fortune of having a herpetologist around or a healthcare worker who is experienced with snakebites. More often than not, the snakebite patient is admitted for observation(2, 3, 66). The wound often needs debridement after five to seven days, according to the species responsible. Those patients remain with sequelae such as permanent contracture of a limb, amputations and sometimes a post-traumatic stress disorder (32, 40). Fortunately, death from snakebites is rare (or rarely reported at least) and usually in the face of co-morbidities or patients with co-morbidities and extremes of age. (67)

Surgical management of snakebites

Debridement is performed in more than 14% of cases, according to Pattinson (32) in his 2017 study in Pietermaritzburg, where less than 5% of patients required fasciotomy. In contrast, Wagener et al. (75), in their study at Ngwelezana Hospital in the north-east of KwaZulu-Natal (in the same year as the

Pattinson study)(35), showed that 34.8% of snakebite victims needed a surgical debridement, with one patient needing fasciotomy. In other studies, surgical treatment was more often a debridement than a fasciotomy(69, 76). The debridement proved beneficial, once the demarcation of the necrotic area was performed. This often happened a week or a couple of days after the snakebite. Fasciotomy was not done routinely, as it has not proved to be essential for most patients, since the swelling mostly happens in the subcutaneous tissues rather than in the muscle compartment (3, 70). A study in the United States noted that fasciotomy was performed if the snakebite patient was primarily seen by a surgeon, rather than a medical toxicologist (66). Wood(40) has shown that ultrasound could be beneficial in diagnosing a compartment syndrome, as it is less invasive than measuring the intramuscular compartment pressure (IMCP), where a needle is used to measure the pressure for making the diagnosis. (40) An IMCP below 10 mmHg is generally considered normal, and an IMCP of 30 mmHg to 50 mmHg requires fasciotomy (40). Nevertheless, an ultrasound, a painless procedure, needs an appropriate high-frequency probe and should be done by an expert hand, otherwise, there is a high risk of bias(40). Most patients who received an antivenom did not need fasciotomy, as there was no true compartment syndrome(40, 69, 76). Blaylock(3, 7, 9) and Wood(40) also noticed that most patients who required antivenom, but did not receive it for diverse reasons, were candidates for surgical intervention; most of the patients also required antibiotics as they often developed sepsis(3).

Use of antibiotics in snakebite

The use of antibiotics in snakebite management remains controversial. Most countries do not use antibiotics as prophylaxis in cases of snakebite(4, 10). In Asia, antibiotics are used in most cases where sepsis has developed. In such instances, they use amoxicillin/clavulanate and quinolone of the second generation such as ciprofloxacin empirically for minor cases, or a third generation cephalosporine in severe cases(77). Antibiotics are used in South Africa if inflammatory markers are raised on admission. Wound infections are typically caused by Gram-positive and Gram-negative aerobic cocci and bacilli. To treat this infection, a broad-spectrum antibiotic is often recommended while awaiting culture results in patients with clear infection. These types of bacteria are commonly found in the mouths of many snakes.(10, 11, 78). However, it remains clear that antibiotics are not given as prophylaxis in snakebite cases(4).

Other complications of snakebite

An ophthalmic injury named venom ophthalmia may occur in the case of the spitting Mozambican Cobra(3, 43). The patient presents with a history of pain, reddish eyes, and exposure to a snake. According to Blaylock (3) and Sithole(43), such cases do not need an antivenom. Even in the most severe case where corneal erosion is noted, a simple washing out of the eyes with water is often the most important first-aid used, followed by anaesthetic drops sometime later; for example, lignocaine and antibiotics are used, according to Blaylock(3). When treating venom ophthalmia in a hospital setting, it is not recommended to use diluted antivenom for topical irrigation of the affected eye. All cases have to be reviewed by an ophthalmologist (3, 43).

Some patients develop rhabdomyolysis due to the swelling and the myoglobin release in their general circulation. It is always advised to use an intravenous fluid on patients with a high chance of developing rhabdomyolysis. Most deaths occur due to acute kidney injury (AKI)(4). In Asia and Africa, significant cases of rhabdomyolysis have been noted. Furthermore, AKI may be due to a snake venom that may have a nephrotoxic effect(4, 79) or hypovolemic shock, as a result of a third space formation causing a kidney injury(54). The AKI may worsen in a setting where traditional healers give victims concoctions that negatively impact kidney function(4, 54, 79).

SUMMARY

It is hoped that the WHO recognising snakebite as a neglected tropical disease has helped improve snakebite management(35, 55, 80). Many countries have followed the WHO recommendations, and significant funds have been allocated to combat snakebite(55). However, snakebites are often prevalent in remote and rural areas where hospital access is difficult(55, 81). Delay in reaching hospital can prolong recovery from snakebite(55). Additionally, traditional healers are often consulted first as they are often located nearby and due to the victim's beliefs(49, 51, 71).

Antivenoms remain the cornerstone of treatment, with specific and relative indications remaining largely at the clinician's discretion despite efforts to develop an appropriate guideline(38, 55). As a premedication before antivenom, adrenalin remains a standard, (despite ambiguous evidence of benefit) especially in countries where antivenoms have allergic effects, as in South Africa(3, 6, 37).

Education of local populations must be undertaken, stressing the preventative measures of wearing appropriate shoes and glasses and knowing the types of snake that bite, when living in an area with a high incidence of snakebite(4, 55). Appropriate first aid must be taught to the local population, and early hospital consultation must be promoted, so that most complications may be avoided, such as permanent contracture of fingers and toes, amputation of limbs, and sometimes loss of vision or post-traumatic stress disorder (4, 55).

A lot remains to be done as an alternative to the current treatment; in this vein, the WHO has been trying to find better antivenoms or more effective and cheaper alternative treatments(4, 55).

This literature review highlights the need to train healthcare workers to identify the dangerous signs of envenomation, such as neurotoxicity, bleeding disorders, and progressive swelling(55). It is also essential for them to be familiar with various available guidelines. Popularising these guidelines is crucial for raising awareness among the population and healthcare workers(3, 55).

A previous study reported high snake antivenom usage in northern Kwazulu-Natal, particularly in uMkhanyakude(2). No recent studies have been conducted in hospitals in that area, underscoring the importance of conducting a descriptive study to correlate with previous research.

References

1. Organization WH. Snakebite envenoming: a strategy for prevention and control. 2019.

2. Darryl W, Sartorius B, Hift R. Estimating the burden of snakebite on public hospitals in KwaZulu Natal, South Africa. Wilderness and Environmental Medicine. 2016;27(1):53-61.

3. Blaylock RS. The identification and syndromic management of snakebite in South Africa. South African Family Practice. 2005;47(9):48-53.

4. Seifert SA, Armitage JO, Sanchez EE. Snake envenomation. New England Journal of Medicine. 2022;386(1):68-78.

5. Blaylock R. Normal oral bacterial flora from some southern African snakes. Onderstepoort journal of veterinary research, 68: 175-182. 2001.

6. Blaylock R. Suggested management of poisonous snakebites in South Africa: current perspectives. 2003. p. 33.

7. Blaylock R. Epidemiology of snakebite in Eshowe, KwaZulu-Natal, South Africa. Toxicon. 2004;43(2):159-66.

8. Blaylock R, Lichtman, AR, Potgieter P. Clinical manifestations Cape cobra (Naja nivea) bites-a report of 2 cases. South African Medical Journal. 1985;68(5):342-4.

9. Blaylock RS. Retrospective analysis of snakebite at a rural hospital in Zululand. S Afr Med J. 1995;85(4):286.

10. Blaylock RS. Antibiotic use and infection in snakebite victims. South African Medical Journal. 1999;89(8):874-6.

11. Blaylock RS. Antibacterial properties of KwaZulu Natal snake venoms. Toxicon. 2000;38(11):1529-34.

12. Blaylock RS. Immediate active movement following Bitis arietans or Naja mossambica venom injection diminishes or prevents necrosis in mice. Toxicon. 2002;40(12):1675-7.

13. Chippaux JP. Estimate of the burden of snakebites in sub-Saharan Africa: a meta-analytic approach. Toxicon. 2011;57(4):586-99.

14. Chippaux JP. Incidence and mortality due to snakebite in the Americas. PLoS Negl Trop Dis. 2017;11(6):e0005662.

15. Chippaux JP. [Envenoming: What Information Do We Need Today and How Do we Present the Data?]. Bull Soc Pathol Exot. 2020;113(1):1-4.

16. Chippaux JP, Diouf A, Massougbodji A, Stock RP, Kane O, Dièye AM, et al. [Report of the 4th International Conference on Envenomations by Snakebites and Scorpion Stings in Africa, Dakar, April 25-29, 2011]. Bull Soc Pathol Exot. 2012;105(3):194-8.

17. Chippaux JP, Massougbodji A, Habib AG. The WHO strategy for prevention and control of snakebite envenoming: A sub-Saharan Africa plan. J Venomous Anim Toxins Incl Trop Dis. 2019;25.

18. Chippaux JP, Saz-Parkinson Z, Amate Blanco JM. Epidemiology of snakebite in Europe: comparison of data from the literature and case reporting. Toxicon. 2013;76:206-13.

19. Chippaux JP, Williams V, White J. Snake venom variability: methods of study, results and interpretation. Toxicon. 1991;29(11):1279-303.

20. Christensen PA. The scope of South African anti-snakebite sera. S Afr Med J. 1960;34:684.

21. Hawgood BJ. Poul Agerholm Christensen MD (1912-1991): antivenom production at the South African Institute for Medical Research. Toxicon. 2001;39(6):749-56.

