CLINICOPATHOLOGICAL STUDY OF SNAKEBITE INJURY RESULTING FROM ZEBRA SPITTING COBRA *(Naja nigricincta nigricincta)* AND PUFF ADDER *(Bitis arietans)*

A THESIS SUBMITTED IN FULL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE (PATHOLOGY)

OF

THE UNIVERSITY OF NAMIBIA

BY

KATRINA NIITETA

201034123

OCTOBER 2022

SUPERVISOR: DR EMMANUEL NEPOLO (UNIVERSITY OF NAMIBIA)

Abstract

Snakebite injury is a significant public health hazard worldwide, with an estimated 1.8 – 2.7 million people bitten annually by venomous snakes, resulting in about 81 000 – 137 8800 deaths. It is frequently overlooked and understudied, and it primarily affects rural and remote areas. Snakebites have been reported to be common in Namibia. The most commonly striking species being the zebra spitting cobra (*Naja nigricincta nigricincta)* and the puff adder (*Bitis areitans*) which are also regarded to be among the most venomous. There is a lack of information on snakebite pathology with few health care facilities equipped to treat snakebites. This study described for the first time, clinical course of patients bitten by *Naja nigricincta nigricincta* (*N. n. nigricincta*) and *Bitis areitans* (*B. a. arietans*) in Namibia. Furthermore, the current study evaluated systemic symptoms of organ damage as well as patient's recovery from snakebite injuries. This was a mixed method, observational study including 20 patients with snakebite injury who presented to and were treated at Namibia's two major referral hospitals, Katutura Intermediate State Hospital and Windhoek Central Hospital. Clinical and laboratory data were gathered from patient hospital records and personal observation. GraphPad Prism (version 8.0.2) software was utilized for the analysis. Out of 20 cases of snakebites, the majority of about 65 % (13) were males, with minors between the age of 0 – 15 years accounting for 65 % (13) of the snakebite cases. *N. n. nigricincta* was responsible for 60 % (12) of the snakebite injuries and 40 % (8) by *B. a. arietans*. Most patients (80 %) admitted to the hospital showed cytotoxic bites, with two cases of dry bites from *B. a. arietans*. Neurotoxicity was observed in 40 % (8) patients bitten by *N. n. nigricincta* and 10 % (2) bitten by *B. a. arietans*. Snake antivenom was only administered to 15 % (3) patients with snakebite injuries. The bite of a *N. n. nigricincta* was associated with anaemia, haemolysis, rhabdomyolysis, kidney damage, and liver damage. Whereas bites form *B. a. arietans* had no systemic damage, beside mild neurotoxicity in the patients. Three patients of the snakebite cases required amputation, with no fatalities, and six required physiotherapy intervention to restore, maintain, and improve most of the participants' mobility and functions. In conclusion, the study demonstrated that in general snakebite injuries is common in Namibia. To reduce chances of complications it is essential that community members present early to health facilities. For the first time, this study documented clinical pathology induced by *N. n. nigricincta* and *B. a. arietans* in Namibia.

Keywords: *N. n. nigricincta*, *B. a. arietans*, cytotoxic, neurotoxic, antivenom, rhabdomyolysis

Table of Contents

CHAPTER 1 1

1. Introduction 1

1.1. Background of the Study 1

1.2. Statement of the Research Problem 4

1.3. Aim and Objective 6

1.4. Research Question 6

1.5. Significance of the Study 6

1.6. Limitation of the Study 7

1.7. Delimitation of the Study 8

CHAPTER 2 9

2. Literature Review 9

2.1. General Overview of the Snakebite Burden 9

2.1.1. Epidemiological Data of Snakebite 9

2.1.2. Classification of Venomous Snakes 11

2.2. Protein Composition of Snake Venom 12

2.2.1. General Snake Venom Toxins 12

2.2.2. Toxins Found in the Venoms of N. n. nigricincta and B. a. arietans 13

2.3. Namibian Health Care System and Snakebite Injuries Treatment 14

2.4. Snakebite Envenomation 14

2.4.1. Pathology of Snakebite Wounds 15

2.4.2. Local Signs of Envenomation 16

2.4.3. Systemic Signs of Envenomation 16

2.5. Universal Snakebite Treatment Protocol 22

2.5.1. First Aid Treatment 22

2.5.2. Primary Health Care 23

2.5.3. Snakebites management guidelines in Namibia 25

CHAPTER 3 27

3. Research Methodology 27

3.1. Introduction 27

3.2. Research Design 27

3.3. Study Population 29

3.4. Sample 29

3.5. Sample size 29

3.6. Research Instrument 30

3.7. Procedure 31

3.7.1. Clinical Assessment 31

3.7.3. Laboratory Methods 32

3.8. Data Analysis 35

3.9. Research Ethics 35

CHAPTER 4 ..... **37**
4. Results **37**
4.1. Introduction **37**
4.2. Baseline Characteristics **37**
4.3. Patient Snakebite Natural History **39**
4.4. The Regional and Species-Specific Distribution of Snakebites **40**
4.5. The Time Between Patient Getting bitten and Receiving Care **42**
4.6. Patient Clinical Presentation and History **44**
4.7. Systemic envenomation **90**
4.7.1. Clinical manifestation **90**
4.8. Treatment of Snakebites **93**
4.9. Patients Functional Outcomes **94**
CHAPTER 5 ..... **95**
5. Discussion **95**
5.1. An Overview **95**
5.2. Patient's Natural History **95**
5.3. Local Effects on Snakebite Patients **98**
5.4. Systemic Effects from Snake Envenomation **99**
5.4.1. Case Discussions on Systemic Envenomation **102**
5.5. Overall Shortcoming and Strength of this Study **103**
CHAPTER 6 ..... **104**
6. Conclusion **104**
CHAPTER 7 ..... **106**
7. Recommendations **106**
Reference **108**
ANNEXURE A: Informed Consent Form **116**
ANNEXURE B: Medical Photography Consent/Assent Form by (81). **122**
ANNEXURE C: Namibian Snake Poster **123**
ANNEXURE D: Snakebite Data Collection **124**
ANNEXURE E: Snakebite Data Collection **125**
ANNEXURE F: Snakebite Data Collection **126**
ANNEXURE G: Snakebite Data Collection **127**
ANNEXURE H: Ethical Clearance Certificate **128**
ANNEXURE I: Ministry of Health and Social Services Research Approval ... **129**

List of Tables

Table 1: Four main protein families present in the vipers and elapids species. 13
Table 2: Abnormal conditions associated with FBC adapted from (56) 19
Table 3: The diagnosis of organ damage 22
Table 4: Characteristics of snakebite patients admitted to KSH and WCH hospital between December 2020 and March 2022. 38
Table 5: Epidemiological grouped characteristic of patients bitten by *N. n. nigricincta* and *B. a. arietans.* 40
Table 6: Case 1 patient laboratory profile 46
Table 7: Case 2 patient laboratory profile 48
Table 8: Case 3 patient laboratory profile 51
Table 9: Case 5 patient laboratory profile 55
Table 10: Case 6 patient laboratory profile 57
Table 11: Case 7 patient laboratory profile 59
Table 12: Case 8 patient laboratory profile 62
Table 13: Case 9 patient laboratory profile 65
Table 14: Case 10 patient laboratory profile 67
Table 15: Case 11 patient laboratory profile 69
Table 16: Case 12 patient laboratory profile 72
Table 17: Case 13 patient laboratory profile 74
Table 18: Case 15 patient laboratory profile 78
Table 19: Case 16 patient laboratory profile 80
Table 20: Case 17 patient laboratory profile 82
Table 21: Case 18 patient laboratory profile 84
Table 22: Case 19 patient laboratory profile 87
Table 23: Case 20 patient laboratory profile 89
Table 24: Patients systemic results 92
Table 25 Surgical interventions in the patients 93

List of Figures

Figure 1: Snakebite injury in Namibia August 2015 and August 2016 adapted from (6). 10
Figure 2: A flowchart outlining the study methodological plan 28
Figure 3: Age distribution among the snakebite patients that was grouped into children (0 - 15), young adults (16 - 30) and older adults (31 - 45). 39
Figure 4: Comparison of snakebites number by *N. n. nigricincta* and *B. a. arietans* by geographical regions 41
Figure 5: Namibian Map with the different snakebite regions 42
Figure 6: Time taken for the patients to reach both primary and secondary health care facilities. 43
Figure 7: Case 1 Images of patient snakebite wounds. 45
Figure 8: Case 2 Images of patient snakebite wounds. 48
Figure 9: Case 3 Images of patient snakebite wounds. 50
Figure 10: Case 4 Images of patient finger. 52
Figure 11: Case 5 Images of patient snakebite wounds. 54
Figure 12: Case 6 Images of patient snakebite wounds. 57
Figure 13: Case 7 Images of patient snakebite wounds. 59
Figure 14: Case 8 Images of patient snakebite wounds. 62
Figure 15: Case 9 Images of patient snakebite wounds. 65
Figure 16: Case 10 Images of patient snakebite wounds. 67
Figure 17: Case 11 Images of patient foot. 69
Figure 18: Case 12 Images of patient snakebite wounds. 72
Figure 19: Case 13 Images of patient face. 74
Figure 20: Case 14 Images of patient foot. 76
Figure 21: Case 15 Images of patient snakebite wounds. 78
Figure 22: Case 16 Images of patient lower back. 80
Figure 23: Case 17 Images of patient face. 82
Figure 24: Case 18 Images of patient face. 84
Figure 25: Case 19 Images of patient face. 86
Figure 26: Case 20 Images of patient snakebite wounds. 89
Figure 27: Clinical pathological features inflicted by N. n. nigricincta snakes 92
Figure 28: Patients functional outcome 94

List of Acronyms

ACU – Acute care unity

ALP – Alkaline phosphatase

ALT – Alanine transaminase

AST – Aspartate transaminase

B. a. arietans – *Bitis arietans*

CK – Creatine kinase

CK-MB – Creatine kinase myocardial band

D – Day

FBC – Full blood count

GGT – Gamma-glutamyl transferase

Hb – Haemoglobin

HCT – Haematocrit

HREC – University of Namibia's Health and Research Committee

ICU – Intensive care unit

INR – International normalised ratio

IQR – Interquartile range

KISH – Katutura Intermediate State Hospital

LDH – L-lactate dehydrogenase

LFT – Liver function test

MCH – Mean cell haemoglobin

MCHC – Mean cell haemoglobin concentration

MCV – Mean cell volume

MI – Myocardial infarction

MOHSS – Ministry of Health and Social Services

MPV – Mean platelet volume

N. n. nigricincta – *Naja nigricincta nigricincta*

NIP – Namibia Institute of Pathology

PLT – Platelets

PT – Prothrombin time

PTT – Partial prothrombin time

RBC – Red blood cell count

RDW – Red distribution width

SAIMR – South African Institute for Medical Research

SD – Standard Deviation

T-Bili – Total bilirubin

TP – Total protein

UNAM – University of Namibia

WBC – White blood cell count

WCH – Windhoek Central Hospital

WHO - World Health Organisation

VICC – Venom induced consumption coagulopathy

Acknowledgements

First and foremost, I would like to express my gratitude to the Almighty for seeing this through. To my supervisor's Dr Emmanuel Nepolo, thank you for supervising me. I sincerely thank Professor Christian Hunter, for his support and mentorship. I further wish to express my gratitude to the staff of Katutura Intermediate State Hospital and Windhoek Central Hospital for assisting me in my data collection. Special gratitude is extended to the Department of Human, Biological & Translational Medical Science at University of Namibia (UNAM); Ottilie Katali, Hilja Eelu, Loide Shipingana, Dr. Zibusiso Mkandla, Erastus Haindongo for the academic support they provided me throughout this journey. Thank you to Mr Mondjila Amkongo and Tuwilika Keendjele for your unrelenting guidance in statistics. My gratitude extends to Prof Quenton Wessels for his administrative support. Last but not least, I would like to thank Ms. Raula Shinana, a wound specialist, who taught me the intricacies of wound healing.

Dedication

This work is dedicated to my mother, Kistofina Kwedhi, who has been and continues to be a source of unwavering support and steadfast fortitude for me throughout my whole life. I am immensely grateful to Sebby for his emotional support.

Declarations

I, Katrina Niiteta, hereby declare that this study is my own work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

KATRINA NIITETA		**OCTOBER 2022**
Name of Student	Signature	Date

CHAPTER 1

1. Introduction

1.1. Background of the Study

Snakebite injury is a major public health concern all over the world and remains a neglected health issue (1). Snake envenomation is one of the most overlooked and understudied public health issue, primarily affecting rural and remote areas (1–3). An estimated 1.8 – 2.7 million people are bitten annually, resulting in over 400,000 amputations and over 90,000 deaths (1,2,4). Asia has the highest rate of snake envenomation (1.2 – 2.0 million people), followed by Africa, which has 435 000 – 580 000 snake envenomation and 20 000 – 32 000 deaths per year (4). According to the World Health Organization (WHO; 2019), every year, between 572 and 811 snakebites occur in Namibia, resulting in 25 to 38 fatalities and 23 to 65 amputations (5). Despite the fact that snakebite injuries are a major concern in Namibia, there is little information available (6). Over the course of a year 2015 - 2016, Windhoek's referral hospitals (Katutura Intermediate State Hospital and Windhoek Central Hospital) recorded 721 snakebites, one-third of which were children under the age of six (6). Additionally, of the 721 patients admitted to Katutura Intermediate State Hospital and Windhoek Central Hospital, 225 suffered some loss of function following the bite, 68 had limbs amputated, and 33 died (6).

The vast majority of fatal and life-threatening snakebites in Africa are caused by vipers such as adders and elapids such as spitting or cytotoxic cobras (7–10). Spitting cobras, such as the zebra, are classified as Elapidae under the genus-group *Naja,* while puff adders are classified as Viperidae under the genus-group *Bitis* (11). (6,12). According to snake removal agents, more than 500 snake species were removed from Namibia's

capital city between 2015 and 2018, with the most common species being 163 *Bitis arietans* (puff adder) and 135 *Naja nigricincta nigricincta* (zebra spitting cobra) (12). Snakes are separated into two groups: venomous and non-venomous, with venomous snakes being the most dangerous (13). Snakes produce venom, which is a highly toxic saliva containing complex protein mixtures that aid in the immobilization and digestion of prey (14). Due to their distinct protein characteristics, these poisonous categories have varying effects on the human body (7). Toxins found in snake venom can have cytotoxic, neurotoxic, hemotoxic, myotoxic, and cardiotoxic effects when administered to humans (6–8). Furthermore, each snake may contain one or more venomous groups (7). Both *N. n. nigricincta and B. a. arietans* have venom that is known to be cytotoxic and hemotoxic, causing severe haemostasis disruption, tissue damage, intense pain, swelling, and necrosis (15,16). Additionally, the venom in these snakes have been reported to induce neurotoxicity in vitro, though these effects are often fairly mild (15). Consequently, these species may also cause envenomation (the ingestion of poisons transmitted through the bite of a poisonous snake), which can lead to renal failure, tissue necrosis, and myolysis (17,18).

Once a patient is bitten by a snake, the venom toxins are delivered straight into subcutaneous tissue, producing swelling, necrosis, and occasionally blistering, culminating in significant swelling that may or may not progress to compartment syndrome (7,19,20). Snakebite wounds may be the result of the bite marks becoming necrotic, and in order to prevent further necrosis from spreading, victims undergo medical removal of dead, damaged, or infected tissues in order to improve wound healing; this process is known as debridement (21). This allows for the re-establishment of vascular blood flow to the wound (21). Fasciotomy procedure, which involves operating on patients to relieve pressure from severe swelling, can also result

in massive snakebite wounds (19). Following that, patients are evaluated to determine whether they require a skin graft or wound closure (19). Snakebite wounds were managed using standard wound care methods to prevent the wound bed from growing and becoming infected (21,22). Thus, the pathological changes in the wound may provide insight into how to manage post-injury or post-snakebite wounds, and consistent wound care also aids in the prevention of further necrosis (22).

In Namibia, venomous snakebites are currently treated in accordance with conventional treatment recommendations by WHO, and the Ministry of Health and Social Services' (MOHSS) guidelines for medical management of snakebite victims (19,23). The therapy consists of analgesics, intravenous fluids, debridement and fasciotomy when necessary, and South African Institute for Medical Research (SAIMR) antivenom, that is manufactured from South Africa (19). Antivenom is the only known antidote for snakebite (11,24–26). Antivenom is generated by injecting snake venom toxins into a horse and extracting and purifying the venom from the horse plasma; as a result, antibodies that can neutralize the venom are produced (25).

South African Vaccine Producers (SAVP), a subsidiary of the South African Institute for Medical Research (SAIMR) and is both private and expensive, which is Africa's only source of antivenom supply (25). Namibia employs SAIMR antivenom, which is classified as monovalent for boomslang bites and polyvalent for viper and elapid bites (25). However, because of the venom of *N. n. nigricincta* is not included in the development and manufacturing of SAIMR polyvalent antivenom, antivenom is not effective against *N. n. nigricincta* bites (19,25). Although the venoms of *Naja mossambica* (*N. mossambica*) and *N. n. nigricincta* have a similar protein makeup, *N. nigricincta* bites are known to be immune to polyvalent antivenom even when delivered on time (19).

Antivenom is essential in the treatment of systemic envenomation; however, it may not be enough to save a patient's life, when administered alone (24). Furthermore, even though it is well established that antivenom neutralizes the systemic effects of snake venom toxins, it has also not been demonstrated to be beneficial in repairing local tissue damage or reversing damage that has already occurred (17). Since the pathophysiology of local tissue injury progresses too rapidly for antibodies to neutralize before irreparable harm occurs (17,27). As a result, the antivenom is not as effective at reversing neurotoxicity caused by presynaptic action on phospholipase (27,28). The majority of doctors do not recommend antivenom because it appears to be ineffective in treating snake envenomation (19,20). Clinical profile and treatment outcome of snakebite patients have not been fully examined, and there is a scarcity of information on snake envenomation in Namibia (22). Little is known, not just in Namibia but also throughout Africa, on the clinical profile and treatment outcomes of snakebite patients by *N. n. nigricincta* and *B. a. arietans* bites.

1.2. Statement of the Research Problem

The national health departments and international health organizations have mostly ignored snakebites (29). In 2009, the World Health Organization (WHO) recognized snakebite envenomation as a neglected tropical disease; in 2013, the WHO removed snakebite off the list of neglected tropical diseases (30,31). In 2017, snake envenomation was classed as Category A of the WHO's Neglected Tropical Diseases list (31). As a result, the burden of snakebite injury is significant in Namibia, with an average of 572 – 811 snakebites reported annually, which can result in an increase in mortality (5,6).

The natural history of venomous snakebites in Namibia from *N. n. nigricincta* and *B. a. arietans* has not been exhaustively studied; it is not entirely understood what causes these venomous snakebites or which regions of the country have the most prevalent species. As a result, it is unknown how much harm this *N. n. nigricincta* and *B. a. arietans* bites actually does, how severe it is, and whether it only causes local or systemic harm. This is because little study has been conducted in Namibia. Therefore, there are challenges associated with these snakebite treatments in Namibia; these challenges include, but are not limited to, delays in seeking medical care, lack of necessary equipment to treat snakebite injuries at health facilities, and medical practitioners who are not well equipped or trained to manage snakebites in Namibia; and thus, treatment depends on the doctor's experience treating snakebite (19). Furthermore, there may be difficulties with antivenom supplies because it is expensive, difficult storing antivenom in isolated rural areas due to temperature storage requirements, and there is no antivenom for *N. n. nigricincta* bites (29).

Namibia has a sparse population, patients with snakebites travel great distances before receiving competent care. Consequently, by the time patients reach a medical facility, they typically have acquired severe oedema. Patient's wounds may extend as a result of surgical intervention to relieve the pressure. There are currently no records of treatment of snakebite wounds in Namibia, particularly those caused by *N. n. nigricincta* and *B. a. arietans* bites. The underlying assumption of this project is to generate sufficient knowledge about snakebite injuries on a larger scale in order to reduce amputations and fatalities. As well as motivate for more antivenom production at a lower cost, as well as the production of antivenom containing the venom of the *N. n. nigricincta* snake. Lastly, to establish an easily adaptable treatment and diagnostic approach for *N. n. nigricincta* and *B. a. arietans* bites.

1.3. Aim and Objective

This thesis aims to investigate the clinical pathology of patients bitten by *N. n. nigricincta* and *B. a. arietans* who presented at Katutura Intermediate State Hospital (KISH) and Windhoek Central Hospital (WCH). It also focused on generating new scientific information to inform evidence-based treatment protocol for Namibian snakebites, particularly those caused by *N. n. nigricincta* and *B. a. arietans*, as well as a functional snakebite database with likely outcomes.

Therefore, specific objectives of this study were to:

1) Describe the natural history of patients bitten by *N. n. nigricincta* and *B. a. arietans* who were treated at KISH and WCH.
2) Document the snakebite wound's progress throughout the patient's management period.
3) Assess the clinical and laboratory profile for systemic evidence of any organ damage.
4) Document the functional outcomes of patients who have been bitten by *N. n. nigricincta* and *B. a. arietans*.

1.4. Research Question

What is the natural history of clinical pathology of *N. n. nigricincta* and *B. a. arietans* snakebites and what are the factors associate with these injuries?

1.5. Significance of the Study

In Namibia, there has not been comprehensive research on the implementation of clinical treatment guidelines for snakebite injuries, as well as patient outcomes after treatment. This study was significant because it contributed to the closure of critical knowledge gaps, allowing future patient care to be more effective in terms of reducing

death and amputations. The purpose of this study was to collect data that will educate healthcare professionals about the acute natural history of *N. n. nigricincta* and *B. a. arietans* snakebites, allowing them to assess future long-term disability and quality of life as a result of snakebite injuries. This research will help enhance the management of snakebite wounds. The study also determines whether *N. n. nigricincta* and *B. a. arietans* bites have long-term consequences on humans, such as organ damage that may result in renal failure or liver failure in the patient. This will be crucial due to the lack of documentation regarding the systemic effects of envenomation by *N. n. nigricincta* and *B. a. arietans*. Functional outcomes may increase awareness of the emotional and physical implications of snakebite injuries in Namibia through collaboration between occupational physiotherapists, social workers, and physicians. Finally, these findings aid in understanding the clinical management of snakebite caused by *N. n. nigricincta* and *B. a. arietans* in Namibia, as well as their relationship to existing guidelines.

1.6. Limitation of the Study

Patients are not always recorded in the snakebite book available at health facilities, making it challenging to enrol new patients in the study. There was discrepancy in the collected patient data, as some patient clinical files lacked key study information, such as laboratory results. The study's data collection was delayed by COVID-19 pandemic outbreak between 2020 and 2021, as the principal investigator was unable to collect data for specific months due to Namibia's lockdown. Additionally, the principal investigator was also unable to collect data anytime they came into contact with a positive COVID-19 case due to the requirement to isolate for a predetermined period. As a result, the study was extended for an additional three months.

1.7. Delimitation of the Study

The study only focused on *N. n. nigricincta* and *B. a. arietans* snakebites, therefore the accurate identification of the snake was really necessary, such that a poster depicting all of the numerous varieties of snakes found in Namibia was placed in both hospitals at all admission sites. In addition, when patients were unable to identify the type of snake that bit them, clinicians also assisted in determining the type of snake by inspecting the fang marks and taking note of the snake description. The study setting was only limited to Namibia's referral hospital both situated in Windhoek (Katutura Intermediate State Hospital and Windhoek Central Hospital); therefore, it does not include snakebite admitted in the northern part of Namibia (Oshakati, Onandjokwe and Rundu Intermediate State Hospitals) which explains the small study sample. The study delimited to a convenience sample from *N. n. nigricincta* and *B. a. arietans* snakebites admitted to Katutura Intermediate State Hospital and Windhoek Central Hospital.