22. Molander M, Nielsen L, Søgaard S, Staerk D, Rønsted N, Diallo D, et al. Hyaluronidase, phospholipase A2 and protease inhibitory activity of plants used in traditional treatment of snakebite-induced tissue necrosis in Mali, DR Congo and South Africa. J Ethnopharmacol. 2014;157:171-80.

23. Molander M, Nielsen L, Søgaard S, Staerk D, Rønsted N, Diallo D, et al. Corrigendum to 'Hyaluronidase, phospholipase A2 and protease inhibitory activity of plants used in traditional treatment of snakebite-induced tissue necrosis in Mali, DR Congo and South Africa'...Molander M et al. Hyaluronidase, phospholipase A2 and protease inhibitory activity of plants used in traditional treatment of snakebite-induced tissue necrosis in Mali, DR Congo and South Africa. J Ethnopharmacology 2014 Nov; 157: 171-80. Journal of Ethnopharmacology. 2015;168:380-.

24. Molander M, Nielsen L, Søgaard S, Staerk D, Rønsted N, Diallo D, et al. Erratum: Corrigendum to 'Hyaluronidase, phospholipase A2 and protease inhibitory activity of plants used in traditional treatment of snakebite-induced tissue necrosis in Mali, DR Congo and South Africa' (Journal of Ethnopharmacology (2014) 157 (171-180)). Journal of Ethnopharmacology. 2015;168:380.

25. Molander M, Saslis-Lagoudakis CH, Jäger AK, Rønsted N. Cross-cultural comparison of medicinal floras used against snakebites. J Ethnopharmacol. 2012;139(3):863-72.

26. Molander M, Staerk D, Mørck Nielsen H, Brandner JM, Diallo D, Kusamba Zacharie C, et al. Investigation of skin permeation, ex vivo inhibition of venom-induced tissue destruction, and wound healing of African plants used against snakebites. J Ethnopharmacol. 2015;165:1-8.

27. Muller G, Modler H, Wium C, Marks C, Veale D. Snake bite in southern Africa: diagnosis and management. CME: Your SA Journal of CPD. 2012;30(10):362-82.

28. Okumu MO, Mbaria JM, Gikunju JK, Mbuthia PG, Madadi VO, Ochola FO, et al. Preclinical efficacy testing of three antivenoms against Naja ashei venom-induced lethality. Toxicon X. 2022;14:100124.

29. Okumu MO, Patel MN, Bhogayata FR, Ochola FO, Olweny IA, Onono JO, et al. Management and cost of snakebite injuries at a teaching and referral hospital in Western Kenya. F1000Res. 2019;8:1588.

30. L. Pantanowitz L, Scott, Lesley**, Southern, J.***, Schrire L. Development of antivenoms in South Africa. South African journal of science. 1998;94(10):464-9.

31. Pantanowitz L, Guidozzi F. Management of snake and spider bite in pregnancy. Obstet Gynecol Surv. 1996;51(10):615-20.

32. Pattinson JP, Kong VY, Bruce JL, Oosthuizen GV, Bekker W, Laing GL, et al. Defining the need for surgical intervention following a snakebite still relies heavily on clinical assessment: The experience in Pietermaritzburg, South Africa. S Afr Med J. 2017;107(12):1082-5.

33. Warrell DA. Venomous bites and stings in the tropical world. Med J Aust. 1993;159(11-12):773-9.

34. Warrell DA. Commissioned article: management of exotic snakebites. Qjm. 2009;102(9):593-601.

35. Warrell DA, Williams DJ. Clinical aspects of snakebite envenoming and its treatment in low-resource settings. The Lancet. 2023.

36. Wood A, Schauben J, Thundiyil J, Kunisaki T, Sollee D, Lewis-Younger C, et al. Review of Eastern coral snake (Micrurus fulvius fulvius) exposures managed by the Florida Poison Information Center Network: 1998-2010. Clin Toxicol (Phila). 2013;51(8):783-8.

37. Wood D, Sartorius B, Hift R. Snakebite in north-eastern South Africa: Clinical characteristics and risks for severity. South African Family Practice. 2016;58(2):62-7.

38. Wood D, Sartorius B, Hift R. Classifying snakebite in South Africa: Validating a scoring system. South African Medical Journal. 2017;107(1):46-51.

39. Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: treatment modalities and outcomes. S Afr Med J. 2009;99(11):814-8.

40. WoodDarryl, Sartorius B, Hift R. Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes. Emergency medicine journal: EMJ. 2016;33(7):477-81.

41. Seifert SA, Oakes JA, Boyer LV. Toxic Exposure Surveillance System (TESS)-based characterization of U.S. non-native venomous snake exposures, 1995-2004. Clin Toxicol (Phila). 2007;45(5):571-8.

42. Tunjić Pejak D, Nesek Adam V, Srzić I. Venomous Snakebites in Croatia, Clinical Presentation, Diagnosis and Treatment. Acta clinica Croatica. 2022;61(Supplement 1):59-65.

43. Sithole HL. The ocular complications of an envenomous snakebite. South African Family Practice. 2013;55(2).

44. Ang LJ, Sanjay S, Sangtam T. Ophthalmia due to spitting cobra venom in an urban setting--a report of three cases. Middle East Afr J Ophthalmol. 2014;21(3):259-61.

45. Castoe TA, de Koning JAP, Hall KT, Yokoyama KD, Gu W, Smith EN, et al. Sequencing the genome of the Burmese python (Python molurus bivittatus) as a model for studying extreme adaptations in snakes. Genome Biol. 2011;12(7):406-.

46. Basse J, Ruha A-M, Baumgartner K, Mullins ME, Greene S, Wax PM, et al. Clinical presentations, treatments, and outcomes of non-native snake envenomations in the United States reported in the North American snakebite registry. Journal of Medical Toxicology. 2022:1-10.

47. Jagpal PS, Williams HA, Eddleston M, Lalloo D, Warrell D, Sandilands EA, et al. Bites by exotic snakes reported to the UK National Poisons Information Service 2009–2020. Clinical toxicology. 2022;60(9):1044-50.

48. Warrick BJ, Boyer LV, Seifert SA. Non-native (exotic) snake envenomations in the U.S., 2005-2011. Toxins (Basel). 2014;6(10):2899-911.

49. Schioldann E, Mahmood MA, Kyaw MM, Halliday D, Thwin KT, Chit NN, et al. Why snakebite patients in Myanmar seek traditional healers despite availability of biomedical care at hospitals? Community perspectives on reasons. PLoS Negl Trop Dis. 2018;12(2):e0006299.

50. Newman WJ, Moran NF, Theakston RD, Warrell DA, Wilkinson D. Traditional treatments for snake bite in a rural African community. Ann Trop Med Parasitol. 1997;91(8):967-9.

51. Nann S. How beliefs in traditional healers impact on the use of allopathic medicine: In the case of indigenous snakebite in Eswatini. PLoS Negl Trop Dis. 2021;15(9):e0009731.

52. Ruha A-M, Kleinschmidt KC, Greene S, Spyres MB, Brent J, Wax P, et al. The epidemiology, clinical course, and management of snakebites in the North American Snakebite Registry. Journal of Medical Toxicology. 2017;13:309-20.

53. Dart RC, Hurlbut KM, Garcia R, Boren J. Validation of a severity score for the assessment of crotalid snakebite. Ann Emerg Med. 1996;27(3):321-6.

54. Govender I, Tumbo J. The management of snakebites in south africa. South African Family Practice. 2019;61(3):51-8.

55. Organization WH. Guidelines for the management of snakebites: World Health Organization; 2016.

56. Hardcastle T, Kajee M, Lachenicht K, van der Walt N. Approach to the diagnosis and management of snakebite envenomation in South Africa in humans: Layperson aspects and the role of emergency medical services. South African Medical Journal. 2023:10-8.

57. Moran NF, Newman WJ, Theakston RD, Warrell DA, Wilkinson D. High incidence of early anaphylactoid reaction to SAIMR polyvalent snake antivenom. Trans R Soc Trop Med Hyg. 1998;92(1):69-70.

58. Weant KA, Johnson PN, Bowers RC, Armitstead JA. Evidence-based, multidisciplinary approach to the development of a crotalidae polyvalent antivenin (CroFab) protocol at a university hospital. Ann Pharmacother. 2010;44(3):447-55.

59. Brown NI. Consequences of neglect: analysis of the sub-Saharan African snake antivenom market and the global context. PLoS Negl Trop Dis. 2012;6(6):e1670.

60. Gutiérrez JM. Global Availability of Antivenoms: The Relevance of Public Manufacturing Laboratories. Toxins (Basel). 2018;11(1).

61. Menzies SK, Litschka-Koen T, Edge RJ, Alsolaiss J, Crittenden E, Hall SR, et al. Two snakebite antivenoms have potential to reduce Eswatini's dependency upon a single, increasingly unavailable product: Results of preclinical efficacy testing. PLoS Negl Trop Dis. 2022;16(9):e0010496.

62. World Health Organization W, Organization WH. WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins. Geneva: WHO. 2010;134.

63. Malasit P, Warrell DA, Chanthavanich P, Viravan C, Mongkolsapaya J, Singhthong B, et al. Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. Br Med J (Clin Res Ed). 1986;292(6512):17-20.

64. Giles T, Čačala SR, Wood D, Klopper J, Oosthuizen GV. A retrospective study of antivenom-associated adverse reaction and anaphylaxis at Ngwelezana Hospital, South Africa. Toxicon. 2022;217:1-4.

65. Buitendag JJP, Variawa S, Wood D, Oosthuizen G. An analysis of paediatric snakebites in north-eastern South Africa. S Afr J Surg. 2021;59(3):97-101
.

66. Lavonas EJ, Ruha A-M, Banner W, Bebarta V, Bernstein JN, Bush SP, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. BMC Emerg Med. 2011;11(1):1-16.

67. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, et al. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med. 2011;8(5):e1000435.

68. J B, S V, D W, Gv O. A comparison between adult and paediatric snakebites and their outcomes in North Eastern South Africa. Toxicon. 2022;208:13-7.

69. Hernandez MC, Traynor M, Bruce JL, Bekker W, Laing GL, Aho JM, et al. Surgical Considerations for Pediatric Snake Bites in Low- and Middle-Income Countries. World J Surg. 2019;43(7):1636-43.

70. Variawa S, Buitendag J, Marais R, Wood D, Oosthuizen G. Prospective review of cytotoxic snakebite envenomation in a paediatric population. Toxicon. 2021;190:73-8.

71. Steinhorst J, Aglanu LM, Ravensbergen SJ, Dari CD, Abass KM, Mireku SO, et al. 'The medicine is not for sale': Practices of traditional healers in snakebite envenoming in Ghana. PLoS Negl Trop Dis. 2021;15(4):e0009298.

72. Gutiérrez JM, Albulescu LO, Clare RH, Casewell NR, Abd El-Aziz TM, Escalante T, et al. The Search for Natural and Synthetic Inhibitors That Would Complement Antivenoms as Therapeutics for Snakebite Envenoming. Toxins (Basel). 2021;13(7).

73. SánchezElda E, Migl C, Suntravat M, Rodriguez-Acosta A, Galan JA, Salazar E. The neutralization efficacy of expired polyvalent antivenoms: An alternative option. Toxicon. 2019;168:32-9.

74. Alirol E, Lechevalier P, Zamatto F, Chappuis F, Alcoba G, Potet J. Antivenoms for snakebite envenoming: what is in the research pipeline? PLoS Negl Trop Dis. 2015;9(9):e0003896.

75. Wagener M, Naidoo M, Aldous C. Wound infection secondary to snakebite. South African Medical Journal. 2017;107(4):315-9.

76. Türkmen A, Temel M. Algorithmic approach to the prevention of unnecessary fasciotomy in extremity snake bite. Injury. 2016;47(12):2822-7.

77. Chen C-M, Wu K-G, Chen C-J, Wang C-M. Bacterial infection in association with snakebite: Aá10-year experience in a northern Taiwan medical center. Journal of Microbiology, Immunology and Infection. 2011;44(6):456-60.

78. de Lima DC, Alvarez Abreu P, de Freitas CC, Santos DO, Borges RO, Dos Santos TC, et al. Snake Venom: Any Clue for Antibiotics and CAM? Evid Based Complement Alternat Med. 2005;2(1):39-47.

79. Martines MS, Mendes MM, Shimizu MHM, Melo Rodrigues V, de Castro I, Filho SRF, et al. Effects of Schizolobium parahyba extract on experimental Bothrops venom-induced acute kidney injury. PLoS One. 2014;9(2):e86828-e.

80. LauridsenLine P, Laustsen AH, Lomonte B, Gutiérrez JM. Toxicovenomics and antivenom profiling of the Eastern green mamba snake (Dendroaspis angusticeps). Journal of proteomics. 2016;136:248-61.

81. Harrison RA, Hargreaves A, Wagstaff SC, Faragher B, Lalloo DG. Snake envenoming: a disease of poverty. PLoS Negl Trop Dis. 2009;3(12):e569-e.

PART B: MANUSCRIPT IN ARTICLE FORMAT

Ready for submission to the *African Journal of Emergency Medicine* AfJEM

Presentation and management of snakebite envenomation in the uMkhanyakude district of KZN

Formatted for AfJEM as per https://www.elsevier.com/journals/african-journal-of-emergency-medicine/2211-419X/guide-for-authors.

Authors: Matamba Jean Benoit Kabeya, Darryl Wood, Peter Hodkinson.

Abstract

Background.

Snakebites have been recognised as a neglected tropical disease by the World Health Organization (WHO) since 2009, and in 2017 it was elevated to Category A. South Africa (SA) has a well-documented prevalence of snakebites, and there has been a recent surge in attention due to dwindling antivenom stocks. uMkhanyakude District in the far northeast of SA uses more antivenoms than elsewhere in SA, and thus seems to have the highest incidence of venomous snakebites in SA, yet no recent study has come from this district to describe snakebite management. Although there are various protocols and guidelines, as well as tools for assessing severity, none are standardised and it remains unclear what local management (and outcomes) result, particularly at the level of a small district hospital with arguably the highest incidence of snakebites in SA.

Methods

A descriptive, retrospective, observational study was undertaken to describe victims of snakebites presenting from 1 September 2019 to 31 August 2022 to a district hospital, Mosvold Hospital. Data were collected from patients' medical records. Information about demographics, clinical presentations, treatments and outcomes was collected and analysed.

Results

A total of 155 snakebite cases presented, including 81 women (52.26%) and 74 men (47.74%). The incidence rate was 58 snakebite cases per 100 000 people per year. Most patients were young, with a median age of 19 years (range 0-94 years), and most bites occurred outdoors (48.70%). Patients were most often bitten on the lower limbs (69.03%), and most presented with minimal swelling - 117 patients (75.48%). Antivenom was administered to 33 patients (21.29%), and 24 (72.73%) of those who received antivenom experienced some form of post-antivenom reaction. Three patients died during their hospital stay, resulting in a mortality rate of 1.2 deaths per 100 000 people per year.

Conclusion

Snakebites are a not infrequent presentations, many requiring admission, antivenom and subsequent management. Specific local protocols for the management of snakebites could help to provide more standardised and earlier care to minimise complications. Expanding knowledge and education about snakebites provided to community members might also improve outcomes and prevent bites.

Keywords

Snakebite,

Management

Antivenom

South Africa

African relevance

- Snakebites continue to pose a significant health challenge in Africa, as the management of such cases lacks standardisation and often relies on an unpredictable and limited supply of antivenom in many parts of the continent.
- There remains a good deal of controversy on when to give antivenom, which doses, any premedication and appropriate surgical management.
- Local protocols for snakebite management are important, as is community education, first aid and early access to health care for snakebite victims.
- Poorly managed snake bites result in prolonged hospital stays, surgical procedures and disabilities and death.

Abbreviations

EC – Emergency Centre

HIC – High Income country.

INR - International normalised ratio

KZN – KwaZulu-Natal

LMIC – Low to middle-income country

SA – South Africa

SASS - South African Snakebite Symposium

TEG/ROTEM – Thromboelastography/Rotational thromboelastometry

WHO - World Health Organization

ZSS - Zululand snakebite severity score

African Journal of Emergency Medicine (AFJEM): Article format

Presentation and management of snakebite victims at uMkhanyakude (Mosvold Hospital)

Authors: Matamba Jean Benoit Kabeya, Peter Hodkinson, Darryl Wood

Wordcount Manuscript: 2993 words

Introduction.

Snakebites are an often overlooked entity, with high morbidity and sequelae, according to the World Health Organization (WHO) (1, 2). It was only in 2009 that snakebites were recognised as a neglected tropical disease by the WHO, and later in 2017, it was prioritized by being made a Category A neglected tropical disease(1, 2). Most literature and guidelines suggest that antivenom administration is critical in managing snakebites(1, 3, 4, 5, 6). Blaylock (7) advised a syndromic approach in South Africa to distinguish presentations between three primary syndromes of Painful progressive swelling, weakness or bleeding. Wood et al.(3) developed a score to help the clinician decide when to give an antivenom, the Zululand snakebite severity score (ZSS) which is now in use in some centres, and includes age, admission delay, white cell count, platelet, haemoglobin and International normalised ratio (INR) (3). Other than antivenom (and various proposed medications to reduce anaphylaxis, pyrogenic reactions and serum sickness), management may include antibiotics, surgical fasciotomy and debridement; all controversial and without clear guidelines in South Africa (3, 6, 8, 9, 10).

Wood et al. (4) through tracking the supply of antivenom in South Africa, found that uMkhanyakude District in the far north-east of Kwazulu-Natal used the most antivenom and thus had the highest prevalence of snakebite presentation to hospitals, yet no recent study has come from this district. There was therefore a need to carry out a study on snakebites from the "epicentre" where most of the snakebite cases in the province have occurred (4). The Mosvold Hospital, in Ingwavuma is one of several district hospitals in the uMkhanyakude district, anecdotally thought to see the most snakebites in the district (11, 12).

The early administration of antivenom to snakebite victims remains a major challenge in uMkhanyakude district. Many patients seek alternative care from traditional healers before proceeding to a clinic or hospital (9, 13). Those who do receive antivenom in hospitals may present late and consequently require further and protracted treatment. Snakebites are highly seasonal in the uMkhanyakude area and are seen predominantly in the rainy summer months (November to March) (9, 14, 15). No recent studies describe snakebite presentations or management in the uMkhanyakude district. This study therefore seeks to describe snakebite incidence, treatment and outcomes at Mosvold Hospital.

Methods

Study design and data collection

This study is of a retrospective observational design that aims to provide a description of all individuals who sought medical assistance for snakebites at Mosvold Hospital during the period from 1 September 2019 to 31 August 2022. The analysis includes patients of all ages and geographical locations and seeks to offer a detailed account of this population's demographics, clinical characteristics and outcomes.

Setting.