CHAPTER 2

2. Literature Review

2.1. General Overview of the Snakebite Burden

2.1.1. Epidemiological Data of Snakebite

Snakebite injury is common throughout the world, but it is often a neglected and overlooked condition that contributes significantly to morbidity and mortality (3,10,32). Snakes are among the most feared creatures on the planet, and despite the significant negative impact it has on humans, snakebite has not been properly recognised by both national and international health policies, leading to its classification as a neglected tropical disease (2,10). Scarcity of antivenom (due to insufficient investments, high antivenom costs, incorrect clinical application, and inconsistent quality standards), and difficulty accessing a health-care facility are all factors that contribute to increased mortality (2,4,8,10,33).

Global estimates of snake envenomation indicate that approximately 1.8 – 2.7 million people are bitten by snakes each year, resulting in at least 81 000 – 137 880 deaths and over 400 000 amputations (4). Asia has the highest rate of snake envenomation 1.2 – 2.0 million people, and 57 000 – 100 00 deaths annually, followed by Africa with a rate of one million snake envenomation and deaths ranging from 10 000 to 32 000 per year (4,5). Sub-Saharan Africa has an estimation of 90 000 - 420 000 people envenomated each year (7,8,10). Snakebite epidemiological data is limited, therefore determining snakebite injury prevalence in Africans may be difficult (5,7,8,10). Furthermore, because Africa lacks reliable snake species identification systems, confirming the type of snake has also been challenging (7). As a result, there may be a delay in care therapy as the species is unknown.

Hundreds of snakebites occur each year in Namibia, resulting in catastrophic mortality, limb loss, and paralysis (6). However, there is very little clinical support, and there is insufficient research on snake envenomation (6). Namibia is a vast and dry country with a small population, with the majority of people (57 %) living in rural areas such as villages and farms (6). According to the World Health Organization (WHO; 2019), Namibia was reported to have had 572 – 811 snakebite cases annually (5). Between August 2015 and August 2016, about 721 snakebites were reported at Windhoek's referral hospitals (Katutura Intermediate State Hospital and Windhoek Central Hospital); 569 of these snakebites happened outside the city and were referrals from smaller health centres across the country according to Hunter et al. (6). Furthermore, the majority of the cases were children, and encountered during the summer months. The article also reported that approximately 33 people died as a result of snakebite envenomation, 225 people experienced loss of muscle function, 68 people lost limbs due to amputations, and approximately 50 people were paralysed (Figure 1).

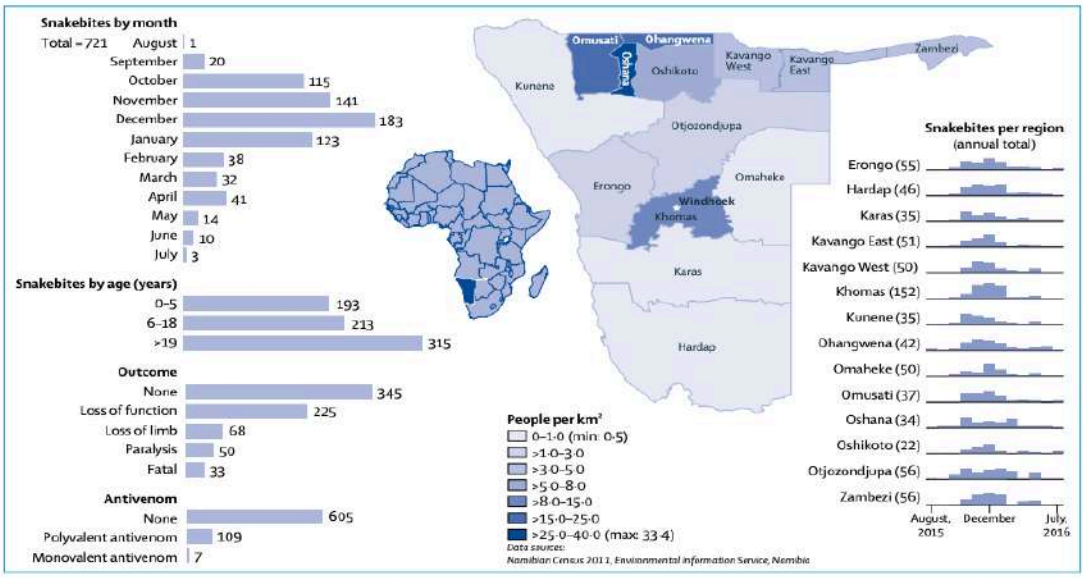


Figure 1: Snakebite injury in Namibia August 2015 and August 2016 adapted from (6).

Although the combined mortality rate in Africa has not been well defined, the most vulnerable populations are children and agricultural workers such as farmers and cattle herders (7,8,10). Furthermore, vipers such as adders and spitting or cytotoxic cobras are responsible for the majority of fatal and life-threatening snakebites in Africa (7–10). According to Hauptfleisch et.al (12), 182 snake species found in Windhoek, the *B. a. arietans* had the highest percentage (35.7 %), followed by the *N. n. nigricincta* with 29.1 %, both of which are highly venomous. As a result, this suggests that *N. n. nigricincta* and *B. a. arietans* are the most common snake species in Namibia, and are thus responsible for the majority of snakebite incidents.

Snake species, in general, are seasonal and prefer particular climatic conditions; for example, because they are ectothermic, they thrive in warmer climates, which explains why more snakes are spotted during the summer months (11,34). Furthermore, as prey for food, they tend to target/bite those who are sleeping, particularly on the floor especially spitting cobras snakes such as *N. n. nigricincta* (7,20,35). Snake envenoming is likely to occur in remote and rural areas, where individuals live in substandard housing and have limited access to health care (4,32,36,37). Males are more frequently bitten than females, and children more than adults (34,38).

2.1.2. Classification of Venomous Snakes

Snakes are divided into two groups: poisonous and non-poisonous (39). Most people, however, cannot distinguish between poisonous and non-poisonous snakes (4,39). Poisonous snakes, also known as venomous snakes, have hollow, grooved fangs (one or two fangs) that they use to bite their victims and inject venom toxins into them (40). A snake can inject its venom into its prey in two ways: the venom is either injected through the fangs after a bite or the snake spits toxin-containing saliva at their victims' eyes, as is seen in the spitting cobra (40).

There are three venomous snake families: Elapidae (elapid), Viperidae (vipers), and Colubridae (11). Elapids are snakes with short fangs, such as cobras, king cobras, kraits, coral snakes, Australasian snakes, and sea snakes. Whereas, vipers are described as having rather long fangs and are classified into two subfamilies, Viperinae and Crotalinae. Due to the significant damage that these snake species cause to humans, both the snake families have been known to be of the highest clinical interest (7). Locally known as zebra spitting cobras, *Naja nigricincta nigricincta* is classified as Elapidae under the genus-group *Naja*, while *Bitis arietans* is classified as Viperidae under the genus-group Bitis (11). The most common snake species in Namibia are the *Naja nigricincta nigricincta* (*N. n. nigricincta*) and *Bitis arietans* (*B. a. arietans*), which account for the majority of bites (6,12).

2.2. Protein Composition of Snake Venom

2.2.1. General Snake Venom Toxins

Snake venom toxins are complex protein mixtures composed of enzymes, non-enzymatic polypeptide toxins, and non-toxin proteins that alter normal human physiology (13). Furthermore, snake venom toxins' primary functions are hydrolases, which cause pathogenesis (41). This in turn allows the snake to immobilise and digest their prey (42). Snake venom toxins are derived from enzymes with pharmacological and toxicological effects on humans, and composition differs by species (43). The four main protein families found in snake venom toxins are phospholipase A2s (svPLA2s), metalloproteases (SVMPs), serine proteinases (SVSPs), and three-finger toxins (3FTxs) (44). The secondary protein families into which venom toxins are classified are L-amino acid oxidases (LAAO), kunitz peptides (KUN), disintegrins (DIS), cysteine-rich secretory protein (CRiSP), and C-type lectins (CTL). Finally, venom

toxins include minor protein families such as acetylcholinesterase, hyaluronidase, serine proteinases, phosphodiesterase inhibitors, and others. The various domains and ligand binding properties of these proteins result in a range of cytotoxic, neurotoxic, haemotoxic, myotoxic, and cardiotoxic effects when inflicted on humans (7).

2.2.2. Toxins Found in the Venoms of *N. n. nigricincta* and *B. a. arietans*

Viper venom toxins contain disintegrins and metalloproteinases (SVMPs), which are responsible for the destruction of coagulation profiles, resulting in haemorrhage (Table 1) (10,45). SVMPs degrade the structure and function of extracellular cell membrane (ECM), causing bleeding, cell necrosis, and endothelial cell damage (46). Furthermore, elapids and vipers' venom both consist of three finger toxins and acetylcholinesterase, which cause peripheral muscle paralysis by blocking the nicotinic acetylcholine receptor at the neuromuscular junction (10,45,47). Both viper and elapid venom also consist of phospholipase A2s (svPLA2s), also known as haemolytic or myolytic phospholipases A2 cause cell membrane and tissue damage by destroying red blood cells (48). Finally, both viper and elapid venom consist of serine proteinases (SVSPs) toxins, these are substances in the venom that also influence platelet production (10,45).

Table 1: Four main protein families present in the vipers and elapids species.

Toxin	Species	Action Mechanism	Reference
SVMPs	Vipers	Local and systemic haemorrhage, myonecrosis, blistering, hypovolemia and inflammation.	(49,50)
3FXTxs	Vipers and Elapids	Impairs the neuromuscular transmission	(49)
PLA2s	Vipers and Elapids	Neurotoxicity, cardiotoxicity, myotoxicity, haemorrhage, oedema, convulsion, hyperalgesia, inflammation, hypotension, inhibition of platelets aggregation, anticoagulant and induced haemolysis.	(49,51)
SVSPs	Vipers and Elapids	Affects coagulation, platelet aggregation, fibrinolysis, complementary system and immune system.	(49,51)

Metalloproteases (SVMPs), three-finger toxins (3FTxs), phospholipase A2s (svPLA2s), and serine proteinase all form part of the serine proteinase (SVSPs) family.

2.3. Namibian Health Care System and Snakebite Injuries Treatment

Lack of medical facilities in Namibia especially in rural areas makes it difficult for snakebite victims to receive medical attention on time, as they are often several hours away from the nearest health facility, which may also not be adequately equipped to handle these medical situations (45). Snake identification is important in the diagnosis and management of snakebite as differences in snake age, size, species and venom type affect treatment decisions and allow clinicians to anticipate any complications that may occur, improving overall prognosis (34). However, this is frequently impossible in cases where victims do not have this information, or are unaware of the initial cause of injury (19,23). As a result, treatment may be delayed, potentially resulting in preventable cell death and necrosis (23). In Namibia, the treatment options for snakebite are restricted to medical supportive care (such as fluids, pain medication, limb elevation etc.) and monovalent or polyvalent antivenom from the South African Institute of Medical Research (SAIMR), depending on the type of snake species (45).

2.4. Snakebite Envenomation

According to the WHO (2010) (7), the amount of venom secreted during a snakebite is impacted by a number of factors, including the type and size of the snake species, the number of fangs injected into the skin, the intensity of the bite, the snake's age and body type, the victim's allergic response to the snake toxins, and whether there are repeated bites (3,7,10). Larger snakes are more likely to produce more venom compared to the smaller snakes (7). Moreover, bites from venomous snakes do not always result in venom injection; some are referred to as "dry bites", where no venom or toxin is injected after a bite (3,10). This could be due to mechanical inefficiency or the snake's control over venom discharge (7,10). Another possibility is that the small

amount of venom injected maybe insufficient to cause clinical symptoms (10). Scientists are still uncertain as to why snakes inject venom or have dry bites (3,7,10).

2.4.1. Pathology of Snakebite Wounds

Generally, when a patient is bitten by a cytotoxic snake, the venom toxins are delivered straight into subcutaneous tissue, resulting in swelling, necrosis, and occasionally blistering, culminating in significant swelling that may or may not progress to compartment syndrome (7,19,20). Agricultural workers have been identified as a particularly vulnerable group of persons who are frequently bitten by snakes, with bites typically occurring on the hand, leg, foot, ankles, or lower limbs when herding cattle or resting beneath a tree (11,34). It is believed that bites by *N. n. nigricincta* and B. *a. arietans* will result in clinical manifestations such as necrosis and significant local oedema (1,3,7). These signs might manifest as early as six hours after the bite and can be associated with or without neurotoxicity (3,7,35,52). Due to significant local blistering and necrosis caused by the venom toxins, amputation of the bitten digit or even the entire limb may be necessary in some cases (7). Debridement surgery, which removes dead tissue to prevent additional injury, can enlarge snakebite wounds. Alternately, fasciotomy, in which surrounding tissue is sliced open to relieve pressure, may cause wounds to spread (7,19).

If there is any evidence of necrosis in the bite site from *B. a. arietans* debridement is performed at a later stage, usually 5-7 days after the bite (7,19). In contrast, debridement of *N. n. nigricincta* bites are performed as soon as the patient arrives at the health-care facility if there is evident necrosis at the bite site (19). As for severe oedema, it may result in intracompartmental pressure syndrome (IPS), which is difficult to diagnose in snakebite patients (19,53). Therefore, most patients are subjected to numerous unnecessary fasciotomy procedures (19). Direct measurement

of intracompartmental pressure with a Stryker Needle or ultrasound demonstration of intramuscular swelling are the most reliable ways for confirming IPS in patients before performing fasciotomy. Given that both *N. n. nigricincta* and *B. a. arietans* bites cause necrosis and severe oedema, patients who have been bitten by these snakes may require surgical intervention, resulting in snakebite wounds (3,7). Snakebite wounds have not been fully examined, and there is a scarcity of information on snake envenomation (22).

2.4.2. Local Signs of Envenomation

General pathology in snake envenomated patients is characterised by immediate pain, local bruising, and severe swelling 10 – 20 minutes after the bite (7). However, a physical examination of envenomation may reveal an oedematous, cold, immobile, and impalpable bite site; additionally, these patients may experience compartmental syndrome (10,11). Patients may experience early signs of necrosis, blistering, demarcating darkening of the skin, paleness of the skin, loss of sensation, and the odour of putrefaction, which is the rotting of flesh specifically those of *N. n. nigricincta* and *B. a. arietans* (1,7,10). As a result, local envenomation spreads quickly from the site of the bite and is tender in the enlargement of lymph nodes, indicating the spread of venom to the lymphatic system (10). When venom enters the body and enters the lymphatic system, it forms strips that separate necrotic tissue from normal tissue, sometimes forming blisters around these lesions and causing loss of limb function (7). The lymphatic system can also cause neutrophil leucocytosis, which activates the immune system's complement specific for the *N. n. nigricincta* (7,10,11).

2.4.3. Systemic Signs of Envenomation

Systemic envenoming from both elapid and viper bites may cause organ and tissue damage, can be fatal, and may cause permanent damage (11). Although complications

from snake envenoming are uncommon, patients may present or experience severe neuromuscular paralysis, rhabdomyolysis, or thrombotic microangiopathy with acute renal failure at a later stage (54). According to the WHO (2010), clotting factors are commonly known to be disrupted by venom toxins, resulting in bleeding and clotting disorders, particularly in viper bites (7). The first sign of disturbed coagulation is bleeding after a snakebite from the fang or puncture site, which is caused by defibrinated blood that will not clot and has impaired platelet function. Thrombocytopenia may also occur (55). Moreover, it may also cause systemic bleeding where patients may pass dark brown/black urine (7). In addition, the venoms of the *N. n. nigricincta* and *B. a. arietans* have been shown to cause neurotoxic symptoms such as collapse (hypotension, shock), nausea, vomiting, diarrhoea, severe headaches, drowsiness, heaviness of the eyelids, and ptosis, all of which are among the most common symptoms associated with systemic envenomation (1,7,10,19). Systemic bleeding and neurotoxicity are both signs of severe envenomation (10). Snakebite victims may also develop compartment syndrome, which can lead to arrhythmias from myocardial infarction as a result of hypotension (7,10).

2.4.3.1 Clinical Pathology of Snakebites

2.4.3.1.1. Full Blood Count and Blood Smears

The most common and frequently requested haematological blood test is full blood count (FBC) in snakebite patients (10,11,56–58). It is used as an engine to monitor and investigate disease progression in snakebite patients (57). FBC parameters include white blood cell count (WBC), red blood cell count (RBC), haemoglobin (Hb), haematocrit, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), red distribution width (RDW), platelets (PLT), mean platelet volume (MPV), neutrophils, lymphocytes, monocytes, eosinophils and

basophils (23,56). During inflammation, for instance, a full blood count is performed to determine the white blood cell (WBC) count, which includes neutrophils, basophils, and monocytes (59).

The major purpose of an FBC is to evaluate whether or not the patient has anaemia or haemolysis, which is common in patients with *N. n. nigricincta* bites (20). In anaemia, there is a decrease in red blood cell count, haemoglobin and haematocrit, whether the total and differential WBC supports the diagnosis of infection, and whether the platelet count is within the range that influences haemostasis (60,61). Haemolysis is the breakdown of red blood cells (such as anaemia), but can result in increased unconjugated bilirubin, aspartate transaminase (AST) and creatine kinase (CK) (62). Neutrophilia is frequently seen in patients with burns, bacterial infections, and tissue necrosis such as bites from *N. n. nigricincta* and *B. a. arietans*, which aids in directing investigation to a specific diagnosis (7,10,57). Furthermore, the reticulocyte count is an important test used to assess erythrocyte production following a snakebite injury (60).

Peripheral blood smears provide important information about blood cell abnormalities, and are especially useful in determining anaemia and assessing blood cell morphology in snakebite patients (58,60,61). In blood smears, the alteration of erythrocyte shapes caused by disease is examined, such as target cells, schistocytes, stomatocytes, helmet cells (seen in microangiopathic haemolytic anaemia) and spherocytes (immune mediated haemolytic anaemia and hereditary spherocytosis), and nucleated erythrocytes are examined in patients with haemolysis (10,60). Thrombocytopenia due to a decreased platelet count may be observed in patients within 24 hours of the bite, and patients who have suffered systemic envenomation may also experience nonspecific leukocytosis and lymphopenia (9,10,54). Furthermore, thrombocytopenia

can also be detected in patients with liver disease (63). The table below contains a list of criteria, with the FBC parameter associated with each condition, as well as the cut-off values for confirming the condition (Table 2).

Table 2: Abnormal conditions associated with FBC adapted from (56)

Condition	Abnormal value
Thrombocytosis (PLT · 10^9/L)	> 411
Thrombocytopenia (PLT · 10^9/L)	< 100
Granulocytosis (WBC · 10^9/L)	> 9
Granulocytopenia (WBC · 10^9/L)	< 1
Lymphopenia (WBC · 10^9/L)	< 1
Lymphocytosis	> 6.5%
Monocytosis	> 7%
Eosinophilia	> 7%

2.4.3.1.2. Snakebites Induced Coagulation

A vascular response, the formation of a haemostatic platelet plug, and the formation of a fibrin clot are all part of normal haemostasis (64). Each of these responses may be deficient in patients with snakebite injury, resulting in a haemorrhagic diathesis that is more or less distinctive (64). Prothrombin time (PT) is a measure of the extrinsic pathway of clotting which is dependent upon clotting factors produced by the liver (9,64,65). A raised PT value will have a higher internationalised ratio (INR), and is indicative of a reduced ability in blood clotting (64). Specific conditions, such as liver disease, thrombophilia (excessive clotting), and haemophilia (inability to clot normally), can also disrupt coagulation (64,66).

Venom induced consumption coagulopathy (VICC), is the most common coagulation associated with snake envenomation, and is linked to disseminated intravascular coagulation (DIC) (54). VICC is diagnosed by measuring the patient's PT, INR, activated partial thromboplastin clotting time (PTT), fibrinogen, and D-dimer levels, which are used to determine the likelihood of excessive bleeding or the development of clots (thrombosis) in the patient's blood vessels. (9,54). D-dimer is a protein

fragment produced by the body during the dissolution of a blood clot, also known as fibrin degradation (67). VICC patients may have d-dimer levels that are 100-1000 times higher than the normal assay cut off reference range, a high INR, a prolonged PTT, and low or undetectable fibrinogen levels in their bodies (9,54).

An elevated INR could be due to a decrease in clotting factor synthesis caused by chronic liver disease, vitamin K deficiency, or anticoagulant (54,68). Equally, it could be the result of DIC (54), which is a serious disorder in which the proteins that control blood clotting are overactive, resulting in severe bleeding (68). It is diagnosed by prolonged PT, reduced platelet count, reduced fibrinogen, and abnormalities with liver patients (68).

2.4.3.1.3. Biochemical Tests

Electrolytes (potassium, chloride and sodium), urea and creatinine levels, liver function tests (LFTs), and CK levels are all measured to rule out organ damage such as kidney injury, liver damage and cardiac damage (54). LFT tests include total protein (TP), albumin, total bilirubin (T-Bili), alkaline phosphatase (ALP), alanine transaminase (ALT), AST, gamma-glutamyl transferase (GGT), L-lactate dehydrogenase (LDH) (62). CK is usually normal upon admission, but it rapidly increases between 24- and 48-hours post-injury, rising from 1000 U/L in mild cases to > 10000 U/L in severe cases (54).

Creatinine is a waste product of normal muscle tissue breakdown that the body filters in the kidney and excretes in urine (65). The ability of the kidneys to handle creatinine is referred to as creatinine clearance rate, and this helps estimate how quickly blood moves through the kidneys, which is referred to as glomerular filtration rate (GFR) (65). Certain elapids and vipers are capable of causing acute kidney injury, which can be lethal, but is uncommon (1,3,4,7,10,13). Individuals with kidney damage exhibit an

increase in creatinine and a decrease in urine output (65). Kidney damage is diagnosed by an increase in creatinine concentration of more than 0.3 mg/dL within 48 hours, an increase in creatinine concentration of more than 50 % above baseline within 7 days, a decrease in GFR below the normal baseline, and/or a decrease in urine output of more than 0.5 mL/kg/hr for more than 6 hours (58,65).

Elevated CK, AST, and LDH levels indicate myotoxicity, a clinical muscle injury, that is confirmed with the presence of rhabdomyolysis especially if CK is raised more than 5 times the normal limit (20,58). Rhabdomyolysis is degeneration of muscle tissue accompanied by the release of breakdown products into the bloodstream, usually determined by raised AST 5 times more than the normal, and is a common complication of kidney injury (20,58). Extensive and severe myocardial lesions are characterised and may have been reported in some snakebite patients, where the enzymes released are similar to myocardial infarction (MI) (58). The results do not usually demonstrate any cardiac muscle involvement; however, the presence of myotoxicity could lead to MI if cardiac markers creatinine kinase myocardial band (CK-MB) or troponin T are elevated (58).

AST is found in the liver, heart, muscles, kidney, and red blood cells, whereas ALT is found only in the liver. Liver damage is indicated by AST and ALT levels that are two times higher than normal (62). Additionally, ALP, GGT, and bilirubin levels may be normal or slightly elevated in individuals with liver damage (62). Finally, a decrease in Albumin, a protein that is entirely produced by the liver, also results in chronic liver disease (62). Coagulation abnormalities with prolonged PT and an INR value greater than 1.5 are also signs of liver damage (Table 3) (69).

The mechanism of systemic damage of snakebite toxins is not fully understood (1,3,4,7,10). However, because of the range of their effects organs such as the kidney,

liver and heart are at risk of damage (4,9). Table 3 illustrates the laboratory value used to assess the damage of the specific organs such as the kidney, liver and heart.

Table 3: The diagnosis of organ damage

	Creatinine	**AST, ALT**	**ALP, GGT**	**Bilirubin**	**Albumin**	**INR**	**CK**	**LD**	**Ref**
Kidney damage	↑↑ to ↑↑↑	-	-	-	-	-	-	-	(65)
Liver damage	-	↑ to ↑↑↑	Normal to ↑↑	Normal to ↑↑	Normal to ↓↓	Normal to ↑↑	↑↑	-	(62)
Cardiac damage	-	↑ to ↑↑↑	-	-	-	-	↑↑ to ↑↑↑	↑↑ to ↑↑↑	(54)

Key: - Absent/ not needed, ↑ increase mildly, ↑↑ increased moderately, ↑↑↑ increases intensively. Ref indicates reference.

2.4.3.2. Investigations Through Laboratory Tests Done in Namibia

It has been reported that blood work is performed in the same manner as in any other snakebite case in Namibia, which helps rule out any long-term damage done to the body as a result of snakebite injury (7,19). The majority of laboratory tests done on snakebite patients consist of a full blood count (FBC), differential count (diff count), peripheral blood smears, urea and electrolyte blood test (U&E), liver function test (LFT), creatine kinase (CK), s-haptoglobin, s-myoglobin, thyroid function test (TFT), random cortisol, blood crossmatch, and clotting profiles such as INR, d-dimer, and fibrinogen (19). Patients are also subjected to urinalysis tests to detect proteins, myoglobin, and haemoglobin where applicable (19).

2.5. Universal Snakebite Treatment Protocol

2.5.1. First Aid Treatment

As soon as a victim is bitten, the victim should be kept calm and still to slow the spread of venom toxins (7–10). First aid should be administered before or while transporting the patient to an emergency care facility (7,19). First aid includes laying or sitting the victim down with the site below the level of the heart, keeping the individual calm,

washing the wound with soapy water, and covering the bite with a clean and dry dressing if one is available (19). Some individuals seek traditional treatment before approaching the health care facility. Traditional treatments may include attempting to suck the venom from the wound, application of tight bands (tourniquets), drinking petrol or urine, cutting/slashing the snakebite site, and applying various herbs to the bite site (5,7,10). It is recommended, however, that the victims avoid practising traditional medicine in the future because it has the potential to exacerbate the situation (7,10).

2.5.2. Primary Health Care

Antivenom is the only effective known snake venom antidote, and it is critical in the treatment of systemic envenomation (11). Antivenom is made up of immunoglobulins, which are fragments of antibodies derived from snake venom proteins that are injected or immunised into horses and then extracted and purified from horse plasma to treat venomous snakebites and stings (17,28,70). Antivenom binds to toxins, causing toxin displacement from the receptor and, as a result, toxin elimination, thereby preventing blood, tissue, or nervous system damage (71). Antivenom can be either single-species specific (monovalent antivenom) or multi-species specific (polyvalent antivenom) (17). Some snakebite cases do not result in significant envenomation and do not usually necessitate the use of antivenom (54).

Due to the venom toxins of different snake species, it is impossible to develop a universal antivenom antidote (7,10,25,72,73). In Africa, the procurement of antivenom remains a challenge due to the withdrawal of antivenom production sites, and a lack of funds allocated for local production and capacity (48). Presently, the only source of antivenom in Africa is South African Vaccine Producers (SAVP), owned by the South African Institute for Medical Research (SAIMR) (72). SAIMR, a private institute,

produces two types of antivenoms based on venom toxin compositions, with polyvalent constituting ten snake species: Puff Adder (*B. a. arietans*), Gaboon Adder (*Bitis gabonica*), Rinkhals (*Hemachatus haemachatud*), Green Mamba (*Dendroaspi*), Jameson's Mamba (*Dendroaspi jamesoni*), Black mamba (*Dendroaspi polylepis*), Cape Cobra (*Naja nivea*), Forest Cobra (*Naja subfulva*), Snouted Cobra (*Naja annulifera*), and Mozambique Spitting cobra (*Naja mossambica*), and as for monovalent constituted of Boomslang (*Dispholidus typus*) venom toxins (72). However, because of the venom of *N. n. nigricincta* is not included in the development and manufacturing of SAIMR polyvalent antivenom, antivenom is not effective against *N. n. nigricincta* bites (19,25).

Some facilities or hospitals do not always have antivenom available due to a lack of funds (7,10,19). In general, Africa has been experiencing a supply crisis due to insufficient antivenom production since the early 1990s, resulting in an increase in morbidity and mortality as a result of these accidents (74). With 721 bite incidences in Namibia in 2015 and 2016, only 109 patients received antivenom (6), the reasons for which are unknown due to a lack of published information about snakebite injury. Antivenom is expensive and scarce, so it is only administered when the patient has systemic symptoms or severe local envenoming such as venom-induced consumption coagulopathy, sudden collapse, myotoxicity, neurotoxicity, thrombotic microangiopathy, and renal impairment (10,52,54). Antivenom is also only known to be effective in treating systemic complications; however, it has been discovered that there is limited effectiveness in treating local damage, metabolic dysfunctions, and tissue damage (28). One vial of antivenom is sufficient to neutralise the venom; however, the damage caused by venom is not reversible and may delay overall recovery (54). Antivenom is effective when administered correctly, but it becomes

ineffective when administered incorrectly (administered for the bite of the wrong species, and administration is performed after a significant amount of time has passed and irreversible damage has occurred) (15,19,20). Antivenom administration can potentially result in the patient experiencing an allergic reaction, such as anaphylaxis. If the patient develops an early anaphylactic antivenom reaction, epinephrine can be administered (11).

2.5.3. Snakebites management guidelines in Namibia

The primary treatment for all snakebites in Namibia is outlined in the Ministry of Health and Social Services' snakebites management guidelines (2011), which has been adopted from the World Health Organisation's general first aid guidelines (7,23). Victims are encouraged to seek treatment at the nearest medical facility and advised not to tamper with the bite site, such as by cutting, massaging, applying traditional medicine, or heating it (19,23). Treatment options in Namibia are also limited to monovalent antivenom and polyvalent antivenom from SAIMR (23). For all early, progressive swelling caused by puff adder bites, patients are given 40 mL of antivenom when available (19,23). The polyvalent antivenom SAIMAR has been reported not effective against *N. n. nigricincta* snakebite injury (19,20,25).

All snakebite patients remain within the hospital for local and systemic continuous monitoring (23). Elevation of the limb, pain relief medication, assessment of compartment syndrome, hourly monitoring for any systemic injury, bleeding, and signs of extended necrosis, and debridement after demarcation, which can take 7 to 14 days, aggressive fluid management is implemented (intravenous (IV) – line) and analgesics are administered to the patient after snakebite (19,23). Furthermore, general snakebite treatment guidelines also recommend resuscitation and stabilisation, tetanus toxoid, administration of antibiotics, prophylactic antibiotics (ceftriaxone, amikacin,

amoxyclavulanic acid, or piperacillin tazobactam antibiotics), for spitting cobra (*N. n. nigricincta*) and adders such as *B. a. arietans* and referral to a specialist were necessary (19).A specialist is consulted for patients with bites around the genitals or face area (19). Blood, blood products, plasma, fresh frozen plasma (FFP), or plasma expanders are prescribed for patients who have been bitten where needed, and respiratory support is provided for ventilated patients as needed (23). Wounds are managed in the same way as any other type of wound care, and patients are reviewed to decide whether they require a skin graft or whether they should proceed with wound closure surgery (21). Due to a dearth of study on snakebite wounds in Namibia, particularly those caused by *N. n. nigricincta* and *B. a. arietans* snakes, little information is available for managing wounds inflicted by these snake species.

This research seeks to detect any local and systemic pathological evidence caused by *N. n. nigricincta* and *B. a. arietans* snakes, as well as to aid in the development of a practical methodology for treating snakebites.

CHAPTER 3

3. Research Methodology

3.1. Introduction

This chapter outlines the study procedures in detail. These cover the approaches, methodologies and techniques used in gathering data and evidence for analysis in order to uncover new facts and gain a better understanding of the subject.

3.2. Research Design

The study used an observational descriptive mixed – methods approach. The research was conducted in Namibia at the Katutura Intermediate State Hospital (KISH) and the Windhoek Central Hospital (WCH), both located in the capital city of Windhoek (WHK). The study used secondary data from patient clinical records who had been bitten by *N. n. nigricincta* and *B. a. arietans*. The specific snake species (*N. n. nigricincta* and *B. a. arietans*) were chosen since they are the most frequently encountered in Namibia and account for the vast majority of snakebites (12). Each year, between 572 and 811 cases of snakebite envenomation are documented in Namibia (5). Similarly, between August 2015 and August 2016, 721 snakebites were reported in the WHK referral hospitals (6). As a result, snakebite envenomation is commonly present in Namibia. Figure 2 summarises the overall general technique used in this study to conduct the research.

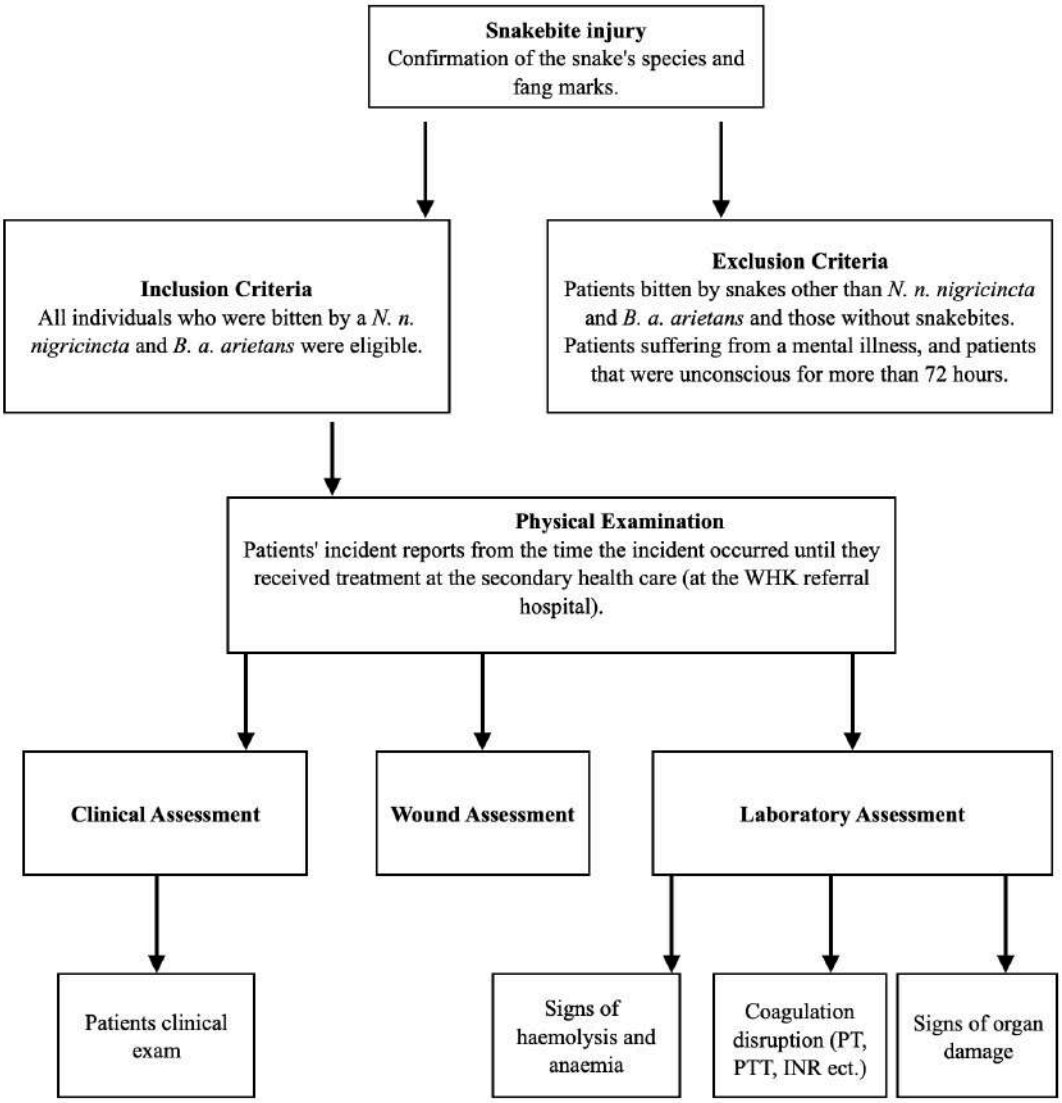


Figure 2: A flowchart outlining the study methodological plan

3.3. Study Population

The study population included all Namibian males and females of different races, ages, educational levels, socioeconomic class, and residents who were bitten by *N. n. nigricincta* and *B. a. arietans* and were presented to KISH and WCH in Windhoek, Namibia between December 2020 – March 2022.

Inclusion criteria

All the patients bitten by *N. n. nigricincta* and *B. a. arietans* presenting to KISH and WCH.

Exclusion criteria

Patients who had been bitten by snakes of species other than these *N. n. nigricincta* and *B. a. arietans* were excluded, as were patients who had not been bitten by snakes Patients with a history of mental illness were excluded from this study due to their inability to complete the consent form. Lastly, unconsciousness is an incredibly rare presentation in snakebites, patients who were unconscious for more than 72 hours were excluded from the study because they were unable to consent.

3.4. Sample

Convenience sampling was used in this study. The study sample included all patients presenting at KISH and WCH over a 15-month period (December 2020 – March 2022) with snakebite injuries associated with *N. n. nigricincta* and *B. a. arietans*.

3.5. Sample size

Based on an earlier study that revealed 721 snakebites recorded at KISH and WCH (8). However; there is no data that has been published indicating which snake was responsible for how many of the 721 snakebites. As a result, it is unknown how many

patients were bitten by *N. n. nigricincta* and how many by *B. a. arietans*, causing difficulties in determining the appropriate estimate for the sample size required in this study. The limited data available suggests that *N. n. nigricincta* and *B. a. arietans* are responsible for the majority of bites in Namibia (12). Therefore, this study recruited 20 patients over 15-month period. These data will be used to make more precise sample size predictions for future studies, as determining sample size was difficult due to the limited data available.

3.6. Research Instrument

For this investigation, photographs were taken with a mobile phone camera (iPhone XS Max 2019). These photographs were used to illustrate wound healing and visual complications, and they were included as figures to show how the wound heals from the day of presentation until discharge. Two consent forms were obtained: one for the study as a whole, as it involved human volunteers (Annexure A), and another for the purpose of photographing the wound (Annexure B). Annexure C comprises a poster with photographs of various types of snakes that have been spotted in Namibia to assist patients with snake identification. Additionally, a data collection strategy was used to collect data in order to record and assess it all. The first data collection tool (Annexure D) was a data sheet that recorded the description of the patient's history, including information from the time the patient was bitten to the time they arrived at the Health Facility. Annexure E is a form that comprises clinical information regarding a patient's personal details, physical examination, and neurotoxicity examination, all of which were collected from the patient's hospital file. Annexure F was used to record information on the patient's wound on a daily basis. Lastly, Annexure G contains the patient's laboratory data. These results were initially recorded in the patient's hospital

file and were received from a diagnostic laboratory known as the Namibia Institute of Pathology (NIP), which is accredited by the Southern African Development Community Accreditation Services. Laboratory testing on the patients were not conducted by the principal investigator, but rather by registered laboratory staff. The principal investigator only recorded the laboratory data of the patient. The instruments used in NIP diagnostic laboratory to conduct the tests in this study were Sysmex 1000 for haematology parameter manufactured from Sysmex and architect i2000 for heart, liver and kidney function tests, manufactured from Abbot. Finally, the NIP diagnostic laboratory also used Life Technologies Corporation's ACL elite equipment to perform bleeding tendency tests like PT, PTT, d-dimer, and others.

3.7. Procedure

3.7.1. Clinical Assessment

Patients were treated by a clinical assessor (Doctor or Nurse) in accordance with Namibian standards for Medical Management of Snakebite Victims (19). Thus, the primary investigator entered the patient's history and physical examination (name, age, gender, date and time of admission, date of antivenom administration, site of the bite, activities at the time of the bite, time of bite, place/location when the incident happened, time and date of bite, time taken to reach primary health centre, time they reached WHK referral hospitals, and visualisation/recognition of the snake) into the data collecting tool. Neurotoxicity symptoms were also documented, which often included drowsiness, limb weakness, sweating, vomiting, difficulty swallowing saliva, ptosis, blurred or double vision, and respiratory muscle paralysis.

3.7.2. Snakebite Wound Assessment

The wound was assessed according to standard wound care procedures by the research team (principal investigator or supervisor), and the data collection tool was completed according to standard wound care procedures (21). There were no interventions performed on the patient other than the description of the wound and photographs of the wound. These were performed during the first assessment and after each dressing change to document any changes that may have occurred.

Specific characteristics were documented on a daily basis, such as whether necrosis was present, the severity of the patient's pain, whether surgical intervention (debridement/Fasciotomy) was used, the medication given to the patients, and the date the patient was discharged. Lastly, the patient's outcome, as well as the wound closure and skin graft, were documented.

3.7.3. Laboratory Methods

Laboratory procedures were requested by a clinical assessor in accordance with standard snakebite care, and were documented by the primary investigator. As a result, these laboratory values are all included in Namibia's snakebite treatment guidelines (19), and hence no intervention was done to the patients in this study. This laboratory measures were relevant in ruling out any systemic envenomation in patients bitten by *N. n. nigricincta* and *B. a. arietans* snakes.

3.7.3.1. Haematological Measurements

Where applicable, the primary investigator recorded full blood count (FBC), reticulocyte count, peripheral/differential smear, prothrombin time (PT), international normalised ratio (INR), partial prothrombin time (PTT), fibrinogen and D-Dimer data from the patient file. These were recorded in order to determine the presence of haemolysis, anaemia, coagulation disruption, and infection severity (11). Peripheral

and differential smears were used to determine the presence of abnormal cells such as target cells, schistocytes, stomatocytes, helmet cells (seen in microangiopathic haemolytic anaemia) and spherocytes (immune mediated haemolytic anaemia and hereditary spherocytosis), and nucleated erythrocytes are examined in patients with haemolysis (60,75). Low haemoglobin (Hb), low red blood cell (RBC), and low haematocrit counts all indicated the presence of anaemia (60,61). Haemolysis was assessed by elevation in unconjugated bilirubin, aspartate transaminase (AST) and creatine kinase (CK) (62). A raised PT value will have a higher internationalized ratio (INR), indicated reduced ability in blood clotting which test extrinsic coagulation pathway (64). Venom induced consumption coagulopathy (VICC) was determined in the patients by d-dimer levels that were between 100-1000 times higher than the normal assay cut off reference range, a high INR, a prolonged PTT, and low or undetectable fibrinogen levels (9,54).

3.7.3.2. Tests for Heart, Liver, and Kidney Function Tests

Serum urea and creatinine, liver function test (LFT), creatine kinase (CK), creatine kinase myocardial band (CK-MB), troponin-t, and myoglobin were recorded as needed to rule out any organ damage such as kidney, liver, or heart failure, as well as the presence of rhabdomyolysis by the principal investigator.

Heart damage was determined by elevated CK, aspartate transaminase (AST), L-lactate dehydrogenase (LDH) indicated myotoxicity, a clinical muscle injury, that was used to confirmed the presence of rhabdomyolysis especially if CK was raised more than 5 times the normal limit (20,58). Rhabdomyolysis was also confirmed by raised AST 5 times more than the normal, and is a common complication of kidney injury and heart injury (20,58). The presence of myotoxicity (Elevated L-lactate dehydrogenase (LDH), CK, and AST) was known to lead to myocardial infarction

(MI) if the cardiac markers, creatinine kinase myocardial band (CK-MB) or troponin T were elevated (58).

Liver damage was indicated by AST and ALT levels that are two times higher than normal (62). Additionally, ALP, GGT, and bilirubin levels may be normal or slightly elevated in individuals with liver damage (62). Finally, a decrease in Albumin, a protein that is entirely produced by the liver, also resulted in chronic liver disease (62). Coagulation abnormalities with prolonged PT and an INR value greater than 1.5 were also signs of liver damage (69).

Kidney damage was diagnosed by an increase in creatinine concentration of more than 0.3 mg/dL within 48 hours, an increase in creatinine concentration of more than 50 % above baseline within 7 days, a decrease in GFR below the normal baseline, and/or a decrease in urine output of more than 0.5 mL/kg/hr for more than 6 hours (58,65). Additionally, a decrease in urine output also indicated damage to the kidney (65).

3.8. Data Analysis

The data were examined using descriptive statistics. Patient's clinical profiles to evaluate organ damage were assessed descriptively by analysing whether laboratory data were within the normal reference range. All the data was cleaned and recorded on an excel sheet. Data was described using means, standard deviation, range, interquartile range (IQR) and mode. The Shapiro-Wilk test was used to determine whether the data was normally distributed, which was reported in means and standard deviation. Data that was not normally distributed, was represented as the median and interquartile range (IQR). For each of the tests, a p value < 0.05 was deemed to indicate a significant difference. The Mann-Whitney test was used to compare the differences between the two snake species, while the analysis of variance (ANOVA) was used to compare the differences in various parameters between the two snake species. Overall, snakebite wounds were described from the time of admission to the day of discharge. The analysis was conducted using GraphPad Prism (version 8.0.2).

3.9. Research Ethics

Ethical clearance to conduct the study was granted by the Ministry of Health and Social Services Ethics Committee (Annexure I) and the University of Namibia's Health and Research Committee (Annexure H). Patients were informed about the study, all patients signed a consent form, and persons under the age of 18 were required to have their parents/guardians sign an accent form on their behalf. Patients who were unconscious had their condition monitored until they were able to provide informed consent; if they remained unconscious for more than 72 hours, they were excluded from the study.

No patients were coerced into participating in this study; participation was entirely voluntary, and participants were free to withdraw at any moment. The study advocates

for the respect of all persons and the protection of their health and rights, particularly those of vulnerable groups such as children, pregnant women, the elderly, and those who are economically or educationally challenged. The study had no direct adverse effect on pregnant women. Concerning the elderly and those who are economically or educationally disadvantaged, the study and consent form were explained to them in plain English and translated into their native language when relevant by a translator. Patients having a history of mental illness were not included in the study due to their inability to offer warranted surrogate consent.

All clinical testing and treatment were conducted by qualified registered medical experts (doctor or nurse). Patients were assured that the study was unrelated to their treatment, and they were given the option of agreeing or disagreeing to participate. As this was an observational study, no intervention was done to the patient; if the patient became ill or uncomfortable throughout the study, a physician/nurse was instantly present to provide appropriate medical treatment. Due to the adherence to confidentiality and anonymity, no names or photographs of patients' faces were utilised in this study, except in cases where the bite was directly on the face. All patient data were filed and stored in a locked closet in a closed office at the University of Namibia (UNAM), with access restricted to the primary investigator and supervisor. The data will be retained for a period of five years. The study did not directly benefit the patients (there was no compensation), but the data will be transmitted to the Ministry of Health and Social Services, where it will be used to help medical professionals assess and treat snakebite injuries more effectively in the future.

CHAPTER 4

4. Results

4.1. Introduction

This chapter presents the study's research findings. All pathological test results, patient medical history, and medication on each patient included in this study were obtained from patient files, as well as the Laboratory and Hospital Informatics Systems.