Mosvold is a district hospital located in the uMkhanyakude district of the KwaZulu-Natal province in South Africa (11, 12). This district is widely recognised as one of the most underprivileged areas within the region. The semi-tropical climate makes the community susceptible to tropical diseases and snakebite (1). Mosvold Hospital provides healthcare services to a population of some 89 000 people, as well as those from neighbouring countries including Swaziland and Mozambique (11, 12). The hospital has eight clinics and a community health centre. Patients are transported from the clinics to the hospital by ambulance services that cover the whole district and province. Mosvold Hospital has 186 beds, with six wards catering to the needs of female, high-care, male, maternity, paediatrics, and tuberculosis patients and a medical staff complement of 12 generalist medical officers (11, 12). This hospital treats an average of 49 000 patients annually, with 17% requiring in-patient admission (11, 12).

Table 1: Indication for antivenom administration according to 2022 South African Snakebite Symposium

- Systemic signs and symptoms or severe spreading local tissue damage
- Signs of neurotoxicity.
- Positively identified Puff Adder, Gaboon Adder, Mozambique Spitting Cobra or Rinkhals with clear signs of severe progressive cytotoxicity
- Unidentified snakebites and evidence of severe progressive cytotoxicity envenomation; with:
    - Swelling of whole hand or foot within one hour
    - Swelling to the knee or elbow in less than six hours (or two joints above bite in six hours)
    - Swelling of the whole limb in less than 12 hours
    - Swelling progression of more than five cm per hour
    - Discoloration of the skin/necrosis at the bite-site
    - Threatened airway due to swelling
    - Clear complication as in Compartment syndrome
    - Thrombocytopenia or raised INR/abnormal TEG/ROTEM

      (The fourth and first bullet define as progressing swelling in this article)
- Boomslang bite identified

From *Hardcastle T, Kajee M, Lachenicht K, van der Walt N. Approach to the diagnosis and management of snakebite envenomation in South Africa in humans: Layperson aspects and the role of emergency medical services. South African Medical Journal. 2023:10-8.*

Snakebite presentations are recorded manually in a designated book located in the EC by the triage nurse at the end of their shift. To ensure accuracy, admission records and other handwritten logbooks were also reviewed to ensure that no snakebite cases were missed. Subsequently, patient medical records for each identified case were requested and collected by a hospital clerk designated for this purpose. In collaboration with the researcher, a trained data collector, extracted and entered the necessary data in a spreadsheet. If a file was missing it was not included in the study, but available files with missing data were still used with a missing data strategy applied.

The patient’s demographic data, snakebite incident location, bite date, time of arrival at the medical facility, referral source, and consultation with traditional healers, if any, were extracted from their medical records. Information of initial presentation, vital signs, Zululand Severity Score (ZSS) (or the components thereof), antivenom administration and any subsequent reactions, length of hospital stay, and any minor surgical interventions were also documented. The snakebite patient's dispositions were classified as follows: death, admission, immediate discharge without any observation (this occurred when the patient brought along an identifiable snake) or follow- up appointments per the medical facility's protocol. It is worth noting that Mosvold is a small district hospital, and most follow-up appointments occur in the OPD, a single unit with the EC. The data was captured in a password-protected Microsoft Excel spreadsheet.

Data analysis

Descriptive statistics such as mean and standard deviation (if normally distributed) or median and range were used when analysing continuous variables. The Shapiro-Wilks test was used to test for normality. For categorical variables, frequencies and proportions were used. The t-test method was used to test means, specifically for the means of hospital stay in the case of snakebite. All statistical tests were conducted at a 5% significance level using appropriate statistical software. Univariable logistic regression was performed for all explanatory variables. Significant variables (at a 5% level) were used to build the multivariable logistic regression model using stepwise forward regression. Any variable that weakened the model was dropped. However, age was added to the multivariable model because it is a clinically a priori factor.

The research was approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF:714/2022), followed by Mosvold Hospital approval and the KwaZulu-Natal Department of Health NHRD Ref: KZ_202211_020.

Results.

Of the 163 patients presenting with snakebite identified; 156 patients' files were retrieved. Seven patients' files were missing, and one patient was excluded as attacked but not bitten by a snake, presumably a type of python (a 17-year-old male strangled by a snake and arrived in hospital with multiple bruises all over his body). Remaining 155 patients (91.7%) for the final analysis (Table 2).

Table 2: Participants characteristics

Variable	Level	Frequency	Percentage
Gender	Female	81	52.26
	Male	74	47.74
Place of snake bite	Indoor	45	29.22
	Outdoor	75	48.70
	Not recorded	34	22.08
Referred from clinic	No	49	31.61
	Yes	99	63.87
	Not recorded	7	4.52
Torniquet applied first	No	40	25.81
	Yes	3	1.93
	Not recorded	112	72.26
Swelling at presentation	None	7	4.52
	Minimal	117	75.48
	Progressive	30	19.35
	Not recorded	1	0.65
Received antivenom	No	122	78.71
	Yes	33	21.29
Snakebite outcome	Admitted	135	87.10
	Discharged from Emergency Centre	17	10.97
	Died	3	1.94
Site of snakebite	Lower limb	107	69.03
	Upper limb	36	23.23
	Other	12	7.74

The incidence rate was 58 snakebite cases per 100 000 people per year (155 snakebite patients over three years, and with a hospital drainage area of approximately 89 000 people) with a slightly higher proportion of female participants (52.26%). The age range of the participants was quite broad, with the oldest individual being 94 years old and the youngest being less than a year old (median 19 years, IQR 18). Ages were not distributed normally (p-value <0.001) (Figure 1).

Nearly two-thirds of patients (99 patients, 63.87%) consulted the local clinic first, prior to being referred to hospital. Unreferred patients (49, 31.61%) had a mean of 3.89 hours, time from snakebite to presentation to hospital and 7.40 hours for clinic referred patients.

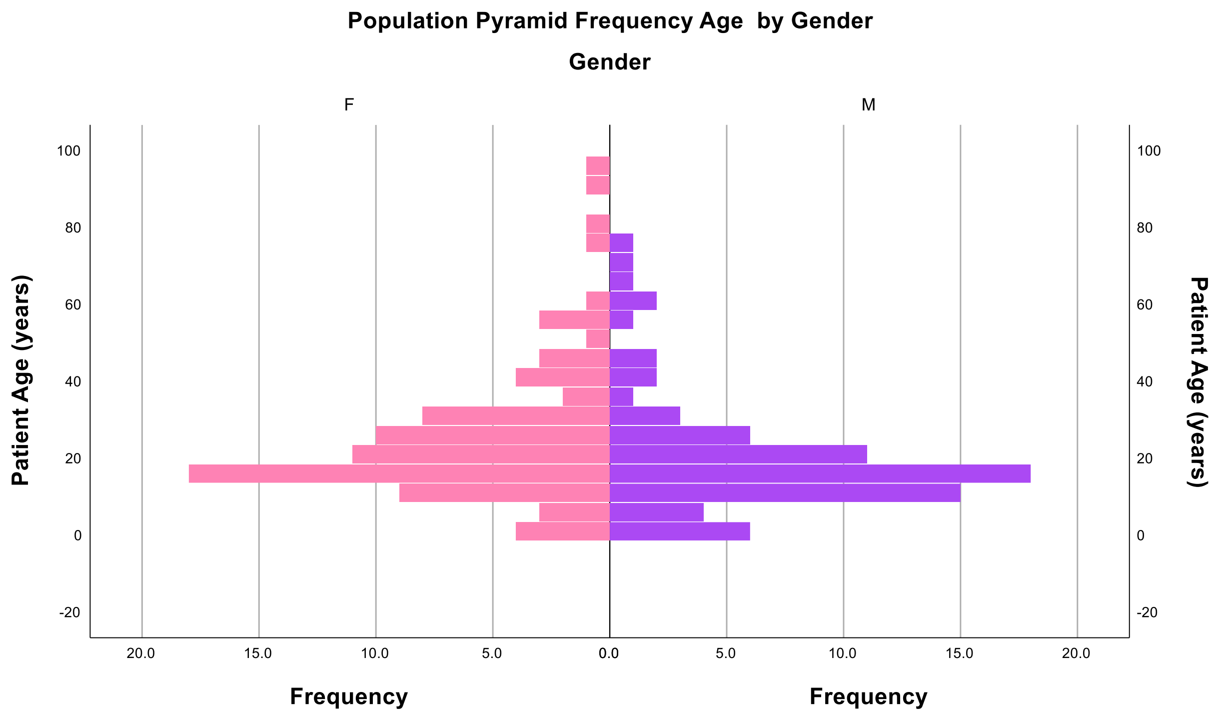

Figure 1: Population pyramid frequency age by gender

Of the 155 patients, 33 (21.29%) were given antivenom and admitted to the hospital (Table 3). During the study period, three patients demised, resulting in a mortality rate of 1.2 deaths per 100 000 people per year. The first was a 28-year-old female who presented with a history of being bitten on her lower limb while walking in the darkness. She presented two hours after the snakebite with slurred speech and confusion, apparently thought to be intoxicated. Moreover, she was admitted to the hospital without antivenom and died less than 12 hours after admission, likely from a neurotoxic snakebite.

The second death was a 56-year-old female patient, presenting one hour after a bite, who died 24 hours after admission. Despite having a raised international normalised ratio (INR) and progressive swelling, she was not given antivenom because of insufficient supply. She probably died of a mixed syndrome. The last patient, who was an 83-year-old female, presenting eight hours after a bite with a ZSS of 2, administered antivenom without serious reaction, but requiring surgical debridement, died three months later from multiple organ failure.