4.2. Baseline Characteristics

A total of 20 patients were admitted to Katutura Intermediate State Hospital (KISH) and Windhoek Central Hospital (WCH), between December 2020 and March 2022. About 17 (85 %) of all patients were referred to Windhoek (WHK) from neighbouring regions, with only 3 (15 %) residing in Windhoek district. Of the 20 patients, two patients were ruled out as having dry bites.

The median age of patients was 10 years (IQR = 4 – 27) (Table 4). The youngest patient was a two-year-old male, and the oldest was a 43-year-old male. Children accounted for a disproportionately large 65 % (13) proportion of snakebite cases in this study (Figure 3). Males accounted for 65 % (13) of the patients presenting with snakebites, while females accounted for the remaining 35 % (7). The lower extremities (such as foot, toes, penile, ankle and leg) 35 % (7) and upper extremities (such as arm, hand, fingers) 35 % (7) were the most frequently targeted bite site areas in this investigation, followed by bites to the face 25 % (5). Summer season was associated with most 85 % (17) of bites, with the other three seasons accounting for the remaining 15 % (3) of bites. Context of bite in terms of activity, the majority of the patients were asleep (50 %) when they were bitten, with the remaining being bitten while engaged in other activities such as playing (20 %), walking (15 %), sitting (10 %), and standing (5 %). In terms of location, 55 % (11) patients were bitten while inside their homes,

while 35 % (7) patients were bitten while in their yards, and 10 % (2) patients were bitten while outside their homes. Finally, the vast majority of snakebite patients reside on farms which accounted for 80 % (16). The study result finding indicated that 60 % (12) of the patients developed severe swelling, 20 % (4) had moderate swelling, 10 % (2) mild swelling, and 10 % (2) had no swelling and were ruled out as dry bite.

Table 4: Characteristics of snakebite patients admitted to KSH and WCH hospital between December 2020 and March 2022.

Population characteristics	**n = 20**
Age, mean years ±SD	15 ± 14
	n (%)
Gender	
Male	13 (65)
Female	7 (35)
Bite site	
Head	5 (25)
Lower Extremities	7 (35)
Upper Extremities	7 (35)
Abdomen	1 (5)
Season of snakebite	
Summer	17 (85)
Autumn	1 (5)
Winter	1 (5)
Spring	1 (5)
Activity of when bitten	
Sleeping	10 (50)
Walking	3 (15)
Sitting	2 (10)
Playing	4 (20)
Standing	1 (5)
Residence of patients	
Farm	16 (80)
Town	3 (15)
Lodge	1 (5)
Location of the bite	
Inside	11 (55)
Yard	7 (35)
Outside	2 (10)
Severity of swelling	
Severe	12 (60)
Moderate	4 (20)
Mild	2 (10)
None	2 (10)

Population characteristics	n = 20
Snake Species	
N. n. nigricincta	12 (60)
B. a. arietans	8 (40)

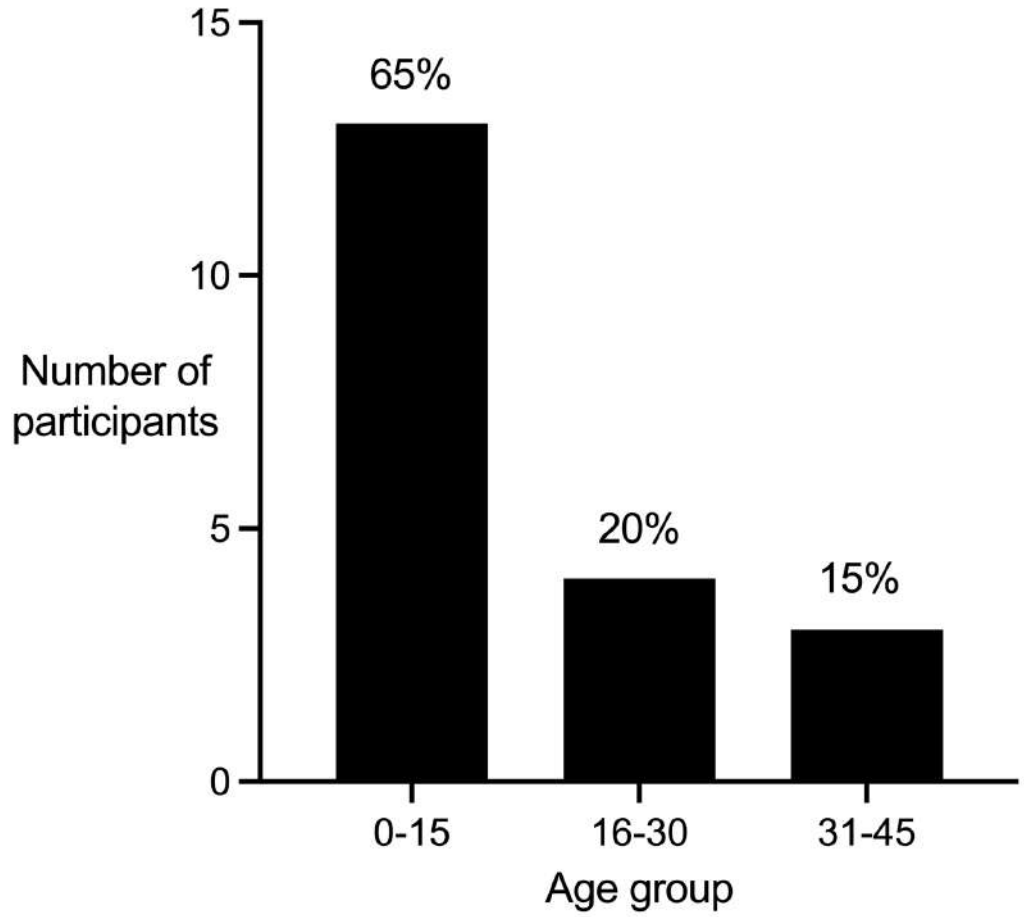


Figure 3: Age distribution among the snakebite patients that was grouped into children (0 - 15), young adults (16 - 30) and older adults (31 - 45).

4.3. Patient Snakebite Natural History

Bites from *N. n. nigricincta* are more common on the head, whereas bites from *B. a. arietans* are more common on the lower extremities 4 (50.0 %), such as the hands. (Table 5). *N. n. nigricincta* snake targets those sleeping 9 (75.0 %), whereas *B. a. arietans* snakes bite when their victims mostly doing anything else other thank sleeping such walking 3 (35.7%) or play 3 (35.7%). There was no significant difference between the population characteristics of two snake species ($p > 0.05$, Table 5).

Table 5: Epidemiological grouped characteristic of patients bitten by *N. n. nigricincta* and *B. a. arietans.*

Population characteristics	***N. n. nigricincta* (n, %)**	***B. a. arietans* (n, %)**	***p* - value**
Age			0.46
0 – 15 years	7 (58.3)	6 (75.0)	
16 – 30 years	4 (33.3)	-	
31 -45 years	1 (8.3)	2 (25.0)	
Gender			>0.99
Male	9 (75.0)	4 (50.0)	
Female	3 (25.0)	4 (50.0)	
Bite site (Body)			0.53
Head	5 (41.6)	-	
Lower Extremities	2 (16.6)	4 (50.0)	
Upper Extremities	4 (33.3)	3 (37.5)	
Abdomen	-	1 (12.5)	
Genitalia	1 (8.3)		
Season of snakebite			0.06
Summer	11 (91.6)	6 (75.0)	
Autumn	-	1 (12.5)	
Winter	-	1 (12.5)	
Spring	1 (8.3)	-	
Activity of when bitten			0.70
Sleeping	9 (75.0)	1 (12.5)	
Walking	-	3 (37.5)	
Sitting	1 (8.3)	1 (12.5)	
Playing	1 (8.3)	3 (37.5)	
Standing	1 (8.3)	-	
Location of the bite			>0.99
Indoor	10 (83.3)	1 (12.5)	
Outdoor	2 (8.3)	7 (75.0)	
Severity of swelling			0.70
Severe	10 (83.3)	2 (25.0)	
Moderate	2 (16.6)	2 (25.0)	
Mild	-	2 (25.0)	
None	-	2 (25.0)	

4.4. The Regional and Species-Specific Distribution of Snakebites

N. n. nigricincta snakes were more prevalent in Kunene region, which had the highest snakebites incidence of 50 % (6) (Figure 4). Whereas, *B. a. arietans* snakebites were more widespread in Hardap region with 37.5 % (3). Between December 2020 and March 2022, no *N. n. nigricincta* snakebites were reported in the Hardap, Omaheke,

or Erongo regions, and no *B. a. arietans* bites were reported in the Kunene region. Figure 5 illustrate how far apart the regions are from one another, which can cause delays in treatment. This is the case, for example, because the majority of *N. n. nigricincta* snakebites occurred in the Kunune region (Figure 4), and the victims needed to be transported to the Khomas region for more appropriate medical care.

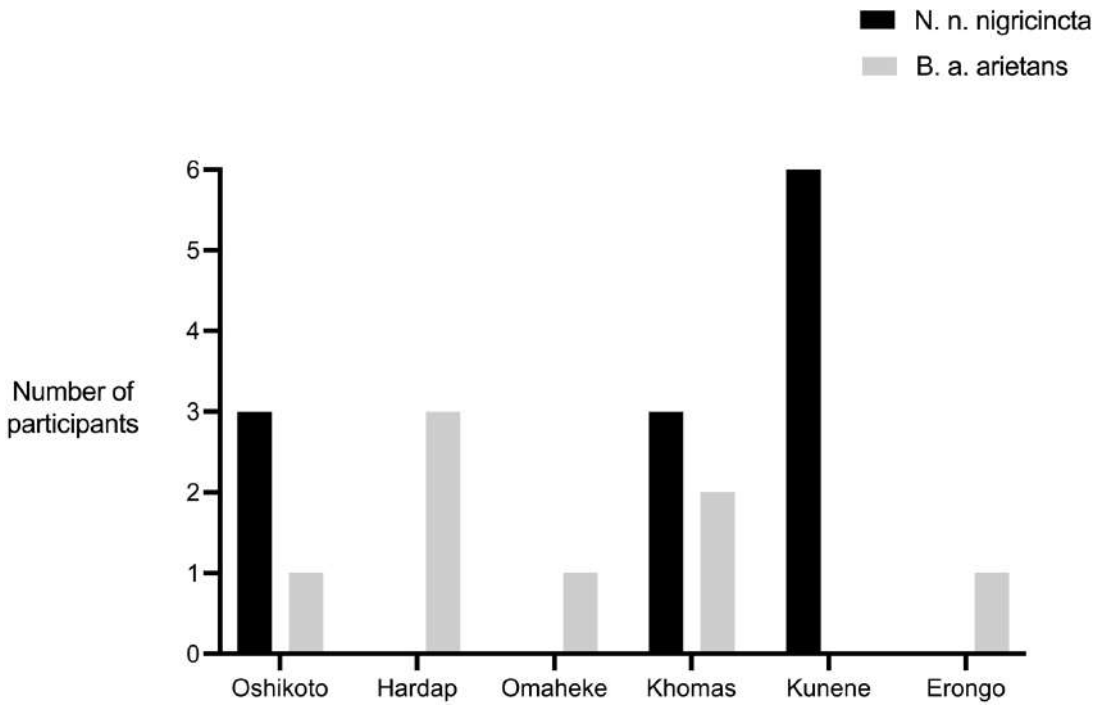


Figure 4: Comparison of snakebites number by *N. n. nigricincta* and *B. a. arietans* by geographical regions

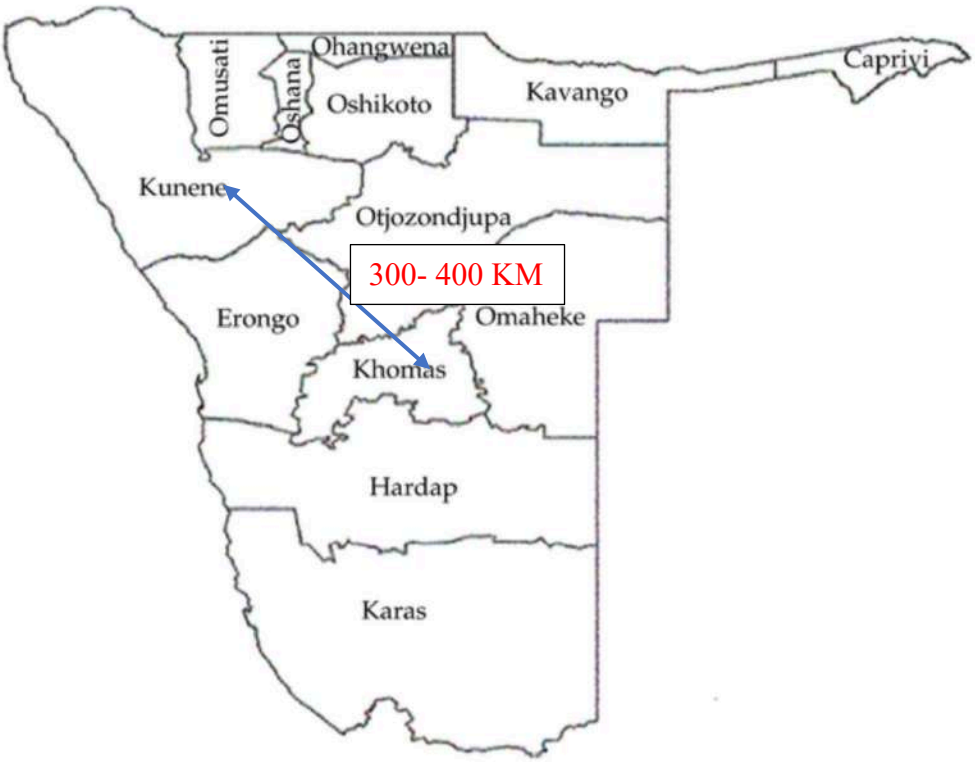


Figure 5: Namibian Map with the different snakebite regions

4.5. The Time Between Patient Getting bitten and Receiving Care

According to this finding, the median time of a bite incident was 16h00 (IQR = 10h25 – 23h00) with a mode of 02h00. Ten patients arrived at the primary health care centre within the first hour of the bite incident (Figure 5). However, the median time taken to get to the primary health care was 1.5 hours (IQR = 1.0 – 4.5 hours). According to the findings, the quickest time it took for patients to reach a primary health centre following a biting incident was 30 minutes, and the longest time it took was two days.

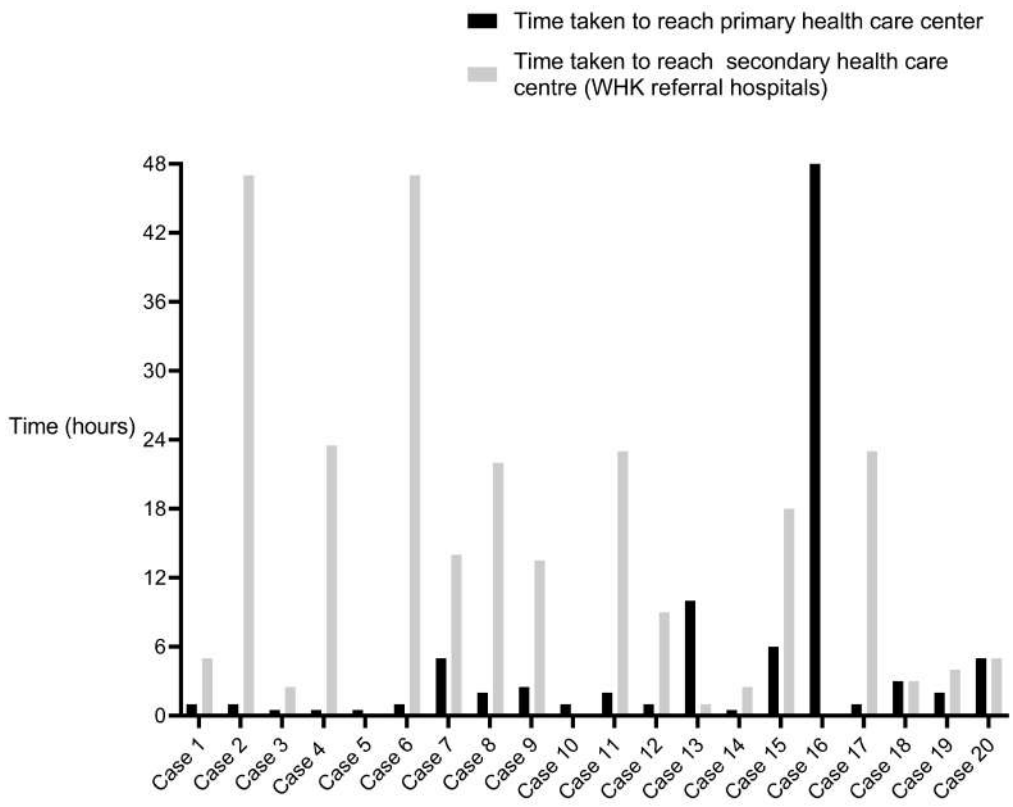


Figure 6: Time taken for the patients to reach both primary and secondary health care facilities.

4.6. Patient Clinical Presentation and History

Case Studies

Case 1: An 11-year-old male was bitten on the face, right supraorbital region, by *N. n. nigricincta* while sleeping on the floor. The incident occurred at 02h00 at a farm in Etosha National Park, about 20 km from Outjo. The patient was rushed to a local hospital within an hour and then transferred to KISH, WHK, where he was admitted to the Acute Care Unit (ACU). He was admitted with significant bilateral supraorbital oedema, respiratory distress, fang marks above the right eye, and skin discoloration around the bite site (Figure 6, D1). There was no antivenom administered to the patient. The patient displayed drowsiness and evidence of hyperaesthesia. His vision and eye movements were normal upon examination. On the second day, he was declared stable, released from the ACU, and admitted to the general ward for additional treatments and observation.

On day one, no laboratory findings were available. The following laboratory findings were obtained on day two (Table 6): Elevated white blood cell count (WBC) 13.9 x 10^9/L (neutrophil count 12.2 x 10^9/L). The red blood cell count (RBC), haemoglobin (Hb), platelets, urea, creatinine, alkaline phosphatase (ALP), and gamma – glutamyl transferase (GGT) levels were all within the normal range. The prothrombin time (PT) was 17.4 seconds (10.2 – 13.2 s), and the international normalised ratio (INR) was 1.55 (0.8 – 1.3). Albumin was decrease 27.0 g/L, while there was an increase in total bilirubin (T-Bili) 29.0 μmol/L, alanine transaminase (ALT) 88.0 IU/L, aspartate transaminase (AST) 451 IU/L, lactate dehydrogenase (LDH) 897 IU/L. Creatine kinase (CK), creatine kinase myocardial band (CK-MB), d-dimer and fibrinogen testing were not carried out. RBC 3.8 x 10^{12} /L, Hb 10.5 x 10^9/L, and HCT 30.4 % levels were all lower on day three. The liver function test (LFT) and CK were not

performed. On day two, a peripheral smear revealed normocytic normochromic anaemia, the presence of spherocytes, WBC indicating neutrophils with toxic granulation, and no blasts. The reticulocyte count was within normal ranges. On day 9 the patient underwent surgical debridement (Figure 6, D9). Necrotic tissue was removed on top of the right eye and from the right upper eyelid. He recovered fully, and was discharged on day 18.

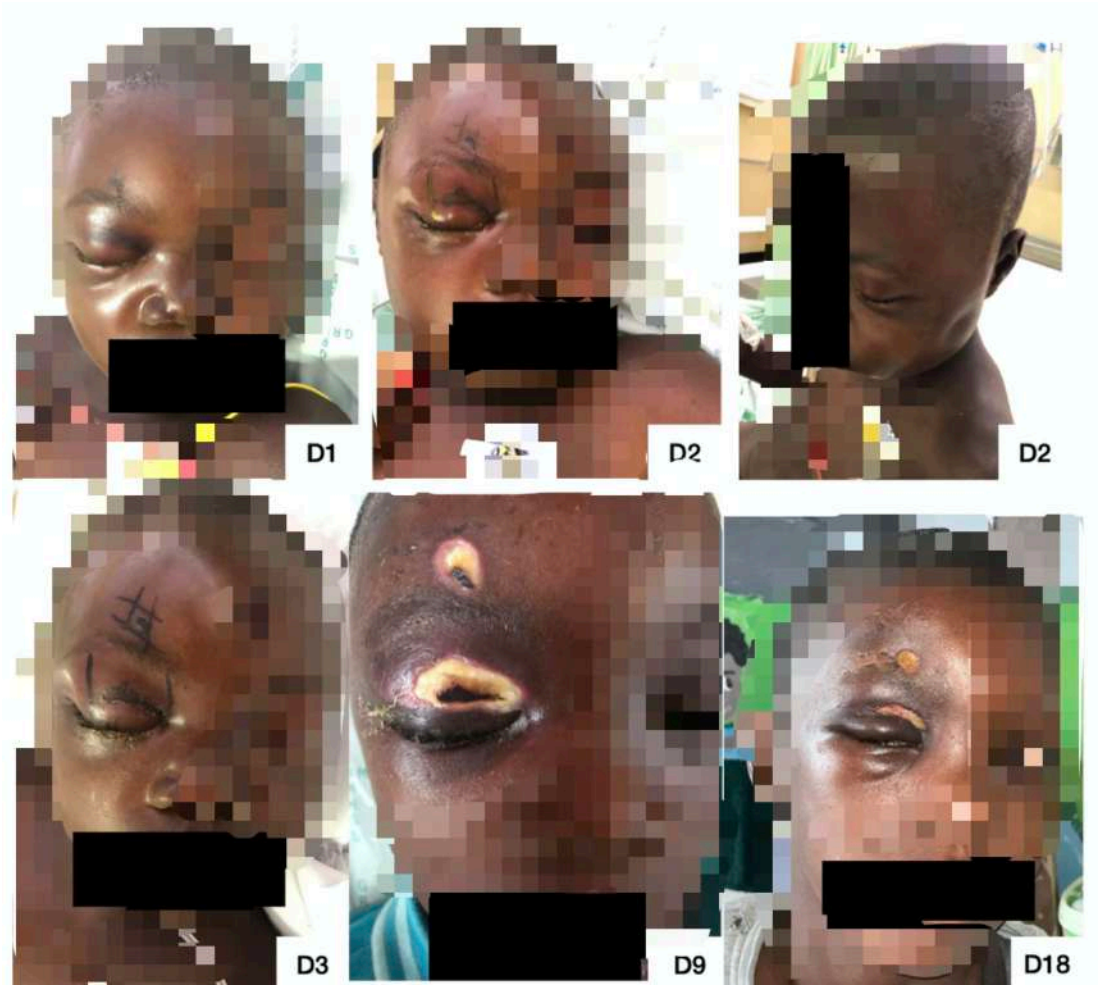


Figure 7: Case 1 Images of patient snakebite wounds.
Wound healing photographs revealed a complete swelling of the face on day one (D1). D2 indicated the growth and extension of necrotic tissue above the right eye (the markings showed many bite marks), and a small modification of the patient's head shape as a result of severe oedema. D3 the oedema began to diminish. D9 necrotic tissue was removed, and the patient was discharged on D18.

Table 6: Case 1 patient laboratory profile

Normal values	**Day 2**	**Day 3**
WBC (4.5 – 13.5 x 10^9/L)	13.9	15.9
RBC (4.0 – 5.0 x 10^{12}/L)	4.3	3.8
Hb (11.5 – 15.5 g/dL)	12.0	10.5
HCT (34.0 – 41.0 %)	33.4	30.4
PLT (173.0 – 360.0 × 10^9/L)	226.0	210.0
Neutrophils (1.5 – 8.0 × 10^9/L)	12.2	13.2
Lymphocytes (1.5 – 6.5 × 10^9/L)	0.7	1.1
Monocytes (0.0 – 0.4 × 10^9/L)	0.9	1.5
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0	0.1
INR (0.8 – 1.3)	1.6	-
PT (10.2 – 13.2 s)	17.4	-
Urea (2.1 – 7.1 mmol/L)	5.4	5.0
Creatinine (26.5 – 88.4 mmol/L)	51.0	47.0
Albumin (36.0 – 51.0 g/L)	27.0	-
T-Bili (0.0 – 20.5 μmol/L)	29.0	-
ALP (103.0 – 373.0 IU/L)	105.0	-
GGT (7.0 – 50.0 IU/L)	10.0	-
ALT (10.0 – 40.0 IU/L)	88.0	-
AST (15.0 – 41.0 IU/L)	451.0	-
LDH (98.0 – 192.0 IU/L)	897.0	-
CK (49.0 – 397.0 IU/L)	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 2: An eight-year-old female was bitten on the fourth toe of her left foot by *B. a. arietans* at 9h00 while walking by the dumpsite in front of the house on a farm 10 km from Rehoboth. Before seeking medical attention, the patient used traditional therapy by applying spirits to the bite site. Within an hour, the patient was transported to a local hospital in Rehoboth, and upon arrival, the patient was given South African Institute for Medical Research (SAIMR) polyvalent antivenom. Due to the patient's poor progression, she was transferred 24 hours after the snakebite event to WCH, WHK. The patient was distressed and in considerable discomfort with moderate oedema on the left foot extending to the leg (Figure 7, D3). There was no indication of necrosis at the fang mark region.

There were no laboratory test results for days one and two. On day three, the patient's laboratory results revealed normal PT and INR values, and an elevated CK level of 446.0 IU/L (Table 7). A full blood count (FBC), a peripheral smear, CK, CK-MB, fibrinogen, d-dimer, and a liver function test (LFT) were not performed. The patient recovered completely, and was discharged on day 10.

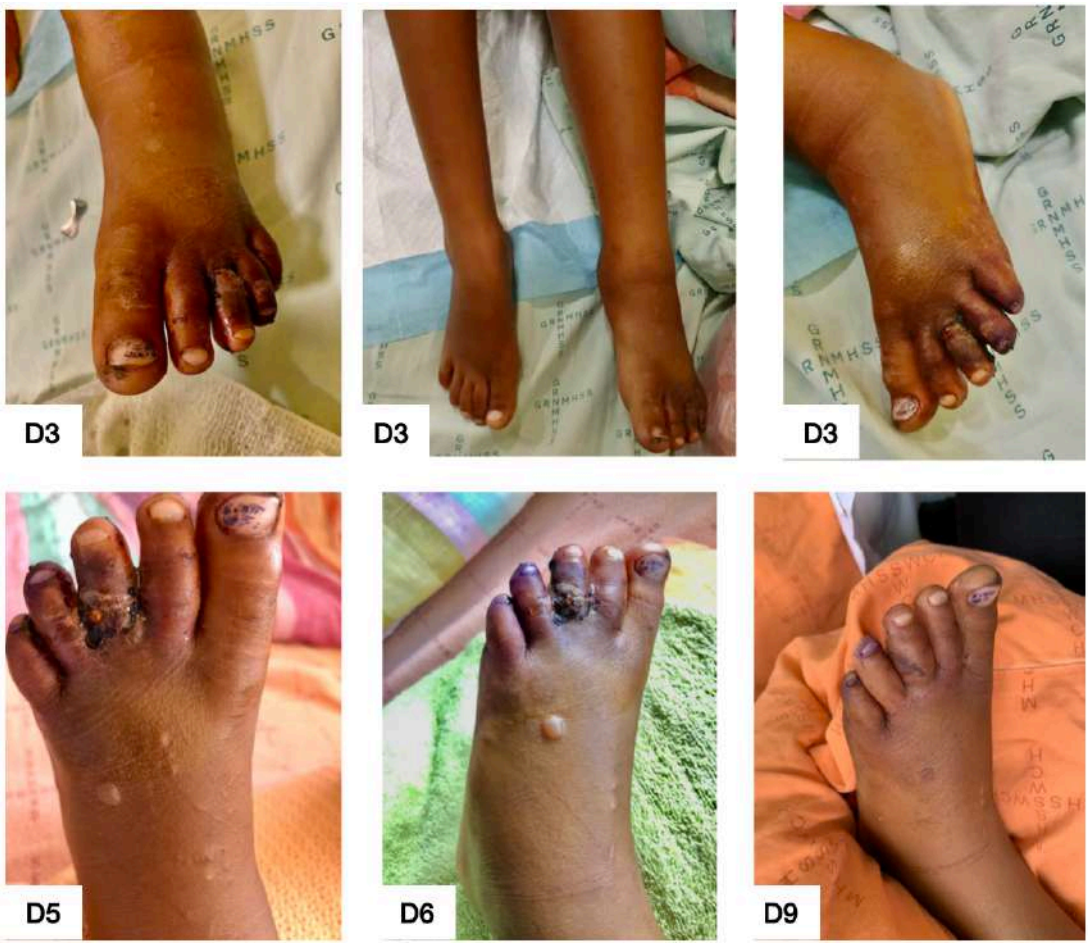


Figure 8: Case 2 Images of patient snakebite wounds.
Wound progression of oedema on the left foot. D3 indicating that oedema has spread to the leg. D5 As a result of the snake venom, blisters formed on the patient's foot. D9 the swelling had gone down and the patient's toe appeared to be healing well.

Table 7: Case 2 patient laboratory profile

Normal values	**Day 3**
WBC (4.5 – 13.5 x 10^9/L)	-
RBC (4.0 – 5.0 x 10^{12}/L)	-
Hb (11.5 – 15.5 g/dL)	-
HCT (34.0 – 41.0 %)	-
PLT (173.0 – 360.0 × 10^9/L)	-
Neutrophils (1.5 – 8.0 × 10^9/L)	-
Lymphocytes (1.5 – 6.5 × 10^9/L)	-
Monocytes (0.0 – 0.4 × 10^9/L)	-
Eosinophils (0.0 – 0.5 × 10^9/L)	-

Normal values	Day 3
INR (0.8 – 1.3)	1.1
PT (10.2 – 13.2 s)	13.3
Urea (2.1 – 7.1 mmol/L)	-
Creatinine (26.5 – 88.4 mmol/L)	-
Albumin (36.0 – 51.0 g/L)	-
T-Bili (0.0 – 20.5 μmol/L)	-
ALP (103.0 – 373.0 IU/L)	-
GGT (7.0 – 50.0 IU/L)	-
ALT (10.0 – 40.0 IU/L)	-
AST (15.0 – 41.0 IU/L)	-
LDH (98.0 – 192.0 IU/L)	-
CK (49.0 – 397.0 IU/L)	446.0
CK-MB (0.0 – 4.8 ng/mL)	-
D-dimer (0.0 - 230.0 ng/mL)	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 3: A 45-year-old male was bitten by *B. a. arietans* on the distal end of his right third finger while sitting under a tree herding cattle, at 10h00 on a farm in Dordabis. The patient was taken to a local clinic within 30 minutes. Three hours after the bite incident, the patient was transferred to KISH, WHK. The patient presented with a slightly swollen right finger (Figure 8, D1) and was in a lot of pain. Despite no documented family history of hypertension, the patient had an extremely high blood pressure. The patient developed cellulitis and significant oedema on his right finger on the second day (Figure 8, D2).

The patients' laboratory results on the first day were as follows (Table 8): Elevated WBC 12.3 x 10^9/L (neutrophil count 11.0 x 10^9/L). The RBC, Hb, HCT, urea, creatinine, PT, and INR levels were all within the normal range. Platelets were reduced

to 153.0 x 10^9/L. CK and LFT testing were not performed. On days three and four, only urea and creatinine were measured, and both were within normal limits. On day six, the FBC, urea, and creatinine levels were all normal. No LFT, CK, CK-MB, d-dimer, fibrinogen, peripheral, or retics smears were performed on any of the days the patient was hospitalised. The patient received SAIMR polyvalent antivenom two days after the snakebite; nonetheless, there was no improvement, and the tip of the right finger was rapidly becoming necrotic and extending all the way down the finger. As a result, the finger was amputated, and the patient was discharged on day 12.

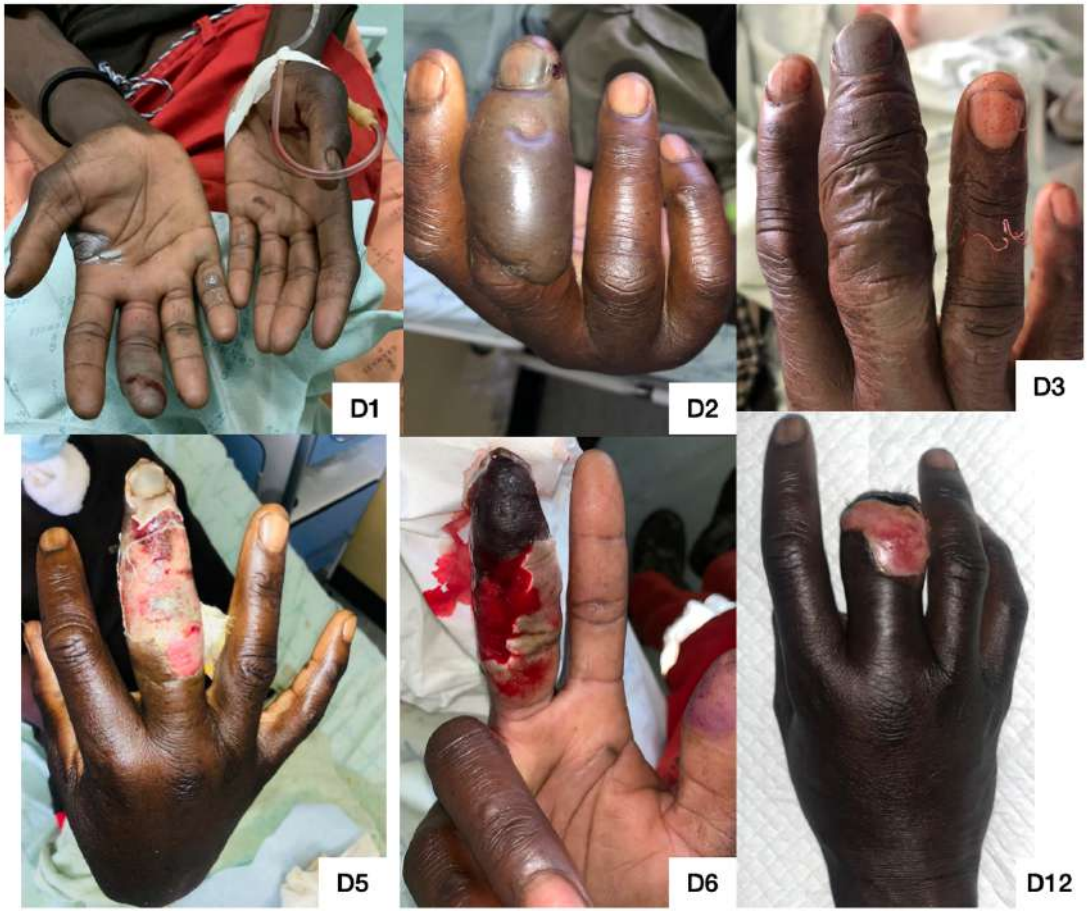


Figure 9: Case 3 Images of patient snakebite wounds.
D1 illustrated images of the wound obtained on the day of occurrence, demonstrating a small amount of oedema. D2 denoted fluid accumulation, which resulted in severe oedema. D3 the incision began to drain spontaneously. D6 indicated the spread of necrotic downwards the finger. D12 image after the patient's right index finger was amputated.

Table 8: Case 3 patient laboratory profile

Normal values	**Day 1**	**Day 3**	**Day 4**	**Day 6**
WBC (3.4 – 8.9 x 10^9/L)	12.3	-	-	7.9
RBC (4.0 – 6.0 x 10^{12}/L)	4.8	-	-	5.5
Hb (13.2 – 16.6 g/dL)	14.3	-	-	16.2
HCT (43.2 – 54.5 %)	43.7	-	-	50.1
PLT (173.0 – 360.0 × 10^9/L)	153.0	-	-	209.0
Neutrophils (1.5 – 8.0 × 10^9/L)	11.0	-	-	5.0
Lymphocytes (1.0 – 4.0 × 10^9/L)	0.7	-	-	2.0
Monocytes (0.2 – 0.8 × 10^9/L)	0.6	-	-	0.5
Eosinophils (0.0 – 0.4 × 10^9/L)	0.1	-	-	0.4
INR (0.8 – 1.3)	0.9	-	-	-
PT (10.2 – 13.2 s)	10.9	-	-	-
Urea (2.1 – 7.1 mmol/L)	-	2.6	3.1	4.5
Creatinine (62.0 – 106.0 mmol/L)	-	77.0	74.0	86.0
Albumin (36.0 – 51.0 g/L)	-	-	-	-
T-Bili (0.0 – 20.5 μmol/L)	-	-	-	-
ALP (32.0 – 91.0 IU/L)	-	-	-	-
GGT (7.0 – 50.0 IU/L)	-	-	-	-
ALT (10.0 – 40.0 IU/L)	-	-	-	-
AST (15.0 – 41.0 IU/L)	-	-	-	-
LDH (98.0 – 192.0 IU/L)	-	-	-	-
CK (49.0 – 397.0 IU/L)	-	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 4: A four-year-old male was bitten on the left fifth digit (pinkie) by *B. a. arietans* in the late afternoon at 14h00. The incident occurred on a farm in Khorixas, as he extended his hand in an attempt to catch the snake. The patient was rushed to a local hospital within 30 minutes of the snakebite incident and later transferred to KISH the following day. The patient presented with oedema of the fifth digit, in addition to moderate neurological symptoms such as drowsiness, limb weakness, and decreased vision. No antivenom was administered to the patient. The swelling subsided on day five, and the patient was discharged on day six (Figure 9). There were no blood laboratory tests performed on the patient. The patient's hand or finger sustained no injury, he recovered completely.

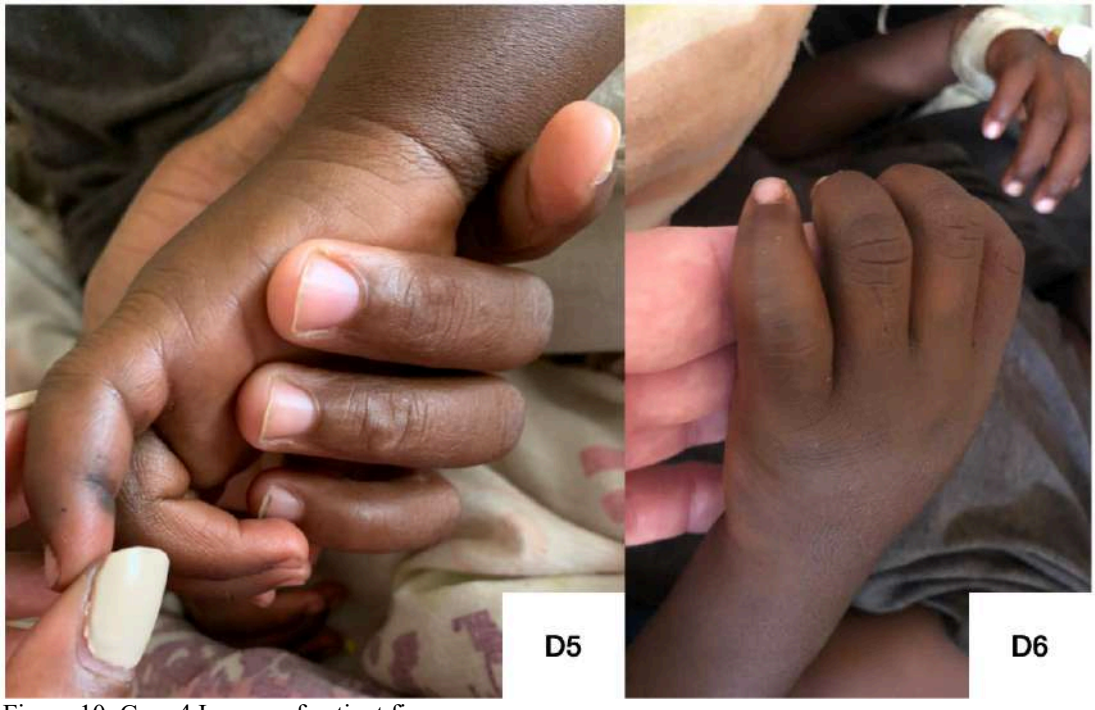


Figure 10: Case 4 Images of patient finger.
D5 indicated patients' bite marks on the left little finger which demonstrated slight necrosis. D6 illustrated swelling of the left little finger.

Case 5: A 29-year-old male was bitten by *N. n. nigricincta* on the left foot slightly below the ankle, at 11h00. The event occurred while standing in his bedroom in Greenwell Matongo, Katutura, Windhoek. The patient was admitted to KISH within 30 minutes, presenting with oedema in his left foot, as well as necrosis around the fang marks on his ankle. The patient displayed drowsiness and limb weakness. The necrotic area was becoming worse and expanded on the third day following the bite incident (Figure 10, D3), necessitating debridement and fasciotomy on day five (Figure 10, D5).

On the first day, only FBC, CK, urea, and creatinine levels were measured, and the patients' laboratory results were as follows (Table 9): WBC count was elevated with 15.8 x 10^9/L (neutrophil count was 13.2 x 10^9/L). RBC, Hb, HCT, platelets, urea, and creatinine levels were all within normal limits. The level of CK was raised by 573.0 IU/L. On day two, the FBC was not performed, but the PT was elevated with 16.9 s and the INR was also elevated by 1.4. WBC was still elevated 10.4 x 10^9/L on day three, as was CK 1712.0 IU/L. RBC, Hb, HCT, urea, and creatinine levels were all normal. On day seven the following parameters dropped, CK to 434 IU/L, RBC to 4.1 x 10^{12} /L, Hb to 11.6 x 10^9/L, and HCT to 35.3 %. WBC levels were within normal limits. Only the FBC test was performed on day nine, and both the WBC 11.0 x 10^9/L and platelet count 460 x 10^9/L became elevated. The levels of RBC, Hb, and HCT remained low. No LFT, CK-MB, d-dimer, fibrinogen, and peripheral or retics smear was performed on any of the days the patient was hospitalised. No antivenom was administered to the patient. On day 35 the patient underwent wound closure and skin graft. As a result, the patient was discharged with muscle weakness on day 41.

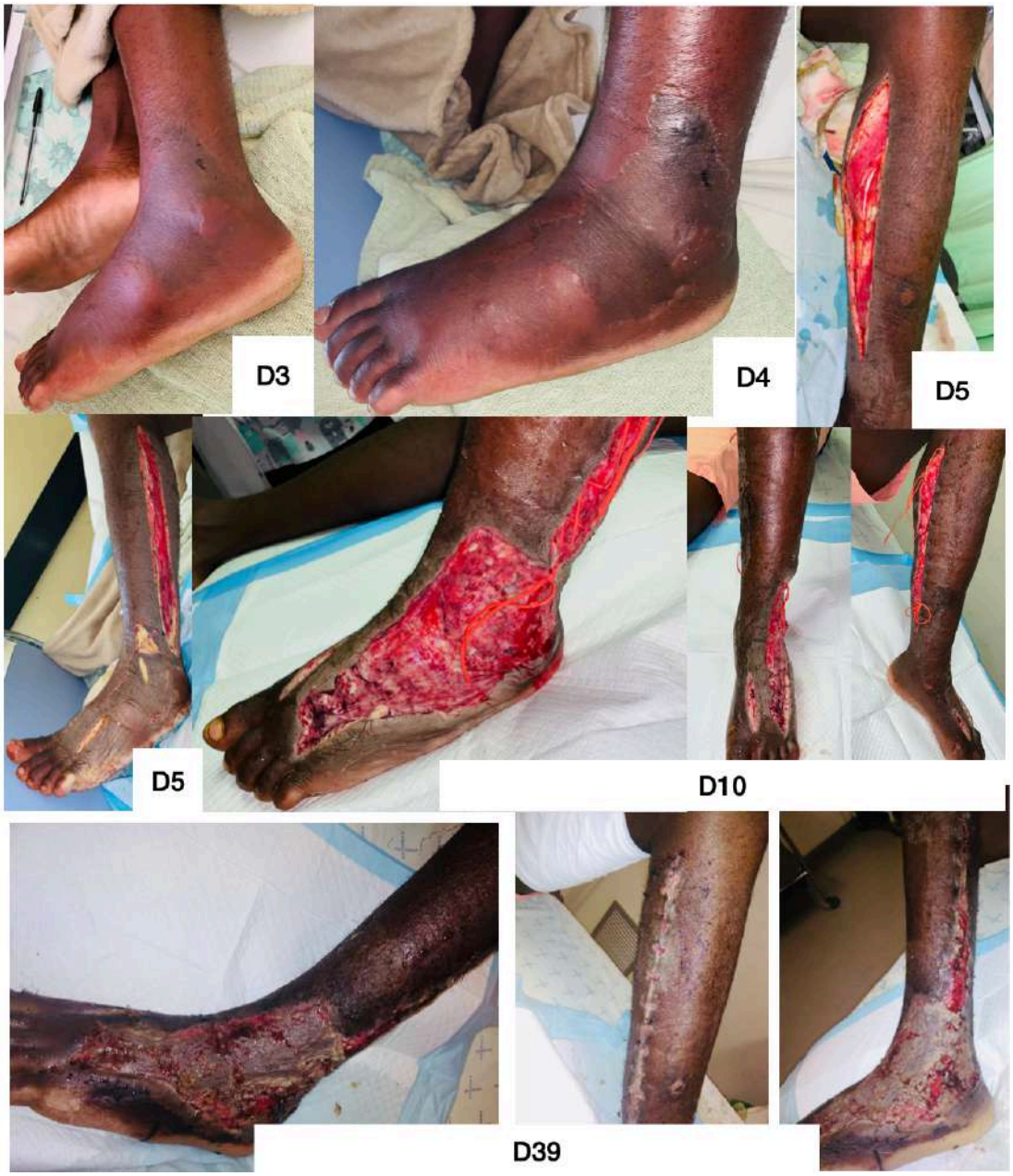


Figure 11: Case 5 Images of patient snakebite wounds.
D3 severe oedema with necrotic tissue around the fang marks on the left foot. D4 demonstrated the formation of blisters and the spread of necrotic tissue. D5 was after the patient underwent surgical debridement and fasciotomy procedure. D10 indicated how much necrotic tissue was removed. D39 depicts four days after the skin graft and wound closure was applied.