Most patients who received antivenom were males, making up almost 64% (21 patients) of the patient population. Most of these patients were bitten indoors (18 patients, accounting for 54.55% of cases), compared to only nine patients (27.27%) who were bitten outdoors. The majority of patients who received antivenom had progressive swelling (27 patients, (81.82%)), while only six patients (18.18%) experienced minimal swelling. Antivenom treatment was almost equally distributed between snakebite patients in the upper and lower limbs, with 13 patients (39.39%) and 15 patients (45.45%), respectively. The Zululand Severity Score was calculated for each patient using available clinical information, as it was not documented by clinicians for any patient.

Table 3: Patients characteristics by antivenom status

Categorical variables			
		Antivenom status	
		Did not receive antivenom	Received antivenom
Variable	**Level**	**N (%)**	**N (%)**
Total Patients	Female and Male	122 (78.71)	33 (21.19)
Gender	Female	69 (56.56)	12 (36.36)
	Male	53 (43.44)	21 (63.64)
Place of injury	Indoor	27 (22.31)	18 (54.55)
	Outdoor	66 (54.55)	9 (27.27)
	Not recorded	28 (23.14)	6 (18.18)
Patient disposition	Admitted	103 (84.43)	32 (96.97)
	Discharged from Emergency Centre	17 (13.93)	0 (0.00)
	Died	2 (1.64)	1 (3.03)
Swelling	None	7 (5.74)	0 (0.00)
	Minimal	111 (90.98)	6 (18.18)
	Progressive	3 (2.46)	27 (81.82)
	Not recorded	1 (0.82)	0 (0.00)
Site of snakebite	Lower limb	92 (75.41)	15 (45.45)
	Upper limb	23 (18.85)	13 (39.39)
	Other	7 (5.74)	5 (15.15)
Continuous variables			
		Median (IQR)	**Median (IQR)**
Age in years		19.5 (18)	15 (11)
Zululand Severity Score		1 (2)	2 (1)
Hospital length of stay in days		2 (3)	5 (7)
Antivenom dose received in vials		-	8 (2)

Patients who received antivenom treatment had a longer hospital stay, with a median of five days, in comparison to those who did not require this treatment, who had a median hospital stay of two days. Typically, patients who required antivenom treatment were administered a median of eight vials.

Out of the 33 patients who received antivenom treatment, 21 (63.64%) were given a premedication containing adrenaline, while five patients (15.15%) received a combination of adrenaline and an antihistamine. Three patients (9.09%) did not receive any premedication. Two patients (6.06%) received a combination of antihistamine and steroid. Additionally, only one patient (3.03%) was given a premedication containing adrenaline, antihistamine and steroid, while another patient received only steroid before receiving antivenom. Some 15 patients (45.45%) were documented to have experienced a pyrogenic reaction, nine (27.27%) experienced anaphylaxis and the balance (9 (27.27%)) did not experience any reaction after receiving the antivenom.

Table 4: Chi square test of association with snakebite disposition

Categorical variables					
Variable	**Level**	**Snakebite outcome**			**P-value**
		Admitted (N =135, 87.10%)	**Discharged from Emergency Centre (N=17,10.97%)**	**Died (N=3, 1.94%)**	
Gender	Female	71 (52.59)	7 (41.18)	3 (100.00)	0.167
	Male	64 (47.41)	10 (58.82)	0 (0.00)	
Place of injury	Indoor	39 (29.10)	4 (23.53)	2 (66.67)	0.124
	Outdoor	63 (47.01)	12 (70.59)	0 (0.00)	
	Not recorded	32 (23.88)	1 (5.88)	1 (33.33)	
Referred from clinic	No	42 (31.11)	6 (35.29)	1 (33.33)	0.170
	Yes	88 (65.19)	10 (58.82)	1 (33.33)	
	Not recorded	5 (3.70)	1 (5.88)	1 (33.33)	
Torniquet applied first	No	37 (27.41)	3 (17.65)	0 (0.00)	0.660
	Yes	3 (2.22)	0 (0.00)	0 (0.00)	
	Not recorded	95 (70.37)	14 (82.35)	3 (100.00)	
Swelling	None	2 (1.48)	5 (29.41)	0 (0.00)	<0.001
	Minimal	104 (77.04)	12 (70.59)	1 (3.33)	
	Progressive	29 (21.48)	0 (0.00)	1 (3.33)	
	Not recorded	0(0.00)	0 (0.00)	1 (3.33)	
Received antivenom	No	103 (76.30)	17 (100.00)	2 (66.67)	0.070
	Yes	32 (23.70)	0 (0.00)	1 (33.33)	
Site of snakebite	Lower limb	95 (70.37)	12 (70.59)	0 (0.00)	0.064
	Upper limb	29 (21.48)	5 (29.41)	2 (66.67)	
	Other	11 (8.15)	0 (0.00)	1 (33.33)	

Of the 33 patients who were administered antivenom, 14 did not require any immediate treatment for any reactions to the antivenom, accounting for 42.42% of the patients. Eight patients, which is 24.24% of the total, were given a combination of antihistamines and steroids. Three patients, 9.09%, were administered adrenaline, antihistamines, and steroids. Two patients, which is 6.06% of the total, received adrenaline as a single treatment, while two other patients were given antihistamines only. The remaining four patients were given midazolam, salbutamol nebulization, or a combination of the previous medications to manage their reactions to the antivenom. Ten patients (30.30%) who received antivenom required surgery while in the hospital, but none underwent a fasciotomy.

There was statistical significance (p<0.001) for the association between swelling at the bite site and the final disposition (death, admission, or discharge from the EC) (Table 4).

Of the 122 patients who did not receive antivenom, three patients had indications for antivenom but were denied due to stock shortages. These cases included 1) a 56-year-old female patient who died 24 hours after admission— not given antivenom despite her having a raised international normalised ratio (INR); 2) ten-year-old male with a painful progressive forearm swelling who spent 13 days in the hospital; and 3) A 15-year-old female presented with blistering around a snakebite on the thigh and an INR of 1,41 spent 11 days in the hospital.

Tab 5: Univariable and multivariable logistic regression model: hospital length of stay (longer stay = 1 (≥3 days); shorter stay = 0 (<3 days))

Variable	Level	Univariable		Multivariable	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Age		1.00 (0.98 – 1.02)	0.838	1.00 (0.98 – 1.02)	0.731
Gender	Female	1			
	Male	0.83 (0.44 – 1.57)	0.571		
Place of injury	Indoor	1		1	
	Outdoor	0.33 (0.15 – 0.72)	0.005	0.46 (0.20 – 1.06)	0.068
	Not recorded	0.5 (0.20 – 1.25)	0.137	0.67 (0.25 1.77)	0.420
Received antivenom	No	1		1	
	Yes	6.48 (2.49 – 16.84)	<0.001	5.24 (1.96 – 13.97)	<0.001

Snakebite victims who received antivenom treatment had a significantly greater likelihood of being hospitalised for a period exceeding three days than those who did not receive antivenom (Table 5). Specifically, the univariable analysis indicates a 548% increase in odds to more than three days in admission relative to victims who did not receive antivenom. In contrast, the multivariable analysis, which incorporates age and location of injury as factors, demonstrated a slightly lower but still substantial 424% increase in odds.

We found a notable rise in the number of snakebite occurrences during the hot summer period from November to March (peaking in February) (Figure 2).

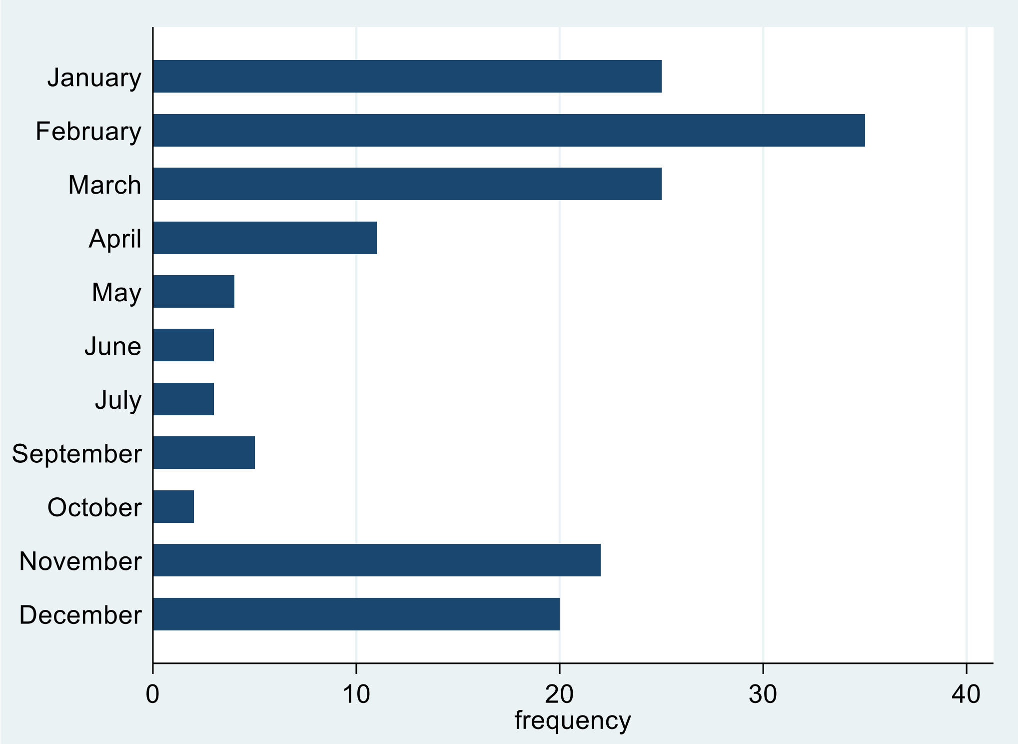

Figure 2: Monthly incidence of snakebite presentations to Mosvold Hospital

Discussion

Despite the WHO's efforts to reduce mortality rates by 50% before 2030, snakebite remains a neglected disease (1). Regions with impoverished living conditions and hot, humid climates similar to uMkhanyakude, experience significant incidences of snakebites(1). This study found that the incidence rate in uMkhanyakude was 58 cases per 100 000 people per year, consistent with a previous study by Wood et al. (4). The highest number of snakebite cases occurred in the summer months between November and March, with the most significant peak recorded in February, accounting for 22.58% of cases, in keeping with international literature (4, 16).

As suggested by the WHO (2), many patients require hospitalization, resulting in significant costs and resource utilization. This study demonstrates a substantial increase in the odds of a longer admission in those patients who received antivenom. It was observed that patients who needed antivenom treatment had more prolonged hospital stays. They had severe symptoms that required antivenom medication. It is interesting to note that out of the patients who needed antivenom but did not receive it (n=3), they either died or had an average hospital stay of 12 days. On the other hand, patients who received antivenom had a shorter average hospital stay of five days. Demonstrating that the SAVP antivenom is effective in reducing hospital stays.

Almost 90% of patients who received antivenom and were admitted to the hospital appear to have been bitten by cytotoxic snakes, with swelling being the primary symptom, in keeping with other Kwazulu-Natal research (14, 17). Additionally, this study revealed that most snakebite victims were young individuals, likely due to the higher number of young people working in fields, herding, hunting, or walking in the dark.

According to our research, 21.29% of patients who suffered from snakebites were administered antivenom. This is a much higher rate compared to two previous studies conducted at Ngwelezana Hospital, which is a regional referral hospital (9, 15) . The two previous studies showed that only 9.05% in 2009 and 6.7% in 2022 of snakebite patients received antivenom (9, 15). Despite the fact that Ngwelezana Hospital receives referred and severe cases from peripheral district hospitals, where antivenom may not be available, our findings indicate that Mosvold Hospital has a high incidence of severe snakebites (9, 15). It also shows that antivenom was used judiciously when needed. However, the percentage of patients who received antivenom in our study is much lower compared to high-income countries, where up to 60% of snakebite patients receive antivenom(6, 18).

At Ngwelezana Referral Hospital, administering adrenaline, as premedication for patients receiving antivenom, is a standard practice, as recommended by local experts(15)(3)(7). In our research, we found that 91% of patients received adrenaline as premedication. Nonetheless, of those who were administered with antivenom, 72.72% reported experiencing certain side effects. These ranged from mild urticaria and vomiting, to a decline in oxygen saturation and hypotension. This figure is comparable to De Silva's randomized control trial (19), where 75% of patients who received antivenom developed acute reactions within 48 hours. Furthermore, side effects were slightly higher than those observed in Giles' study(15) conducted at Ngwelezana Hospital, where about 60% of patients reported experiencing side effects. In the De Silva study (19), it was found that administering a low dose of adrenaline (0.25 ml of a 1:1,000 solution subcutaneously) resulted in a significant reduction of severe antivenom reactions by nearly 43 % in the first hour. In comparison our study found that a similar percentage (42.42%) did not require immediate management after antivenom exposure, likely due to either no side effects or minor side effects that did not require treatment. However, our study was not designed to distinguish between the side effects of those who received premedication and those who did not. The SASS 2022 (13) recommends the use of premedication with adrenaline as a standard practice in South Africa.

Patients who presented directly to the hospital arrived sooner at the hospital than those who were referred from a local clinic. To provide initial care for snakebites while waiting for an ambulance, clinic nurses should be trained to provide first aid (1, 2, 20). Although some people believe clinic nurses can administer antivenom (1, 2, 20) before the ambulance arrives, the WHO (20) and other studies (5, 17, 20), suggest that only medical officers with access to fully equipped resuscitation facilities should administer antivenom as they are better equipped to handle potential anaphylaxis reactions.

At Mosvold Hospital, decisions on administering antivenom are made by two medical officers, one of whom has at least five years of experience after completing their community service. Additionally, one of the senior doctors at Mosvold Hospital, who is part of the SASS team, has been training doctors on the SASS 2022 content. This content is used to determine whether antivenom is necessary(13). Explaining the use of SASS 2022 content before his publication. Although some ZSS elements are used as indicators for administering antivenom, we could not find evidence of direct use of ZSS in patient notes(3). Perhaps because ZSS includes blood results which have a long turn-around time to process, particularly during nighttime. Nonetheless, it is crucial to recognize that antivenom administration is time-sensitive (3).

During the study, several patients required antivenom but did not receive it because of a shortage of supply. There is currently grave concern about dwindling stocks of antivenom in South Africa as reported in the media(21). It remains unclear whether this is a short-term supply issue, or a longer-term inability to provide for the country’s growing population and perhaps increased use of antivenom. While the SAVP has been proven effective in reducing hospital stays and improving patient outcomes, there remains a need to enhance the quality of snake antivenom currently in use (20). As an equine product, it can cause unwanted side effects (20). By improving its quality, we can provide patients with a safer option and expand the use of antivenom to more individuals, as seen in higher-income nations(6, 18).

Death due to snakebite envenomation remains the primary concern of WHO (1, 2) . In this study, we had a mortality rate of 1.2 per 100 000 people per year, with almost two percent of patients presenting with snakebite dying. Of the three patients who died, two deaths were likely preventable had they received antivenom.

Conclusion and recommendations

Snakebites are a prominent concern in the vicinity of Mosvold Hospital and are prevalent in the uMkhanyakude area, particularly during the warmer months from November to March. Healthcare workers and community members need to receive training in identifying snakes in their area and administering appropriate first aid to patients. Additionally, the ambulance referral system must be improved to reduce waiting times from clinic to hospital, and to prioritise urgent transfer of severe snakebites. The SASS 2022(13) approach should be promoted to standardise the management of snakebites in hospitals.

Although tools such as the ZSS and protocols such as that from the SASS are available, it appears that snakebites are not uniformly managed. This is a concern, especially when junior and inexperienced doctors are making decisions. Antivenom is a limited yet potentially life- and limb-saving intervention. Its manufacture should be supported by government and non-governmental organizations, and it should be administered safely and judiciously.

Strengths and limitations

This study is a first to report on snakebite presentations and management at a small district hospital, with an unusually high incidence of snakebites, and severe snakebites requiring antivenom treatment. Although the study's findings may not be generalisable, this is a useful snapshot given the high incidence of snakebite in the area.

Given the rural location and limited ambulance service, it is likely that many patients with snakebite do not present to hospitals, and we cannot provide data on those in this study. Some may have died prior to presentation (likely outcome for severe neurotoxic snakebite), and others have been non- venomous bites. We could also not follow up with patients after discharge to determine their subsequent outcome.

Dissemination of results

The study will be submitted to the University of Cape Town, as part of an MPhil dissertation in Emergency Medicine. The dissertation will be shared with the Kwazulu-Natal province, uMkhanyakude district and Mosvold hospital. Our intention is to share the findings through peer reviewed publications and conference presentations.

Authors' contributions

Authors contributed as follows to the paper: BK 50%, PH 30 % and DW 20 %.
All authors approved the version to be published and agreed to be accountable for all aspects of the works.

Declaration of competing interests.

The authors have no conflicting interest to declare.

REFERENCES

1. World Health Organization. *Guidelines for the management of snakebite*. 2nd Edition. World Health Organization (2016). Available at: https://www.who.int/snakebites/resources/9789290225300/en/.

2. World Health Organization. *Snakebite envenoming: A strategy for prevention and control*. Geneva: World Health Organization (2019)

3. Wood D, Sartorius B, Hift R. Classifying snakebite in South Africa: Validating a scoring system. *South African Medical Journal.* 2017;107(1):46-51

4. Wood D, Sartorius B, Hift R. Estimating the burden of snakebite on public hospitals in KwaZulu Natal, South Africa. *Wilderness and Environmental Medicine*. 2016;27(1):53-61.

5. Seifert SA, Armitage JO, Sanchez EE. Snake envenomation. *New England Journal of Medicine*. 2022;386(1):68-78.

6. Ruha A-M, Kleinschmidt KC, Greene S, Spyres MB, Brent J, Wax P, et al. The epidemiology, clinical course, and management of snakebites in the North American Snakebite Registry. *Journal of Medical Toxicology*. 2017;13:309-20.

7. Blaylock RS. The identification and syndromic management of snakebite in South Africa. *South African Family Practice*. 2005;47(9):48-53.

8. Variawa S, Buitendag J, Marais R, Wood D, Oosthuizen G. Prospective review of cytotoxic snakebite envenomation in a paediatric population. *Toxicon*. 2021;190:73-8.

9. Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: Treatment modalities and outcomes. *South African Medical Journal.* 2009;99(11):814-8.

10. Sloan DJ, Dedicoat MJ, Lalloo DG. Healthcare-seeking behaviour and use of traditional healers after snakebite in Hlabisa sub-district, KwaZulu Natal. *Tropical Medicine & International Health*, 2007;12(11):1386-90.

11. District Health Plan. In: NATAL DOHK, editor. 2020/21.https://www.spotlightnsp.co.za/wp-content/uploads/2020/12/Umkhanyakude_DHP_2018.19.pdfUMKHANYAKUDE.