Table 9: Case 5 patient laboratory profile

Normal values	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**Day 9**
WBC (3.4 – 8.9 x 10^9/L)	15.8	-	10.4	8.8	11.0
RBC (4.0 – 6.0 x 10^{12}/L)	5.6	-	5.2	4.1	4.0
Hb (13.2 – 16.6 g/dL)	15.8	-	14.9	11.6	11.2
HCT (43.2 – 54.5 %)	51.0	-	46.5	35.3	34.2
PLT (173.0 – 360.0 × 10^9/L)	223.0	-	218.0	260.0	460.0
Neutrophils (1.5 – 8.0 × 10^9/L)	13.2	-	8.3	5.9	7.7
Lymphocytes (1.0 – 4.0 × 10^9/L)	2.0	-	1.5	1.9	2.4
Monocytes (0.2 – 0.8 × 10^9/L)	0.6	-	0.5	0.9	0.7
Eosinophils (0.0 – 0.4 × 10^9/L)	0.0	-	0.0	0.0	0.1
INR (0.8 – 1.3)	-	1.4	-	-	-
PT (10.2 – 13.2 s)	-	16.9	-	-	-
Urea (2.1 – 7.1 mmol/L)	4.7	-	3.5	< 2.5	-
Creatinine (62.0 – 106.0 mmol/L)	93.0	-	87.0	61.0	-
Albumin (36.0 – 51.0 g/L)	-	-	-	-	-
T-Bili (0.0 – 20.5 μmol/L)	-	-	-	-	-
ALP (103.0 – 373.0 IU/L)	-	-	-	-	-
GGT (7.0 – 50.0 IU/L)	-	-	-	-	-
ALT (10.0 – 40.0 IU/L)	-	-	-	-	-
AST (15.0 – 41.0 IU/L)	-	-	-	-	-
LDH (98.0 – 192.0 IU/L)	-	-	-	-	-
CK (49.0 – 397.0 IU/L)	573.0	-	1712.0	434.0	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 6: An 11-year-old male was bitten on the right fifth digit by *N. n. nigricincta* around 24h00 midnight. The patient was sleeping on the floor in a shack on a farm 45 km from Outjo when the tragedy occurred. The patient was transported to Outjo State Hospital within an hour, hospitalised, and immediately underwent early debriding. After two days of observation, the patient was transferred to KSH due to severe oedema, and blistering around the hand (Figure 11, D4). The patient was drowsy and had limb weakness.

For the first and second days, there were no laboratory results. The only parameters examined in the patient's laboratory profile were the patient's FBC, urea level, and creatinine level. Thus, the laboratory results obtained for day three (Table 10): An elevated WBC count was 14.4 x 10^9/L and neutrophil count with 12.1 x 10^9/L. The levels of RBC, Hb, HCT, urea, and creatinine were all within normal ranges. Platelets were increased by 375.0 x 10^9/L On day 28, HCT was 41.3 %, and platelets were 544.0 x 10^9/L of which both were elevated. On day 43, only the platelet count was elevated (738.0 x 10^9/L). No LFT, CK, CK-MB, d-dimer, fibrinogen, peripheral, or retics smears were performed on any of the days the patient was hospitalised. Fasciotomy was performed on day four following the bite; nevertheless, the patient's right fifth finger was severely necrotic (Figure 11, D24), and the right fifth digit was amputated (Figure 11, D39).

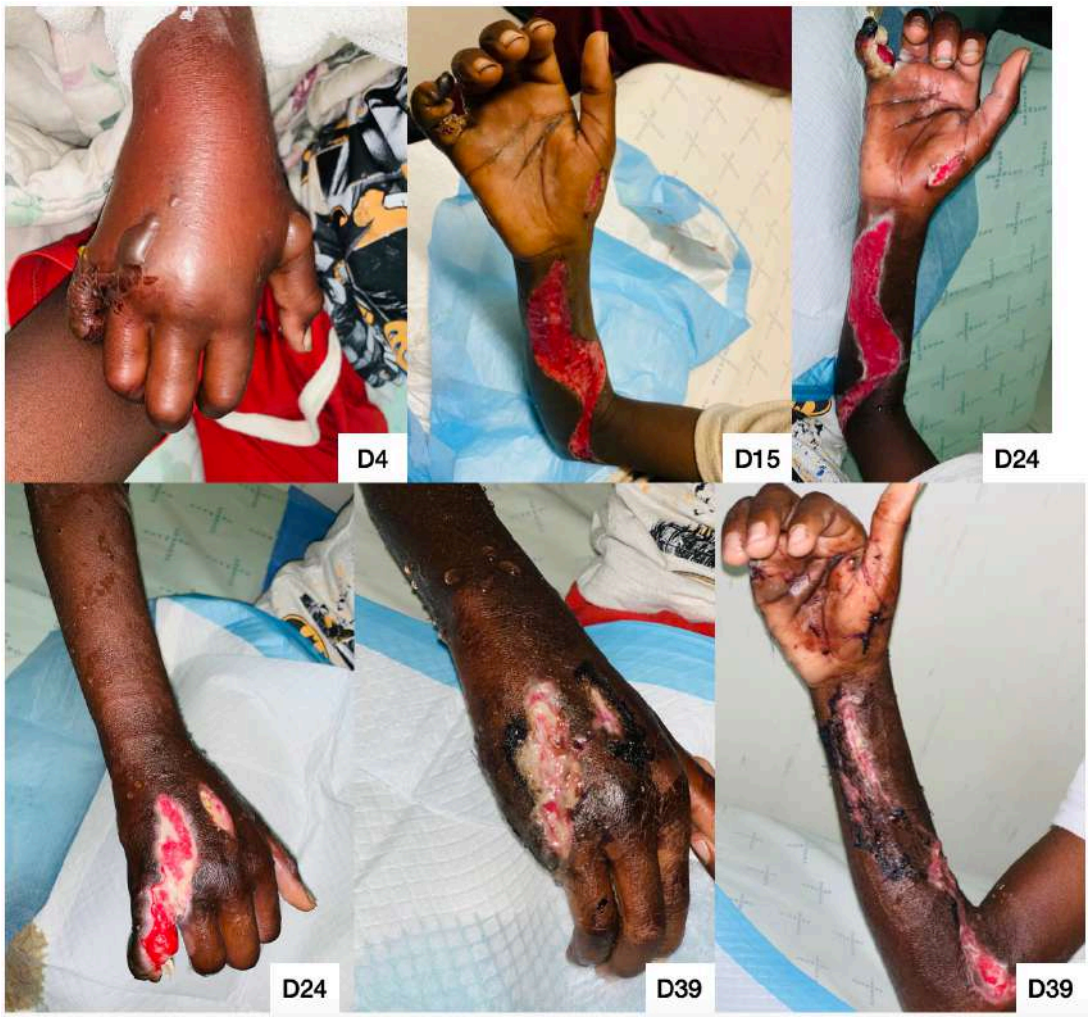


Figure 12: Case 6 Images of patient snakebite wounds.
The D4 image showed the formation of blisters on the right hand. D15 and D24 represent wound healing following a fasciotomy and debridement surgical procedure, however pinkie was still necrotic. D39 represented the end result after the fifth finger was amputated.

Table 10: Case 6 patient laboratory profile

Normal values	**Day 3**	**Day 28**	**Day 43**
WBC (4.5 – 13.5 x 10^9/L)	14.4	5.9	9.0
RBC (4.0 – 5.0 x 10^{12}/L)	4.4	4.9	4.4
Hb (11.5 – 15.5 g/dL)	12.6	13.1	11.9
HCT (34.0 – 41.0 %)	35.6	41.3	37.9
PLT (173.0 – 360.0 × 10^9/L)	375.0	544.0	738.0
Neutrophils (1.5 – 8.0 × 10^9/L)	12.1	2.7	5.1
Lymphocytes (1.5 – 6.5 × 10^9/L)	1.7	2.5	3.1
Monocytes (0.0 – 0.4 × 10^9/L)	0.6	0.6	0.6

Normal values	Day 3	Day 28	Day 43
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0	0.1	0.2
INR (0.8 – 1.3)	-	-	-
PT (10.2 – 13.2 s)	-	-	-
Urea (2.1 – 7.1 mmol/L)	2.3	5.3	4.7
Creatinine (26.5 – 88.4 mmol/L)	38.0	43.0	46.0
Albumin (36.0 – 51.0 g/L)	-	-	-
T-Bili (0.0 – 20.5 μmol/L)	-	-	-
ALP (103.0 – 373.0 IU/L)	-	-	-
GGT (7.0 – 50.0 IU/L)	-	-	-
ALT (10.0 – 40.0 IU/L)	-	-	-
AST (15.0 – 41.0 IU/L)	-	-	-
LDH (98.0 – 192.0 IU/L)	-	-	-
CK (49.0 – 397.0 IU/L)	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT= platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 7: A five-year-old male was bitten on the right foot by *B. a. arietans* while walking through the yard on a farm 110 km north of Rehoboth at 14h00. The patient was admitted to St. Mary's Hospital in Rehoboth 5 hours after the snakebite event and then transferred to KISH in Windhoek the following day. Upon admission to KISH, the patient underwent urgent surgical debridement (Figure 12).

There were no laboratory results on day one to day four. Only FBC, urea, and creatinine levels were measured in the patient. On day five, initial blood results revealed (Table 11), a normal WBC, RBC, Hb, HCT, platelets, urea, and creatinine levels, and a low Hb of 10.4 x 10^9/L. On day 30, urea was 4.1 mmol/L and creatinine was 66.0 mmol/L, both of which were normal. On day 32, only HCT (40.4 %) was

elevated, while platelets (129.0 x 10^9/L) decreased. HCT remained increased (42.6 %) on day 43. On any of the days the patient was hospitalised, no LFT, CK, CK-MB, d-dimer, fibrinogen, and peripheral or retics smears were performed. The patient received no antivenom. The wound was monitored, and the patient was discharged on day 43 with muscle weakness as a consequence.

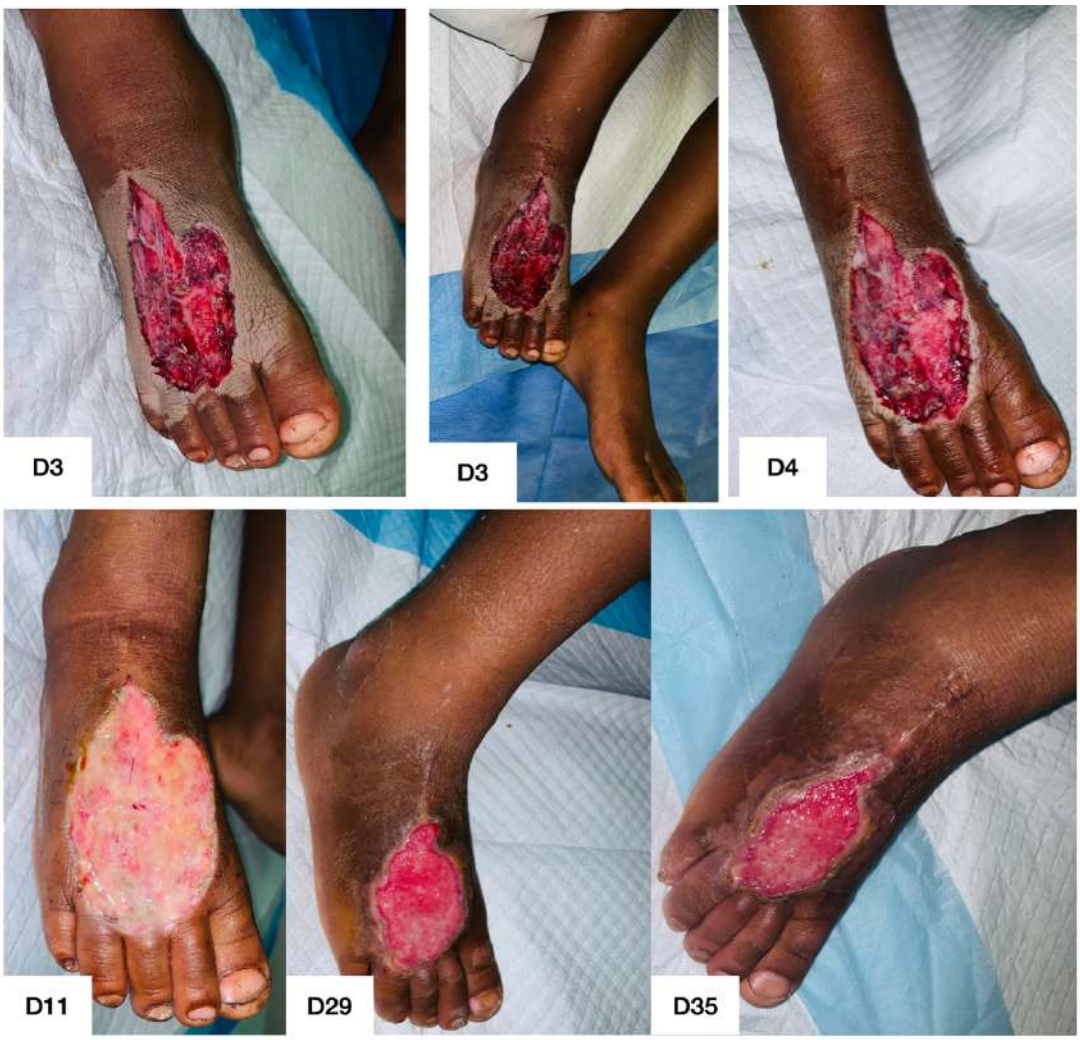


Figure 13: Case 7 Images of patient snakebite wounds.
D3 Images illustrate wound healing after surgical debridement. D11 the edges of the wound were rolled.

Table 11: Case 7 patient laboratory profile

Normal values	**Day 5**	**Day 30**	**Day 32**	**Day 34**
WBC (5.5 – 15.5 x 10^9/L)	6.9	-	11.6	9.4
RBC (3.9 – 5.3 x 10^{12}/L)	4.0	-	4.9	4.9

Normal values	Day 5	Day 30	Day 32	Day 34
Hb (11.5 – 13.5 g/dL)	10.4	-	13.2	13.2
HCT (31.0 – 39.0 %)	34.6	-	40.4	42.6
PLT (173.0 – 360.0 × 10^9/L)	204.0	-	129.0	282.0
Neutrophils (1.5 – 8.5 × 10^9/L)	4.4	-	6.8	4.4
Lymphocytes (2.0 – 8.0 × 10^9/L)	1.9	-	3.7	3.4
Monocytes (0.1 – 1.1 × 10^9/L)	0.4	-	0.8	0.7
Eosinophils (0.0 – 0.7 × 10^9/L)	0.2	-	0.3	0.3
INR (0.8 – 1.3)	-	-	-	-
PT (10.2 – 13.2 s)	-	-	-	-
Urea (1.7 – 8.3 mmol/L)	2.8	4.1	-	3.1
Creatinine (26.5 – 88.4 mmol/L)	38.0	66.0	-	28
Albumin (36.0 – 51.0 g/L)	-	-	-	-
T-Bili (0.0 – 20.5 μmol/L)	-	-	-	-
ALP (103.0 – 373.0 IU/L)	-	-	-	-
GGT (7.0 – 50.0 IU/L)	-	-	-	-
ALT (10.0 – 40.0 IU/L)	-	-	-	-
AST (15.0 – 41.0 IU/L)	-	-	-	-
LDH (98.0 – 192.0 IU/L)	-	-	-	-
CK (49.0 – 397.0 IU/L)	-	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 8: A 9-year-old female was bitten on the right wrist by *N. n. nigricincta* while sleeping at 2h00. The incident happened on a farm in Okaukuejo, Etosha, about 70 km from Outjo. The patient was transported to Outjo State Hospital within two hours and then transferred to KISH the next morning. Upon arrival at KISH the patient underwent urgent surgical fasciotomy (Figure 13). The patient displayed drowsiness and limb weakness.

There were no laboratory results on day one. The following were the patients' laboratory results on day two (Table 12) in the morning: An elevated WBC count 14.7 x 10^9/L, neutrophil 11.7 x 10^9/L, ALT 33.0 IU/L, AST 72.0 IU/L, LDH 406.0 IU/L, and CK-MB 12.1 ng/mL. The levels of RBC, Hb, HCT, platelets, urea, creatinine, albumin, T-Bili, ALP, and GGT were all within normal ranges. Prolonged PT of 19.1 seconds and a high INR of 1.6. On Day two in the evening, the FBC, PT, INR, and urea levels were all within normal ranges. Creatinine was decreased 24.0 mmol/L, and there were no LFT or CK-MB results. No CK, d-dimer, fibrinogen, and peripheral or retics smears were performed on any of the days the patient was hospitalised. No antivenom was administered to the patient. The patient's wound and swelling were monitored, and six days following the fasciotomy, she had wound closure (Figure 13, D10). The patient was discharged on day 14 with muscle weakness.

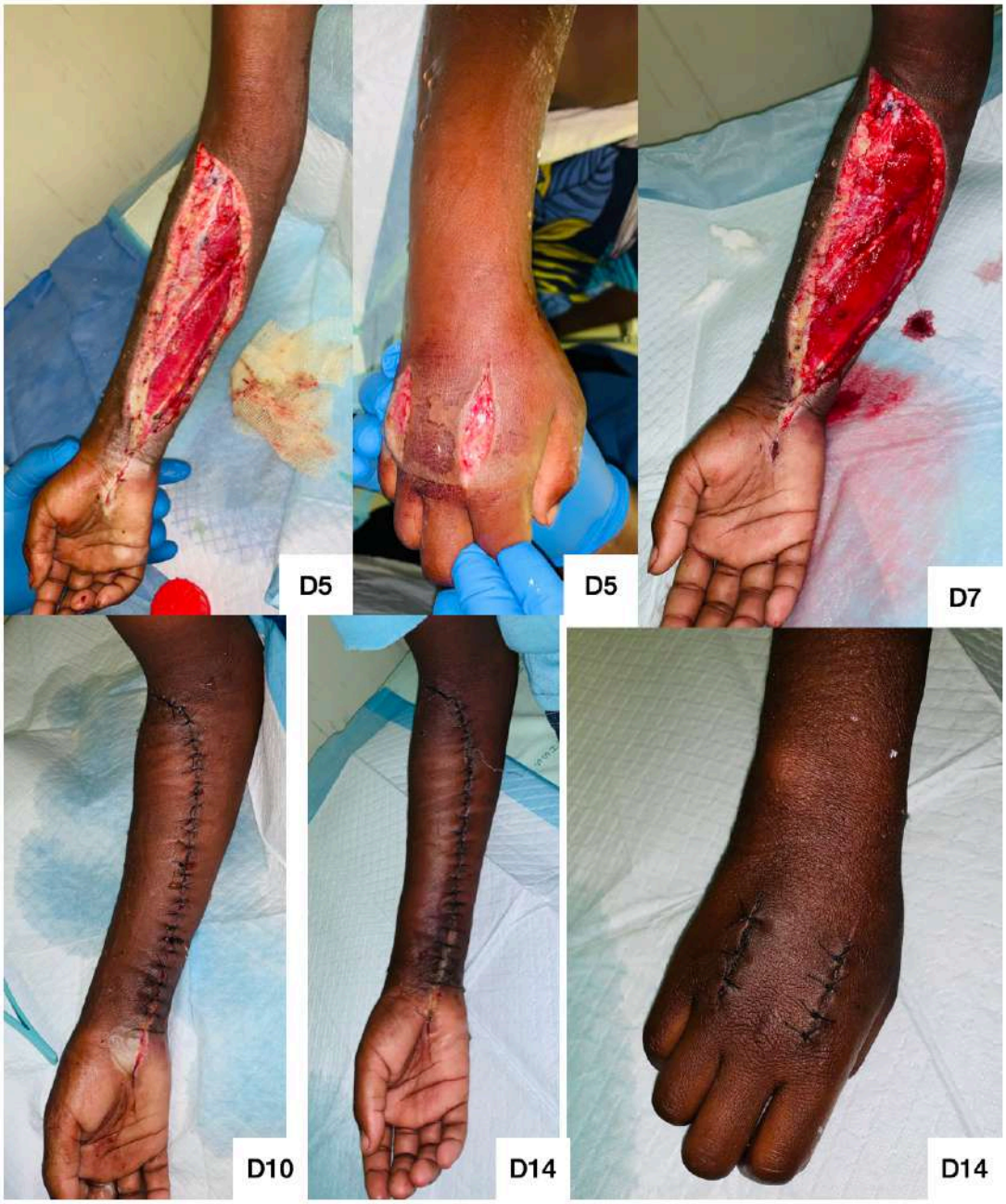


Figure 14: Case 8 Images of patient snakebite wounds.
The D5 images wound progression after a surgical debridement procedure was performed. D10 and D14 indicate wound closure and swelling reduction.

Table 12: Case 8 patient laboratory profile

Normal values	**Day 2 - morning**	**Day 2 - evening**
WBC (5.0 – 14.5 x 10^9/L)	14.7	14.4
RBC (4.0 – 5.0 x 10^{12}/L)	4.5	4.7
Hb (11.5 – 15.5 g/dL)	11.7	12.4
HCT (31.0 – 39.0 %)	36.6	36.4

Normal values	Day 2 - morning	Day 2 - evening
PLT (173.0 – 360.0 × 10^9/L)	396.0	355.0
Neutrophils (1.5 – 8.0 × 10^9/L)	11.7	11.8
Lymphocytes (1.5 – 6.5 × 10^9/L)	1.8	1.4
Monocytes (0.0 – 0.4 × 10^9/L)	1.2	1.2
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0	0.0
INR (0.8 – 1.3)	1.6	1.1
PT (10.2 – 13.2 s)	19.1	11.3
Urea (2.1 – 7.1 mmol/L)	4.4	4.5
Creatinine (26.5 – 88.4 mmol/L)	48.0	24.0
Albumin (36.0 – 51.0 g/L)	36.0	-
T-Bili (0.0 – 20.5 μmol/L)	13.0	-
ALP (118.0 – 360.0 IU/L)	324.0	-
GGT (6.0 – 19.0 IU/L)	9.0	-
ALT (11.0 – 28.0 IU/L)	33.0	-
AST (21.0 – 36.0 IU/L)	72.0	-
LDH (142.0 – 261.0 IU/L)	406.0	-
CK (49.0 – 397.0 IU/L)	-	-
CK-MB (0.0 – 4.8 ng/mL)	12.1	-
D-dimer (0.0 - 230.0 ng/mL)	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatinine kinase myocardial band.

Case 9: A 28-year-old male was bitten by *N. n. nigricincta* while sleeping naked on the floor with his partner at midnight. The incident occurred on a farm in Okaukuejo, Etosha, around 70 km from Outjo. Prior to obtaining medical attention, the patient was compelled into drinking fuel as a traditional remedy shortly after being bitten by the snake. Two hours and thirty minutes later, the patient arrived at the local hospital with acute penile and testicular oedema (Fig 14, D1). He was given a steroid injection and shortly thereafter began vomiting and had diarrhoea. The patient was subsequently

transferred to WCH urology department, where he arrived 16 hours after the snakebite event. The patient received antivenom SAIMR polyvalent. The bite site was necrotic, and with each passing day, the necrosis grew in size, necessitating debridement on day seven (Figure 14, D6 & D8).

On day one, the patients' laboratory results were as follows (Table 13): Elevated neutrophil count 15.0 x 10^9/L and WBC count 16.6 x 10^9/L. RBC, Hb, HCT, platelets, urea, creatinine, albumin, ALP, GGT, and ALT levels were all within normal limits. Prolonged PT of 19.1 s, and high INR of 1.6. T-Bili was 25.0umol/L, AST was 73.0 IU/L, LDH was 370.0 IU/L, and CK-MB was 20.8 ng/mL, all of which were elevated. On day three, PT was still prolonged (14.5 seconds), and a normal INR (1.2), urea (2.5mmol/L) and creatinine (72.0 mmol/L). On day three, no LFT, CK-MB, or FBC were performed. On days four and 26, RBC x 10^{12}/L and HCT levels were both reduced, and no LFT or CK-MB tests were performed on the patient. On any of the days that the patient was hospitalised, no CK, d-dimer, fibrinogen, and peripheral or retics smears were performed. Patient underwent a skin graft on day 31. The patient has made a complete recovery, and was discharged on day 38.