12. Routine Health Data: KwaZulu-Natal 2023 [Available from: https://kz.dhis.dhmis.org.

13. Hardcastle T, Kajee M, Lachenicht K, van der Walt N. Approach to the diagnosis and management of snakebite envenomation in South Africa in humans: Layperson aspects and the role of emergency medical services. *South African Medical Journal*. 2023:10-8.

14. Wood D, Sartorius B, Hift R. Snakebite in north-eastern South Africa: Clinical characteristics and risks for severity. *South African Family Practice*. 2016;58(2):62-7.

15. Giles T, Čačala SR, Wood D, Klopper J, Oosthuizen GV. A retrospective study of antivenom-associated adverse reaction and anaphylaxis at Ngwelezana Hospital, South Africa. *Toxicon*. 2022;217:1-4.

16. Blaylock R. Epidemiology of snakebite in Eshowe, KwaZulu-Natal, South Africa. *Toxicon*. 2004;43(2):159-66.

17. Buitendag J, Variawa S, Wood D, Oosthuizen Gv. A comparison between adult and paediatric snakebites and their outcomes in North Eastern South Africa. *Toxicon*. 2022;208:13-7

18. Lavonas EJ, Ruha A-M, Banner W, Bebarta V, Bernstein JN, Bush SP, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. BMC Emergency Medicine. 2011;11(1):1-16.

19. De Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, et al. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Med.* 2011;8(5): e1000435.

20. World Health Organization. *Guidelines for the production, control and regulation of snake antivenom immunoglobulins*. (2018). Available at: https://www.who.int/bloodproducts/AntivenomGLrevWHO_TRS_1004_web_Annex_5.pdf?ua=1

21. Ellis E. nationwide-snake-antivenom-stockpile-shortage-an-absolute-catastrophe- [press release]. https://www.dailymaverick.co.za/article/2023-04-022023.

PART C: ADDENDA

Addendum 1: Journal Author guidelines (AFJEM)

https://www.elsevier.com/journals/african-journal-of-emergency-medicine/2211-419X/guide-for-authors

Addendum 2: Research proposal

Presentation and management of snakebite victims at uMkhanyakude (Mosvold Hospital)

By

Matamba Jean Benoit Kabeya

MPhil student University of Cape Town

KBYJEA001

This thesis is submitted in partial fulfilment of the requirements for the degree Masters Philosophie Emergency Medicine: Critical Care in the faculty of Health Sciences at the University of Cape Town

Supervisors: Professor Peter Hodkinson, University of Cape Town

Professor Darryl Wood

August 2022

Declaration

I, Matamba Jean Benoit Kabeya, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I further declare the following:

1. I know that plagiarism is a serious form of academic dishonesty.
2. I have read the document about avoiding plagiarism, am familiar with its contents and have avoided all forms of plagiarism mentioned there.
3. Where I have used the words of others, I have indicated this by the use of quotation marks.
4. I have referenced all quotations and properly acknowledged other ideas borrowed from others.
5. I have not and shall not allow others to plagiarise my work.
6. I declare that this is my own work.
7. I attach the summary of the Turnitin match overview.

Signed by candidate

…………………………………………

Signature: MJB Kabeya Date: 25 August 2022

Background

Snakes are primarily found in tropical countries, mainly in some parts of Asia, America and Africa (1-3). In some circumstances, they are imported from other countries (4). According to existing literature, snakebites can cause various symptoms such as swelling, neurological deficits, and bleeding tendencies, which depend on the species of the snake involved (5-7). In South Africa, in some KwaZulu-Natal areas, a tropical climate is noted, explaining the large number of snakebite cases (1, 7).

uMkhanyakude is one of the poorest districts among the eleven districts in KwaZulu-Natal province in South Africa(2). The semi-tropical climate in this district is conducive to tropical diseases and snakes (1, 7).

According to World Health Organization, snakebites are overlooked, leading to high mortality and morbidity (1-3). The majority of the literature and guidelines show that the cornerstone for managing snakebites remains antivenom administration (2, 5-9). However, the antivenom can be challenging to find, depending on the victim's location. It is easy to find appropriate snake antivenom in high-income countries such as the United States of America, and Australia (10, 11). A serum study on a victim can determine which kind of snake is incriminated as they have data on snakes present in their areas (4, 10, 11). But the lack of advanced laboratory investigation in low-income countries may cause difficulty in prescribing antivenom (5, 7). This is why Blaylock (5) advised a syndromic approach, distinguishing symptoms between three primary syndromes of progressive swelling, weakness or bleeding. Wood (7) advised the use of a score to help the clinician decide when to give an antivenom.

The Zululand snakebite severity score (ZSS) is now in use and includes age, admission delay, white cell count, platelet, haemoglobin, and International Normalised Ratio (INR). If the score is above four, the patient must receive an antivenom (7). Other than antivenom (and various proposed medications to reduce anaphylactoid and anaphylactic reactions to antivenom), management may include antibiotics, surgical fasciotomy and debridement; all controversial and without clear guidelines in South Africa(5, 7-9, 12, 13).

Wood (2) tried to locate the area where most snakebites occur, using the central KwaZulu-Natal pharmacy, the only supplier of antivenom in KwaZulu-Natal. The study results found that uMkhanyakude was the district that used the most antivenom, yet no study has come from this district so far. There is therefore a need to carry out a study on snakebites from the "epicentre" where most of the snakebite cases in the province have occurred. The Mosvold Hospital, in Ingwavuma is one of the district hospital in the uMkhanyakude district (2).

Purpose of the study

The administration of antivenom to snakebites victims in good time remains a major challenge in uMkhanyakude district, KwaZulu Natal. Many patients seek alternative care from traditional healers before proceeding to a clinic or hospital (3, 6, 12). The few victims who receive antivenom in hospitals are often delayed and may require further treatment. Snakebites are highly seasonal in uMkhanyakude area and are seen predominantly in the rainy summer months (November to March) (1-3). No recent studies describe snakebite presentations or management in the uMkhanyakude district. This district is thought to have the highest snakebite incidence in South Africa (2). This study therefore seeks to describe snakebite incidence, treatment, and outcomes at Mosvold hospital.

Research question

What was the presentation and management of snakebite victims at Mosvold Hospital from 1 September 2019 to 31 August 2022?

Aim and objectives.

The study aims to determine the incidence of snakebite at Mosvold Hospital and its management.

The objectives which will help to address the aim are to:

1. Quantify the number of snakebite cases (admissions and discharges) attended to at Mosvold Hospital from 1 September 2019 to 31 August 2022.
2. Describe the clinical presentations of patients presenting with snakebites (symptoms, syndromes, and bloods results).
3. Describe the hospital-based management, (including antivenom administration, if any) and outcomes of snakebite presentations.

Methodology

Study design

This study is a descriptive, retrospective observational study.

Study setting and/or population.

The study will include all the victims of snakebite from 1 September 2019 to 31 August 2022, irrespective of their age and sex, who were attended to at Mosvold Hospital. Prior data suggests that approximately forty patients per year are expected for the study, meaning around 120 patients in a three-year period. Snakebites presented in the area primarily in the summer months November to March, and this period includes three full summer periods.

Recruitment and enrolment

All patients who visited Mosvold Hospital with a suspected snakebite have included in the study, irrespective of their age, sex, or location. The researcher purposely selected all snakebite victims who visited Mosvold hospital from 1 September 2019 to 31 August 2022. This period was chosen as the patient records in the emergency department registry office are kept for a maximum of three years before they are moved to another storeroom where it would be difficult to find the files.

Missing files have not been included. Available files with missing data have been included in the study and missing data strategy has been applied. Random missingness tests were conducted, followed by an analysis of the missing value pattern. If less than five percent of data were missing, the study proceeded unchanged. However, if the missing data exceeded five percent, a pairwise exclusion strategy was implemented. The statistician was consulted for further assistance in managing missing data.

Research procedures and data collection methods

The current practice is that all snakebite cases attending Mosvold Hospital are registered by hand by the triaging nurse at the end of their shift in a specific book kept in the emergency unit. In order to cross-reference patients who might not be entered in this book, triage and admission records (all handwritten logbooks) were also screened for any identified snakebite patient. Medical records for each identified case are then requested, and data extracted to a purpose-made spreadsheet (Appendix 1).

A designated hospital clerk collected all the files after work hours in the registry office once the snakebite patients' file numbers are handed to him by the researcher. No training was necessary as it is a part of his routine tasks to collect designated files from records. Data extraction and entry was performed by data collectors who were the researcher's colleagues, and the researcher. All are working in the same facility. Before data extraction, the researcher gave training to the second data collector, explaining which data he is expected to collect and how to insert them into an excel sheet without more information so that the process can be blinded. Strict confidentiality has been asked of him. Weekly, ten per cent of the data collected by the second data collector was double-checked by the principal researcher to check accuracy of the second data abstractor (14).

Information collected from the patient folders includes: age, gender, where the snakebite took place, date of the snakebite, hospital or clinic arrival time, where the patient came from (referral or from the scene), and whether a traditional healer was consulted first, initial complaints, normal or deranged vital signs, whether ZSS (Zululand Severity Score) was used (and if so the scoring), whether they received antivenom and if so noting any reaction to the antivenom, time spent in hospital and whether minor surgery was performed. The outcome is noted as death, discharge or any follow-up.

Data been captured in a Microsoft Excel Spreadsheet.

Data analysis

Continuous variables have been analysed using descriptive statistics (mean and respective standard deviation if normally distributed, or median and range have been used). The Shapiro Wilk's test was used for a normality test. Categorical variables are described using frequencies and proportions. The t-test method is used to test the means, that is, the means of hospital stay in the case of snakebite. The incidence of snakebite cases in Mosvold Hospital was then calculated with the proportion of cases receiving antivenom and the proportion of patients having cytotoxic, hemotoxic, neurotoxic or mixed syndromic presentations.