Figure 15: Case 9 Images of patient snakebite wounds.
D1 image taken two hours and thirty minutes after the incident, illustrating fang marks on the superficial fascia of the penis, with the area surrounding the bite marks being darker than the rest of the genital area. D2 illustration of gradual penis swelling that has progressed to the scrotum, as well as the appearance of bleeding signs at the bite sites. D3 the skin peeled off, revealing the fang mark on the penis and the darker zone extending into the scrotum. D6 necrosis developed on the sixth day. D8 following the debridement operation. D37 was taken after the patient underwent successful skin graft operation.

Table 13: Case 9 patient laboratory profile

Normal values	**Day 1**	**Day 3**	**Day 4**	**Day 6**	**Day 26**
WBC (3.8 – 8.8 x 10^9/L)	16.6	-	8.7	7.9	6.0
RBC (4.5 – 6.0 x 10^{12}/L)	4.8	-	4.4	5.5	4.4
Hb (13.2 – 16.6 g/dL)	15.1	-	13.4	16.2	13.3
HCT (43.2 – 54.5 %)	45.6	-	40.1	50.1	41.0
PLT (173.0 – 360.0 × 10^9/L)	216.0	-	216.0	209.0	240.0
Neutrophils (2.0 – 7.5 × 10^9/L)	15.0	-	5.3	5.0	2.7
Lymphocytes (1.0 – 4.0 10^9/L)	0.6	-	2.3	2.0	2.6
Monocytes (0.2 – 0.8 × 10^9/L)	1.1	-	0.9	0.5	0.5
Eosinophils (0.0 – 0.4 × 10^9/L)	0.0	-	0.2	0.4	0.2
INR (0.8 – 1.3)	-	1.2	-	-	-

Normal values	Day 1	Day 3	Day 4	Day 6	Day 26
PT (10.2 – 13.2 s)	-	14.5	-	-	-
Urea (2.1 – 7.1 mmol/L)	4.1	2.5	2.8	4.5	4.1
Creatinine (62.0 – 106.0 mmol/L)	74.0	72.0	68.0	86.0	74.0
Albumin (35.0 – 50.0 g/L)	44.0	-	-	-	-
T-Bili (0.0 – 20.5 μmol/L)	25.0	-	-	-	-
ALP (32.0 – 91.0 IU/L)	72.0	-	-	-	-
GGT (7.0 – 50.0 IU/L)	18.0	-	-	-	-
ALT (10.0 – 40.0 IU/L)	33.0	-	-	-	-
AST (15.0 – 41.0 IU/L)	73.0	-	-	-	-
LDH (98.0 – 192.0 IU/L)	370.0	-	-	-	-
CK (49.0 – 397.0 IU/L)	-	-	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	20.8	-	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 10: A two-year-old male was bitten on the left leg by *N. n. nigricincta* while playing in the yard on a farm at Dan Viljoen in WHK at 15h00. The patient was admitted to WCH with severe leg oedema, necessitating an urgent fasciotomy and debridement. The patient displays drowsiness and limb weakness.

The patient's laboratory parameters that were measured were the FBC, CK, urea, and creatinine levels (Table 14). On the first day, preliminary blood results revealed a low Hb of 10.4 x10^9/L and creatine of 20.0 μmol/L. The levels of WBC, RBC, Hb, HCT, platelets, CK, and urea were all within normal ranges. On day two, all FBC parameters were normal, and no CK, urea, or creatinine tests were performed. No PT, INR, Fibrinogen, LFT, CK, CK-MB, d-dimer, and peripheral or retics smears were performed on any of the days the patient was hospitalised. Antivenom was not

administered to the patient. The wound was monitored, and the patient was discharged on day 30 with leg muscle weakness as a consequence (Figure 15, D30).

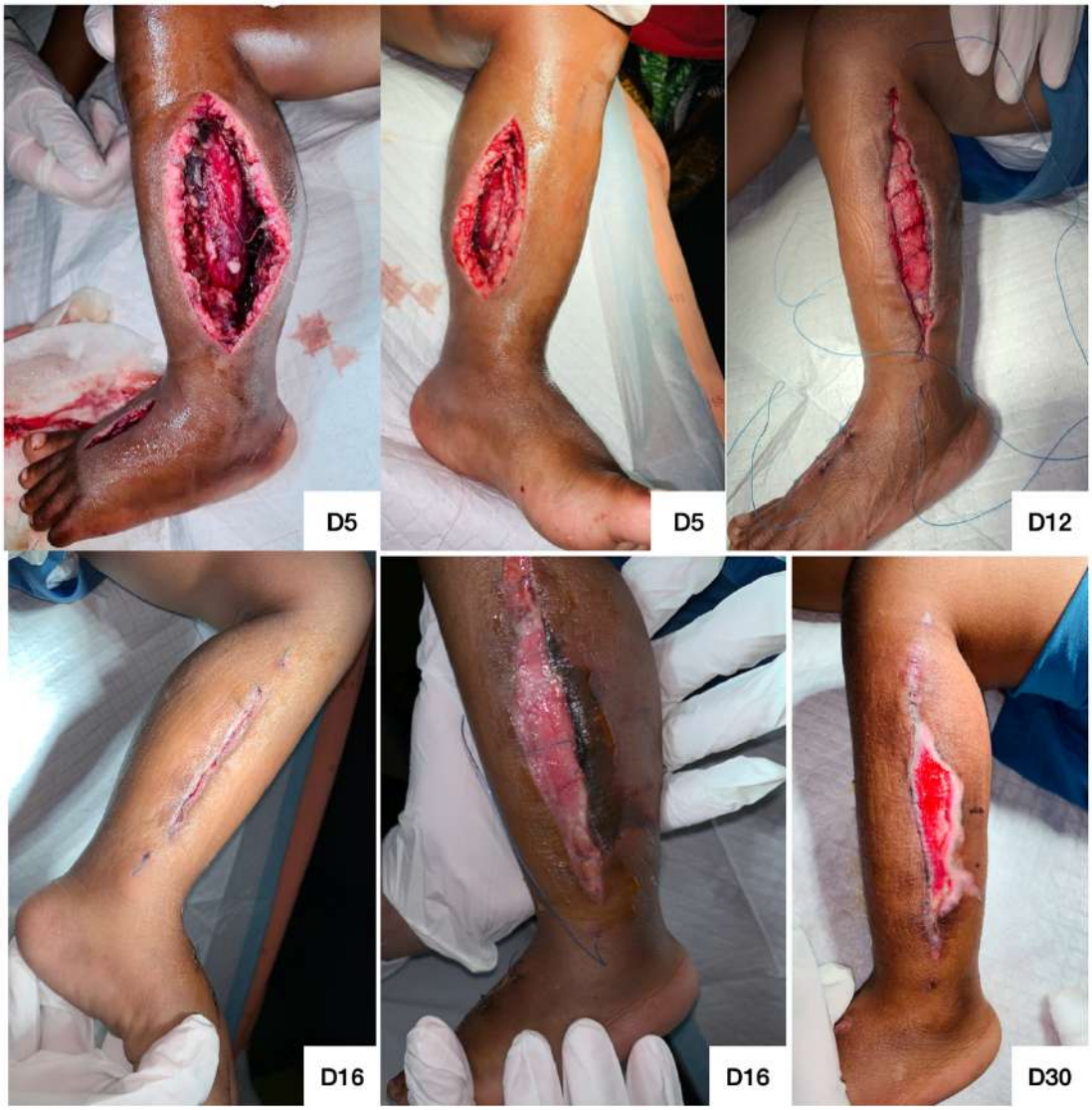


Figure 16: Case 10 Images of patient snakebite wounds.
D5 wound healing images after fasciotomy and debridement surgical procedure. D12 indicated slow progression of wound closure. D30 indicates the extent to which the wound healed over time.

Table 14: Case 10 patient laboratory profile

Normal values	**Day 1**	**Day 2**
WBC (6.0 – 17.5 x 10^9/L)	10.7	6.7
RBC (3.7 – 5.3 x 10^{12}/L)	4.1	4.7
Hb (10.5 – 13.5 g/dL)	10.2	12.6
HCT (31.0 – 39.0 %)	32.2	36.1
PLT (173.0 – 360.0 × 10^9/L)	232.0	209.0

Normal values	Day 1	Day 2
Neutrophils (1.5 – 8.5 × 10^9/L)	8.3	3.7
Lymphocytes (4.0 – 10.5 × 10^9/L)	1.9	2.2
Monocytes (0.1 – 1.1 × 10^9/L)	0.5	0.8
Eosinophils (0.1 – 0.8 × 10^9/L)	0.0	0.0
INR (0.8 – 1.3)	-	-
PT (10.2 – 13.2 s)	-	-
Urea (1.7 – 8.3 mmol/L)	5.1	-
Creatinine (26.5 – 88.4 mmol/L)	20.0	-
Albumin (36.0 – 51.0 g/L)	-	-
T-Bili (0.0 – 20.5 μmol/L)	-	-
ALP (103.0 – 373.0 IU/L)	-	-
GGT (7.0 – 50.0 IU/L)	-	-
ALT (10.0 – 40.0 IU/L)	-	-
AST (15.0 – 41.0 IU/L)	-	-
LDH (98.0 – 192.0 IU/L)	-	-
CK (49.0 – 397.0 IU/L)	161.0	-
CK-MB (0.0 – 8.0 ng/mL)	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 11: A four-year-old female was bitten on the left foot by *B. a. arietans* at 23h00. The patient sustained the injury while playing in the yard on a farm in Asab, Mariental district. Two hours after the snakebite incident, she was sent to the local hospital and was later transferred to KSH the next day. Immediately following the snakebite incident, the patient was treated with fuel and methylated spirits by pouring them on the bite site. Upon admission at KSH, the patient displayed minor oedema extending all the way down her leg and into her private regions (Figure 16, D1).

On day one, the patients' laboratory results were as follows (Table 15): There was elevated neutrophil count of 13.3 x 10^9/L and WBC count was 16.1 x 10^9/L. RBC, Hb, HCT, platelets, creatinine, albumin, T-Bili, GGT, ALT, and AST levels were all within normal limits. The LDH level were high (500.0 IU/L). Urea and ALP tests were not carried out. On day three, the only parameter that was elevated was HB (11.0 x 10^9/L), and no LFT was performed. On any of the days the patient was hospitalised, no PT, INR, CK, CK-MB, d-dimer, fibrinogen, peripheral or retics smears were performed. No antivenom was administered to the patient The swelling subsided over time, and there was no damage to the patient's leg or private region.

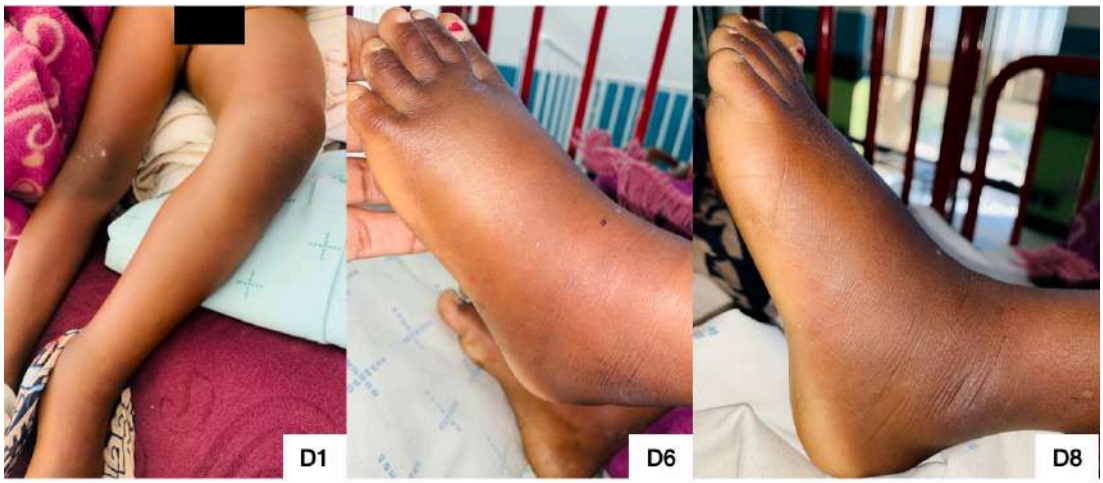


Figure 17: Case 11 Images of patient foot.
Patient's images after snakebite incident in accordance to the days, indicating how the swelling subsided (D1 to D8).

Table 15: Case 11 patient laboratory profile

Normal values	**Day 1**	**Day 3**
WBC (5.5 – 15.5 x 10^9/L)	16.1	8.6
RBC (3.9 – 5.3 x 10^{12}/L)	4.8	4.0
Hb (11.5 – 13.5 g/dL)	13.3	11.0
HCT (31.0 – 39.0 %)	38.5	33.9
PLT (171.0 – 388.0 × 10^9/L)	315.0	270.0
Neutrophils (1.5 – 8.5 × 10^9/L)	13.3	3.9

Normal values	Day 1	Day 3
Lymphocytes (2.0 – 8.0× 10^9/L)	1.8	3.5
Monocytes (0.1 – 1.1 × 10^9/L)	1.0	0.8
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0	0.3
INR (0.8 – 1.3)	-	-
PT (10.2 – 13.2 s)	-	-
Urea (1.7 – 8.3 mmol/L)	-	2.7
Creatinine (26.5 – 88.4 mmol/L)	40.0	34.0
Albumin (31.0 – 48.0 g/L)	40.0	-
T-Bili (0.0 – 20.5 μmol/L)	3.0	-
ALP (60.0.0 – 321.0 IU/L)	-	-
GGT (6.0 – 19.0 IU/L)	12.0	-
ALT (10.0 – 32.0 IU/L)	19.0	-
AST (15.0 – 60.0 IU/L)	43.0	-
LDH (142.0 – 297.0 IU/L)	500.0	-
CK (49.0 – 397.0 IU/L)	-	-
CK-MB (0.0 – 4.8 ng/mL)	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 12: A three-year-old male was bitten on the right middle finger around 17h00 by a *B. a. arietans*. The incident occurred in the patient's yard on a farm near Omatjete, where he attempted to grab the snake but was ultimately bitten. The patient was rushed to the local clinic and then transported within two hours to Omaruru State Hospital. Soon after, he was transferred to KISH in Windhoek, where he arrived 10 hours later. The patient presented with severe oedema of the hand, discoloration at the bite region on examination at KISH. The patient also displayed drowsiness, limb weakness, vomiting and blurred vision. The patient underwent debridement on day three (Figure 17, D2).

There were no laboratory results on day one. The patients' laboratory results on day two were as follows (Table 16): There was a high RBC count of 5.3 x 10^{12}/L, a high HCT count of 39.5 %, and a high platelet count of 434.0 x 10^{9}/L. WBC, Hb, PT, INR, urea, and creatinine levels were all within normal limits. On day four, Hb dropped to 10.1 x 10^{9}/L. RBC 4.4 x 10^{12}/L, HCT 32.1%, and platelets 358.0 x 10^{9}/L were all within normal limits. On day six, WBC was 5.0 x 10^{9}/L lower, Hb remained low, and platelets increased to 389.0 x 10^{9}/L. No LFT, CK, CK-MB, d-dimer, fibrinogen, and peripheral or retics smears were performed on any of the days the patient was hospitalised. The patient received no antivenom. The wound of the patient was monitored, and wound closure procedures were performed on day eight. The patient was discharged on day 23 with muscle weakness.

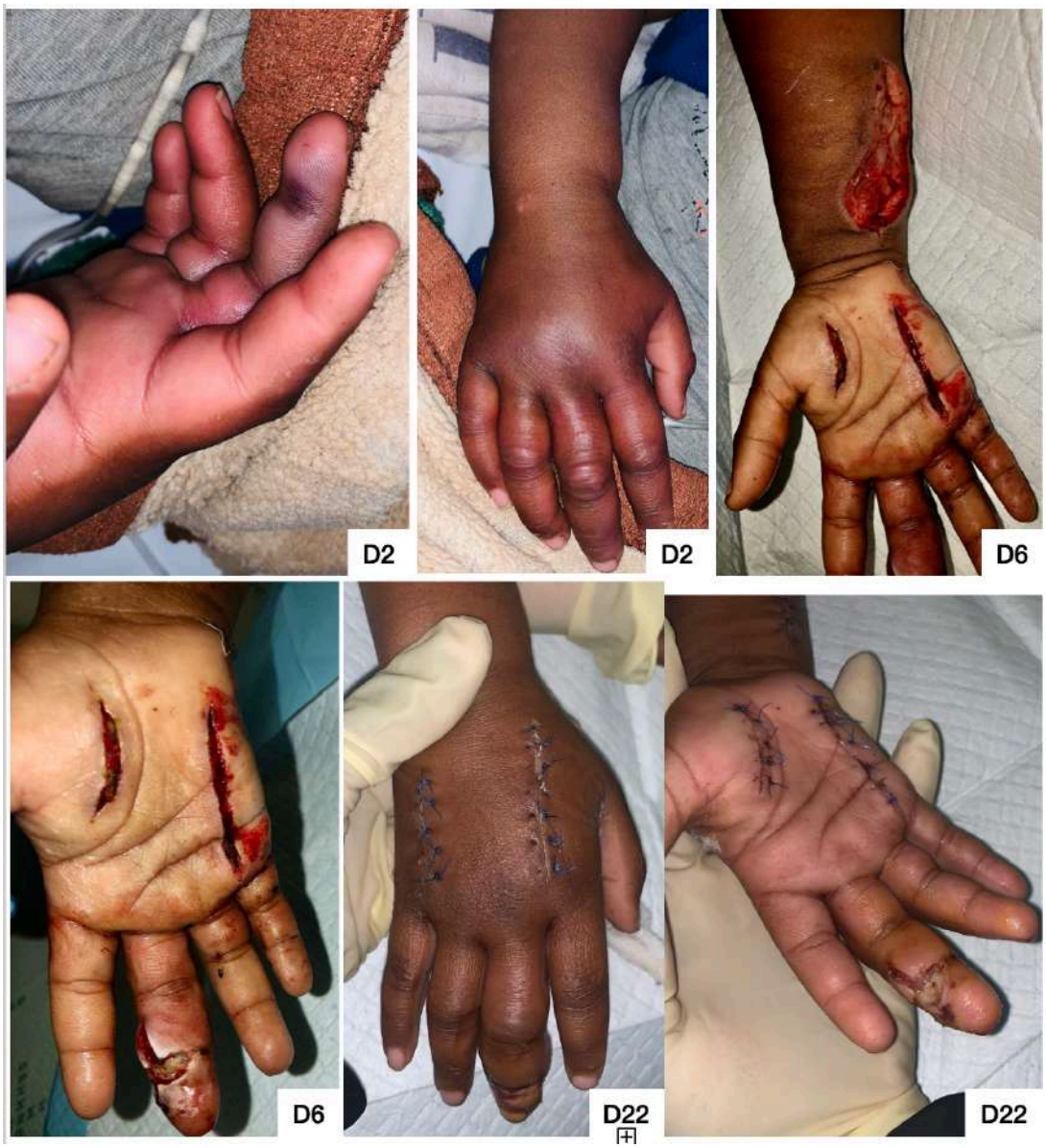


Figure 18: Case 12 Images of patient snakebite wounds.
D2 the images show discoloration of the right middle finger and severe hand oedema respectively. D6 wound image after surgical debridement and fasciotomy. D22 illustrated wound healing following wound closure.

Table 16: Case 12 patient laboratory profile

Normal values	**Day 2**	**Day 4**	**Day 6**
WBC (5.5 – 15.5 x 10^9/L)	9.9	6.1	5.0
RBC (3.9 – 5.3 x 10^{12}/L)	5.3	4.4	4.5
Hb (11.5 – 13.5 g/dL)	12.5	10.1	10.6
HCT (31.0 – 39.0 %)	39.5	32.1	33.0
PLT (173.0 – 360.0 × 10^9/L)	434.0	358.0	389.0

Normal values	Day 2	Day 4	Day 6
Neutrophils (1.5 – 8.5 × 10^9/L)	7.7	3.9	3.2
Lymphocytes (2.0 – 8.0 × 10^9/L)	1.5	1.6	1.3
Monocytes (0.1 – 1.1 × 10^9/L)	0.6	0.5	0.4
Eosinophils (0.0 – 0.7 × 10^9/L)	0.0	0.0	0.1
INR (0.8 – 1.3)	1.1	-	-
PT (10.2 – 13.2 s)	13.0	-	-
Urea (1.7 – 8.3 mmol/L)	4.0	3.5	4.6
Creatinine (26.5 – 88.4 mmol/L)	48.0	34.0	45.0
Albumin (36.0 – 51.0 g/L)	-	-	-
T-Bili (0.0 – 20.5 μmol/L)	-	-	-
ALP (103.0 – 373.0 IU/L)	-	-	-
GGT (7.0 – 50.0 IU/L)	-	-	-
ALT (10.0 – 40.0 IU/L)	-	-	-
AST (15.0 – 41.0 IU/L)	-	-	-
LDH (98.0 – 192.0 IU/L)	-	-	-
CK (49.0 – 397.0 IU/L)	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 13: A five-year-old male was bitten on the face, right supraorbital region while sleeping on the floor in a shack at 01h00 by an *N. n. nigricincta*. The incident happened on a farm in Dan Viljoen, Windhoek district. The patient was transported to WCH 11 hours after the event, where he got admitted in the intensive care unit (ICU). On examination the patient's face was swollen, and was unable to open both eyes (Figure 18, D4). After spending a day in the ICU, the patient was transferred to the ward.

The patients' laboratory results on day one was as follow (Table 17): The elevation of neutrophil count was 13.1 x 10^9/L, and the WBC was 14.4 x 10^9/L. There was a high

Hb of 14.0 x 10^9/L, a high HCT of 40.7 %, a high PT of 15.4 s, and a high INR of 1.3. The levels of RBC, platelets, d-dimer, urea, creatinine, albumin, ALP, and ALT were all within normal ranges. T-Bili 75.0 µmol/L, GGT 19.0 IU/L, AST 98.0 IU/L, and LDH 620.0 IU/L levels were all also elevated. CK was not carried out. On day two WBC increased to 19.5 x 10^9/L, as did PT to 19.3 s and INR to 1.7. There were no LFT, CK, CK-MB, fibrinogen, and peripheral or retics smears performed on any of the days the patient was hospitalised. The swelling subsided over time, and the patient was discharged on day eight.

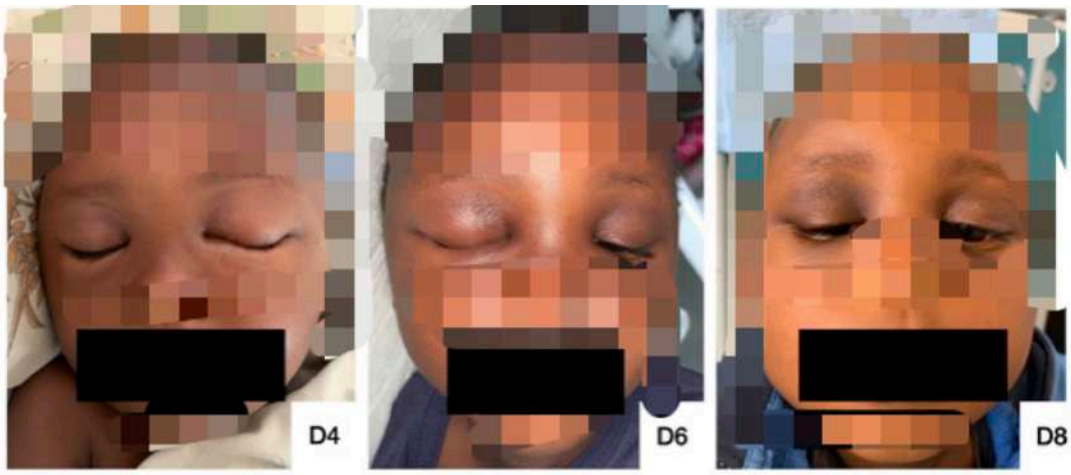


Figure 19: Case 13 Images of patient face.
D4 image of the patient following discharge from the intensive care unit with both eyes still swollen. D6 the left eye is functional and able to see, whereas the right eye is still swollen. D8 both eyes were able open and were functioning normally.