All statistical tests were applied at a five per cent significance level. Excel and appropriate statistical software have been used for data analysis. In order to receive guidance on statistical calculations, it was necessary to consult with a statistician.

Description of risks and benefits

Study approval was sought from the UCT Health Research Ethics Committee (HREC), and all the study documents, including data collection tools, were sent for approval before the start of the study. Approval was then sought from Health Research and Knowledge Management (HRKM), which is the secretariat of the KwaZulu-Natal Health Research and Mosvold Hospital.

This study had an overall minimal risk as the data were collected retrospectively. Patient names were not collected; only hospital numbers used to identify records. Data was stored securely in a password-protected computer by the student, and securely shared within the research team only. This study seeks to describe the seasonal distribution of snakebites, look for trends, and compare groups that received antivenom and those that did not. This study aimed at giving a clear message about snakebite presentation and management practices at Mosvold Hospital. Ultimately, it is hoped the hospital will be equipped to know how many snakebite cases they can expect each year. The study will potentially provide for educating healthcare workers, as well as the community about the need for avoidance, first aid treatment and healthcare following snakebites.

Informed consent process

A waiver of consent was requested, as the study used only routinely collected patient records. The study did not affect patient care, and all data was anonymised. The authorisation was made by the KwaZulu-Natal health department and Mosvold Hospital; The study started only when all the authorizations had been sought.

Privacy and confidentiality

Another essential step considered during data collection was the participants' privacy. Identification information was not collected; a unique identity was assigned randomly to each participant. Access to patient charts was limited to the research team only. Information was captured on Microsoft Excel sheets. Access to this information has been restricted to the researcher, and it is password protected. The data has been handed to the university at the end of the study.

Reimbursement for participation

This is a retrospective study where data is extracted from files existing at the hospital. Hence there is no direct involvement of participants who might have required reimbursement.

Strengths and limitations

The data collected for this study cannot be used for causal inference due to high confounding. Also, the study findings cannot be generalised since the study has been limited to one hospital in the district due to limited resources.

This is one of the first studies in the district about snakebite and will be a steppingstone for further research. It will help to emphasize the need for an early hospital visit and the first aid which has to be given.

Dissemination of findings

The dissertation will be submitted to the University of Cape Town. The dissertation will be shared with the Kwazulu-Natal province, uMkhanyakude district and Mosvold hospital as they have to be aware of the study findings. Lastly, the intention is to share the findings through peer reviewed publications and conference presentations.

Timeline

EMDRC: 8 weeks

HREC (ethics): 12 weeks

Hospital, District and provincial approval: 4 weeks

Data collection: 12 weeks

Analysis: 12 weeks

Write up: 8 weeks.

Budget

Item	Description	Total cost
Paper for printing and notes, including photocopying	R500	R500
After-hours motivation for the clerk and data collector	R100/Hr/person for 48 Hrs. R100 X 48Hrs X 2 persons	R9600
Statistician/hours	R400/Hr for 8 Hrs	R3200
Total		R13300

The study will be self-funded.

References

1. Blaylock R. Epidemiology of snakebite in Eshowe, KwaZulu-Natal, South Africa. *Toxicon*. 2004;43(2):159-66.

2. Darryl W, Sartorius B, Hift R. Estimating the burden of snakebite on public hospitals in KwaZulu Natal, South Africa. *Wilderness & Environmental Medicine*. 2016;27(1):53-61.

3. Musah Y, Ameade EPK, Attuquayefio DK, Holbech LH. Epidemiology, ecology and human perceptions of snakebites in a savanna community of northern Ghana. *PLoS Neglected Tropical Diseases.* 2019;13(8):e0007221-e.

4. Warrick BJ, Boyer LV, Seifert SA. Non-native (exotic) snake envenomations in the U.S., 2005-2011. *Toxins* (Basel). 2014;6(10):2899-911.

5. Blaylock R. The identification and syndromic management of snakebite in South Africa. *South African Family Practice.* 2005;47(9):46-53.

6. Hernandez MC, Traynor M, Bruce JL, Bekker W, Laing GL, Aho JM, et al. Surgical considerations for pediatric snake bites in low-and middle-income countries. *World journal of surgery.* 2019;43(7):1636-43.

7. Wood D, Sartorius B, Hift R. Classifying snakebite in South Africa: Validating a scoring system. *South African Medical Journal.* 2017;107(1):46-51.

8. Silva A, Hodgson WC, Isbister GK. Antivenom for Neuromuscular Paralysis Resulting From Snake Envenoming. *Toxins* (Basel). 2017;9(4):143.

9. Malasit P, Warrell DA, Chanthavanich P, Viravan C, Mongkolsapaya J, Singhthong B, et al. Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *British Mededical Journal* (Clin Res Ed). 1986;292(6512):17-20.

10. Ruha A-M, Kleinschmidt KC, Greene S, Spyres MB, Brent J, Wax P, et al. The Epidemiology, Clinical Course, and Management of Snakebites in the North American Snakebite Registry. *Journal of Medical Toxicology.* 2017;13(4):309-20.

11. Lavonas EJ, Ruha A-M, Banner W, Bebarta V, Bernstein JN, Bush SP, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emergency Medicine*. 2011;11:2-.

12. Variawa S, Buitendag J, Marais R, Wood D, Oosthuizen G. Prospective review of cytotoxic snakebite envenomation in a paediatric population. Toxicon. 2021;190:73-8.

13. Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: treatment modalities and outcomes. *South African Medical Journal*. 2009;99(11).

14. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: where are the methods? *Annals of emergency medicine*. 1996;27(3):305-8.

Appendices

Table 1. History data sheet.

Will include:

Age

Gender

Place of injury

Date of injury

Time of injury

Time of presentation to hospital >7 hours

Referred from the clinic?

Consulted a traditional healer?

Was tourniquet applied as first aid?

Table 2. Clinical data sheet

Will include:

Blood pressure (BP in mmHg)

Heart rate (HR in beat per minute)

Oxygen saturation (SpO_2 in %)

Glasgow Coma Scale (GCS)

White cell count (WCC >10.10^9/L)

Platelet (PLT <92.10^9/L)

Haemoglobin (Hb <7.1 g/dL)

International normalised ratio (INR >1.2)

Site of bite: Upper limbs, lower limb or other

Swelling: present or not

Zululand Snake Severity Score: Used or not? Scoring if used.

Table 3 Management of snake bite

Will include:

Antivenom: Given or not, any reaction if given?

Surgery: Any surgery done?

Table 4. Outcome

Will include:

Time spent in hospital (hours)

Discharge

Death

Addendum 3: UCT ethic approval, Hospital approval, Province approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

08 November 2022

HREC REF: 714/2022

A/Prof P Hodkinson
Division of Emergency Medicine
F51, OMB
Email: peter.hodkinson@uct.ac.za
Student: KBYJEA001@myuct.ac.za

Dear A/Prof Hodkinson

**PROJECT TITLE: PRESENTATION AND MANAGEMENT OF SNAKEBITE VICTIMS AT UMKHANYAKUDE (MOSVOLD HOSPITAL)-
(MPHIL CANDIDATE-DR MATAMBA KABEYA)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to local KZN approval.

Approval is granted for one year until the 30 November 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Matamba Kabeya will also be involved in this study.

Please quote the HREC REF 714/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/ref 714.2022

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
CEOs Office

Private Bag X2211, Ingwavuma, 3266
Ingwavuma Magistrate road, Ingwavuma, 3968
Tel: 035 591 0122 Fax: 035 591 0148 Email: [illegible]
www.kznhealth.gov.za

Enquiries: Dr. B. Mung'omba
Telephone: 035 591 0122 Ext.104

11th November 2022

Dear Matamba J.B. Kabeya

I have a pleasure in informing you that permission has been granted to you by the Mosvold hospital Research and development Committee to conduct research in Ingwavuma area entitled:

"Presentation and management of snakebite victims at uMkhanyakude (Mosvold Hospital)"

Please note the following

1. Please ensure that you adhere to all protocols, policies, procedures, and guidelines of the Department of Heath regarding this research.
2. ***This research will only commence once this office receives approval of your study from the KZN Department of Health Research and Ethics Committee (PHREC) in the KZN Department of Health.***
3. Application to PHREC is done online via the National Health Research Database (NHRD): http://nhrd.hst.org.za
4. Please ensure that this office is informed before you commence your research
5. The hospital will not provide any resources for this research other than hospital records that you may require.
6. Please provide the hospital with a copy of your final write-up or publication

Sincerely yours

Signed by candidate

DR. B. MUNG'OMBA
CHIEF EXECUTIVE OFFICER
MOSVOLD HOSPITAL

GROWING KWAZULU-NATAL TOGETHER

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

Health Research & Knowledge Management

NHRD Ref: KZ_202211_020

Dear Dr MJB Kabeya
(UCT)

Approval of research

1. The research proposal titled '**Presentation and management of snakebite victims at uMkhanyakude (Mosvold hospital)**' was reviewed by the KwaZulu Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Mosvold hospital.

2. You are requested to take note of the following
   a. ***Kindly liaise with the facility manager BEFORE your research begins.*** *This is to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   b. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Dr. G Khumalo on 033-395 3189.

Yours Sincerely

Signed by candidate

Dr E Lutge

Chairperson, Provincial Health Research Committee

Date 17/11/2022

Fighting Disease, Fighting Poverty, Giving Hope