Table 17: Case 13 patient laboratory profile

Normal values	**Day 1**	**Day 2**
WBC (5.5 – 15.5 x 10^9/L)	14.4	19.5
RBC (3.9 – 5.3 x 10^{12}/L)	4.8	4.2
Hb (11.5 – 13.5 g/dL)	14.0	12.1
HCT (31.0 – 39.0 %)	40.7	33.0
PLT (173.0 – 360.0 × 10^9/L)	352.0	322.0
Neutrophils (1.5 – 8.5 × 10^9/L)	13.1	17.8
Lymphocytes (2.0 – 8.0 × 10^9/L)	0.7	0.9

Normal values	Day 1	Day 2
Monocytes (0.1 – 1.1 × 10^9/L)	0.5	0.8
Eosinophils (0.0 – 0.7 × 10^9/L)	0.0	0.0
INR (0.8 – 1.3)	1.28	1.62
PT (10.2 – 13.2 s)	15.4	19.3
Urea (1.7 – 8.3 mmol/L)	4.2	3.5
Creatinine (26.5 – 88.4 mmol/L)	40.0	34.0
Albumin (36.0 – 51.0 g/L)	39.0	-
T-Bili (0.0 – 20.5 μmol/L)	75.0	-
ALP (110.0 – 341.0 IU/L)	209.0	-
GGT (6.0 – 16.0 IU/L)	19.0	-
ALT (11.0 – 39.0 IU/L)	26.0	-
AST (15.0 – 60.0 IU/L)	98.0	-
LDH (155.0 – 290.0 IU/L)	620.0	-
CK (49.0 – 397.0 IU/L)	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-
D-dimer (0.0 - 230.0 ng/mL)	222.9	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 14: A five-year-old female was bitten on the right foot by *B. a. arietans* while walking in the yard at 19h00 in Otjomuise, WHK. The patient was admitted to KISH three hours after the incident. On examination there were no signs of envenomation or oedema (Figure 19). The patient's bite was determined to be a dry snakebite; however, the patient was admitted to the hospital for observation according to the guidelines before being discharged on day two. No laboratory work up was done on the patient.

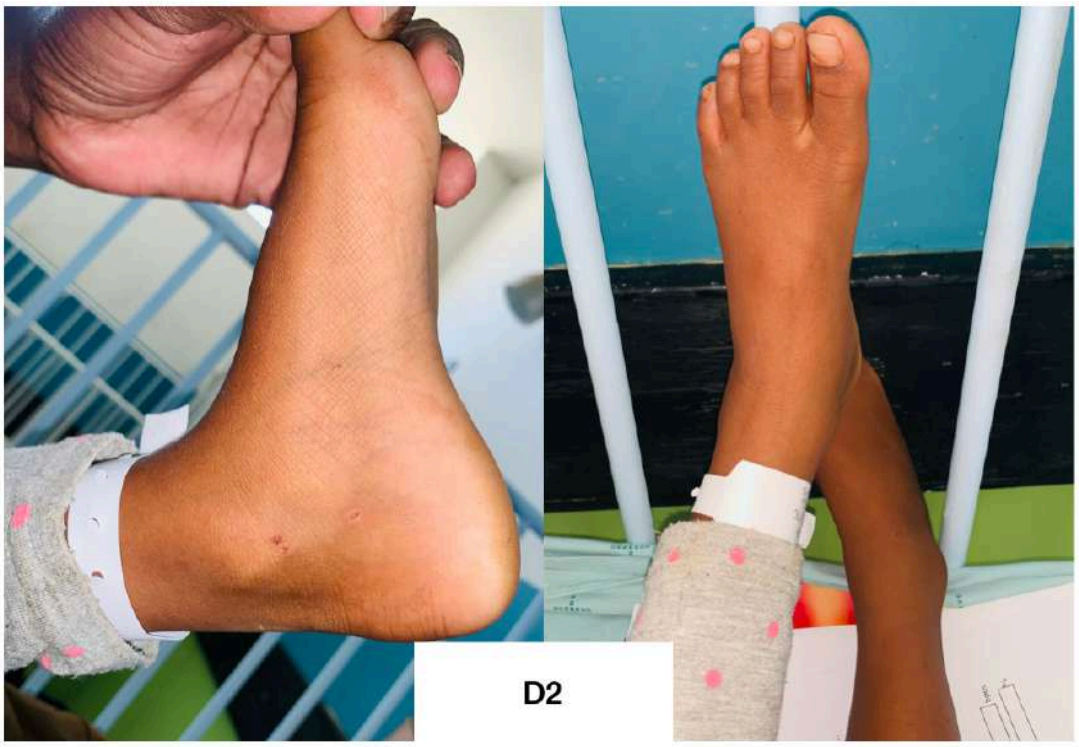


Figure 20: Case 14 Images of patient foot.
D2 indicated the bite marks on the patient's right foot are shown in the left image, and there were no signs of foot swelling in the right image.

Case 15: A 43-year-old male was herding cattle and resting under a tree on a farm near Outjo at 11h00 when he was bitten on the left middle finger by *N. n. nigricincta*. The patient was transported to a local hospital six hours after the incident, where a debridement surgical procedure was conducted on day one (Figure 20, D1). He was transferred to KISH, WHK the next morning for further management. The patient's left middle finger and hand at whole were swollen upon examination, necessitating an urgent surgical fasciotomy and debridement at KISH. Following the snake bite, the patient had difficulty urinating.

There were laboratory results on day one. However, on day two (Table 18), patients' laboratory results revealed a high WBC count of 10.3 x 10^9/L and a high RBC count of 6.7 x 10^{12}/L. Platelets was low at 129.0 x 10^9/L. Hb, HCT, PT, INR, urea, creatinine, albumin, T-Bili, ALP, GGT, and ALT levels were all within normal bounds. Urea 8.8

mmol/L and creatinine 141.0 mmol/L were both elevated, while GFR was reduced to 15.0 mL/min. Albumin was 30.0 g/L, AST was 64.0 IU/L, and LDH was 343.0 IU/L, both of which were high. On Day three, a decrease in the following parameters: RBC was 4.3 x 10^{12}/L, Hb was 9.9 x 10^{9}/L, HCT was 32.2 %, and platelet count was 71.0 x 10^{9}/L. RBC, Hb, HCT, and platelets remained low on day five.

A differential smear of the patient revealed microcytic hypochromic anaemia, moderate anisocytosis and target cells, and thrombocytopenia. On any of the days the patient was hospitalised, no CK, CK-MB, d-dimer, fibrinogen or retics smears were performed. The wound of the patient was monitored, and wound closure procedures were performed gradually on day nine. The patient sought physiotherapy on day 31 in order to relieve discomfort, promote recovery, and maintain full mobility. The patient was discharged on day 35 with muscle weakness.

Figure 21: Case 15 Images of patient snakebite wounds.
D1 image of the left middle was taken six hours after the bite incident. D2 following first debridement, as well as an indication of hand swelling. D5 following the second debridement and fasciotomy surgical procedure. D35 images depicted the healing of a patient's wound.

Table 18: Case 15 patient laboratory profile

Normal values	**Day 2**	**Day 3**	**Day 5**
WBC (3.8 – 8.8 x 10^9/L)	10.3	7.3	5.7
RBC (4.5 – 6.0 x 10^{12}/L)	6.7	4.3	4.3
Hb (13.2 – 16.6 g/dL)	15.4	9.9	10.0
HCT (43.2 – 54.5 %)	49.6	32.2	31.2
PLT (173.0 – 360.0 × 10^9/L)	129.0	71.0	78.0
Neutrophils (2.0 – 7.5 × 10^9/L)	6.5	4.9	3.8
Lymphocytes (1.0 – 4.0 × 10^9/L)	2.8	1.9	1.3
Monocytes (0.2 – 0.8 × 10^9/L)	0.9	0.5	0.4
Eosinophils (0.0 – 0.4 × 10^9/L)	0.1	0.0	0.1

Normal values	Day 2	Day 3	Day 5
INR (0.8 – 1.3)	1.1	-	-
PT (10.2 – 13.2 s)	13.8	-	-
Urea (2.1 – 7.1 mmol/L)	8.8	6.6	2.5
Creatinine (62.0 – 106.0 mmol/L)	141.0	83.0	70.0
Albumin (36.0 – 51.0 g/L)	30.0	-	-
T-Bili (0.0 – 20.5 μmol/L)	11.0	-	-
ALP (32.0 – 91.0 IU/L)	48.0	-	-
GGT (7.0 – 50.0 IU/L)	12.0	-	-
ALT (10.0 – 40.0 IU/L)	24.0	-	-
AST (15.0 – 41.0 IU/L)	64.0	-	-
LDH (98.0 – 192.0 IU/L)	343.0	-	-
CK (49.0 – 397.0 IU/L)	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 16: A 35-year-old female was bitten on the left lower back by a *B. a. arietans* at 23h00 while sleeping on the floor of a shack on a farm in Stinkwater, Dordabis district. Two days after the bite incident, the patient was transported to a local clinic and then transferred to WCH, WHK. The patient appears to be in good health, awake and attentive, with no signs of envenomation or oedema on examination (Figure 21). The patient snakebite was considered as a dry bite.

Blood tests revealed no abnormalities (Table 19), with the exception of a low albumin level of 29.0 g/L and a slightly elevated LDH level of 195.0 IU/L. The patient was only admitted in the hospital for one night for observation before being discharged. The patient fully recovered.

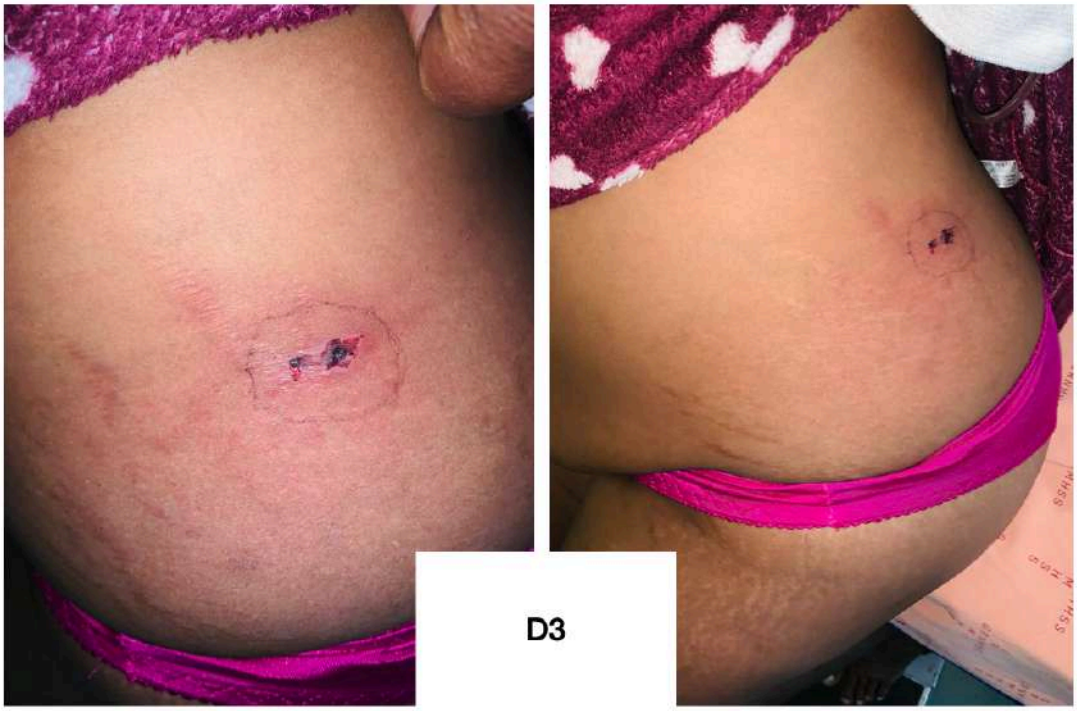


Figure 22: Case 16 Images of patient lower back.
D3 denoted bite marks on the patient's left lower back, and no sign of swelling.

Table 19: Case 16 patient laboratory profile

Normal values	**Day 3**
WBC (3.4 – 8.9 x 10^9/L)	4.5
RBC (3.9 – 5.3 x 10^{12}/L)	4.3
Hb (11.1 – 14.7 g/dL)	12.4
HCT (36.9 – 49.1 %)	39.8
PLT (171.0 – 388.0 × 10^9/L)	172.0
Neutrophils (2.0 – 7.5 × 10^9/L)	2.5
Lymphocytes (1.5 – 6.5 × 10^9/L)	1.2
Monocytes (0.0 – 0.4 × 10^9/L)	0.3
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0
INR (0.8 – 1.3)	1.0
PT (10.2 – 13.2 s)	11.8
Urea (2.1 – 7.1 mmol/L)	3.8
Creatinine (35.5 – 88.4 mmol/L)	56.0
Albumin (36.0 – 51.0 g/L)	29.0
T-Bili (0.0 – 20.5 μmol/L)	5.0

Normal values	Day 3
ALP (32.0 – 91.0 IU/L)	69.0
GGT (7.0 – 50.0 IU/L)	24.0
ALT (7.0 – 35.0 IU/L)	15.0
AST (15.0 – 41.0 IU/L)	18.0
LDH (98.0 – 192.0 IU/L)	195.0
CK (49.0 – 397.0 IU/L)	-
CK-MB (0.0 – 4.8 ng/mL)	-
D-dimer (0.0 - 230.0 ng/mL)	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 17: A 22-year-old female was bitten on the left ear by *N. n. nigricincta* around 23h00 while sleeping on the floor in a shack in Outjo. The patient was transported to a local hospital within an hour and then transferred to KISH the following day. The patient was admitted to the ACU for the day before being discharged the following day to the ward. The patient's left side of face was severely swollen and necrotic around the fang marks upon examination (Figure 22, D2).

No laboratory results were obtained for the patient on day one. On day two, laboratory results (Table 20) revealed that patients had a high WBC count of 18.0 x 10^9/L and a high neutrophil count of 16.6 x 10^9/L. The levels of RBC, Hb, HCT, platelets, INR, urea, creatinine, albumin, ALP, GGT, and ALT were all within normal limits. The following parameters were raised: PT (14.5 s), T-Bili (32.0 µmol/L), AST (46.0 IU/L), and LDH (474.0 IU/L). On day three and four, WBC remained elevated. The patients Hb which was 10.9 x 10^9/L and HCT which was 34.3 % both declined on day four. No CK, CK-MB, d-dimer, fibrinogen, peripheral or retics smears were performed on

any of the days the patient was hospitalised. On day four, once the patient's facial swelling receded, she was discarded.

Figure 23: Case 17 Images of patient face.
D2 image shows severe facial swelling as well as necrosis at the bite site. The D3 image shows the reduction in facial oedema.

Table 20: Case 17 patient laboratory profile

Normal values	**Day 2**	**Day 3**	**Day 4**
WBC (3.4 – 8.9 x 10^9/L)	18.0	16.9	11.2
RBC (3.9 – 5.3 x 10^{12}/L)	5.2	4.6	4.1
Hb (11.1 – 14.7 g/dL)	13.6	12.3	10.9
HCT (36.9 – 49.1 %)	42.8	38.6	34.3
PLT (171.0 – 388.0 × 10^9/L)	315.0	293.0	227.0
Neutrophils (2.0 – 7.5 × 10^9/L)	16.6	13.2	6.7
Lymphocytes (1.5 – 6.5 × 10^9/L)	1.0	2.5	2.4
Monocytes (0.0 – 0.4 × 10^9/L)	0.3	0.9	0.8
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0	0.2	1.2
INR (0.8 – 1.3)	1.2	-	-
PT (10.2 – 13.2 s)	14.5	-	-
Urea (2.1 – 7.1 mmol/L)	3.2	4.2	2.7
Creatinine (35.0 – 88.0 mmol/L)	64.0	62.0	57.0
Albumin (35.0 – 50.0 g/L)	42.0	-	-
T-Bili (0.0 – 20.5 µmol/L)	32.0	-	-
ALP (32.0 – 91.0 IU/L)	86.0	-	-

Normal values	Day 2	Day 3	Day 4
GGT (7.0 – 50.0 IU/L)	23.0	-	-
ALT (7.0 – 35.0 IU/L)	22.0	-	-
AST (15.0 – 41.0 IU/L)	46.0	-	-
LDH (98.0 – 192.0 IU/L)	474.0	-	-
CK (49.0 – 397.0 IU/L)	-	-	-
CK-MB (0.0 – 4.8 ng/mL)	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 18: A 28-year-old male was bitten on the nose (left side) by *N. n. nigricincta* around 1h30 while sleeping, Ongava lodge, Etosha. Within three hours, the patient was taken to a private hospital in Otjiwarongo, and six hours later, he was transferred to KSH in Windhoek. The patient's examination revealed a minor swelling on the left side of his face (Figure 23).

No laboratory results were obtained for the patient on day one. On day two the patient's laboratory profile was completed, and all parameters (FBC, LFT, urea, creatinine, PT, and INR) were within normal limits, with the exception of high WBC 12.7 x 10^9/L and LDH 291.0 IU/L (Table 21). The patient had a full recovery and was discharged on day six.

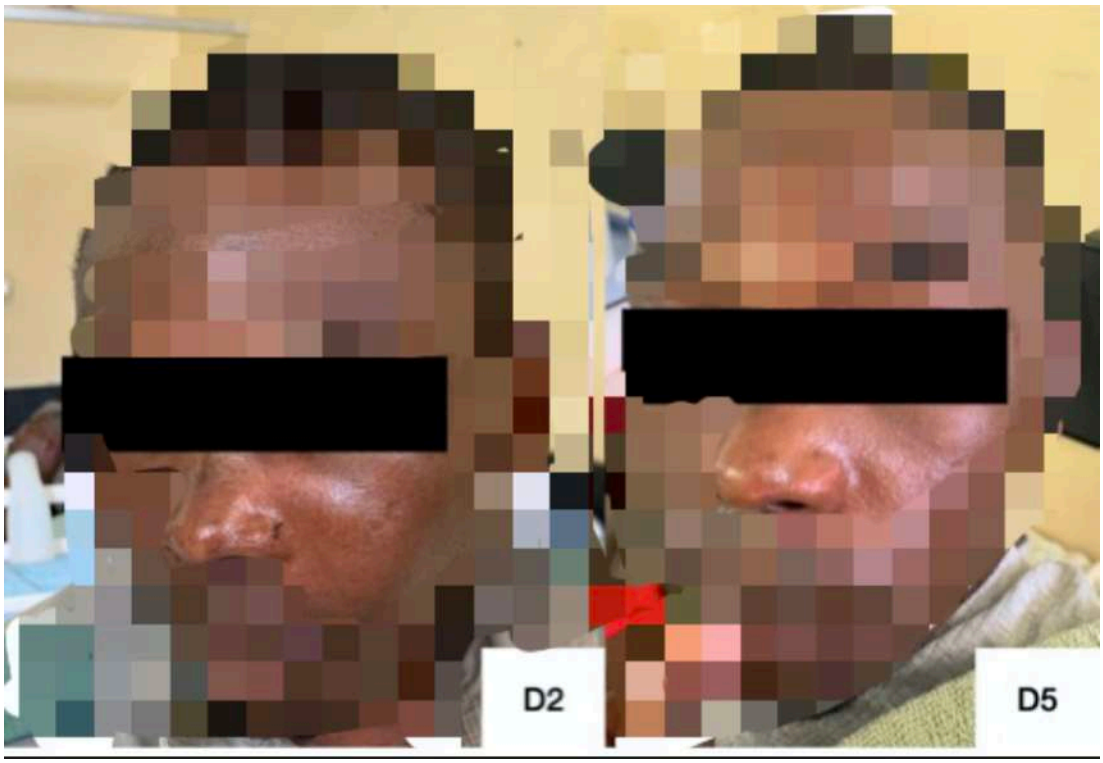


Figure 24: Case 18 Images of patient face.
D2 image shows minor swelling on the left side of his face, particularly around the nose and slight necrosis at the fang marks. D5 is an indication of reduced facial swelling and complete recovery.

Table 21: Case 18 patient laboratory profile

Normal values	**Day 2**
WBC (3.8 – 8.8 x 10^9/L)	12.7
RBC (4.5 – 6.0 x 10^{12}/L)	5.1
Hb (13.2 – 16.6 g/dL)	15.3
HCT (43.2 – 54.5 %)	45.8
PLT (173.0 – 360.0 × 10^9/L)	180.0
Neutrophils (2.0 – 7.5 × 10^9/L)	11.8
Lymphocytes (1.0 – 4.0 × 10^9/L)	0.5
Monocytes (0.2 – 0.8 × 10^9/L)	0.3
Eosinophils (0.0 – 0.4 × 10^9/L)	0.1
INR (0.8 – 1.3)	1.1
PT (10.2 – 13.2 s)	10.4
Urea (2.1 – 7.1 mmol/L)	3.2
Creatinine (62.0 – 106.0 mmol/L)	71.0
Albumin (36.0 – 51.0 g/L)	39.0

Normal values	Day 2
T-Bili (0.0 – 20.5 μmol/L)	17.0
ALP (32.0 – 91.0 IU/L)	72.0
GGT (7.0 – 50.0 IU/L)	37.0
ALT (10.0 – 40.0 IU/L)	29.0
AST (15.0 – 41.0 IU/L)	37.0
LDH (98.0 – 192.0 IU/L)	291.0
CK (49.0 – 397.0 IU/L)	-
CK-MB (0.0 – 8.0 ng/mL)	-
D-dimer (0.0 - 230.0 ng/mL)	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 19: A four-year-old male was bitten on the right eye in the infraorbital region by *N. n. nigricincta* at 2h00, on a farm in Outjo while sleeping on the floor of a shack. The patient was taken to a local hospital within an hour and then transferred six hours later to KSH, WHK. Upon examination, the patient's entire right side of the face was severely swollen 12 hours later (Figure 24, D1.5), he also displayed blurred vision, limb weakness and was unable to swallow saliva. On day two, the patient went for surgical procedure fasciotomy and debridement on the face, and was admitted to the ACU for two days before being discharged to the ward. An ophthalmologist was consulted by the patient to assess the condition of the eye and to ensure that there was no infection or damage done to the eye on day seven.

The patient's laboratory results revealed (Table 22) on day one, patients had a high WBC count of 17.5 x 10^9/L and a high neutrophil count of 16.3 x 10^9/L. The levels of RBC, Hb, HCT, platelets, urea, creatinine, albumin, T-Bili, and GGT were all within normal limits. ALP 319.0 IU/L, ALT 42.0 IU/L, AST 90.0 IU/L, and LDH 566.0 IU/L were all also elevated in the patient. Hb dropped to 10.7 x 10^9/L on day three, and

albumin dropped to 32.0 g/L. ALT, AST, and LDH levels remained elevated. RBC 8.9 x 10^{12}/L decreased on day four. Hb remained low on day nine. No CK, CK-MB, d-dimer, peripheral, or retics smears were performed on any of the days the patient was hospitalised. At the bite site, the patient had epithelial damage and necrosis. On day 17, the patients underwent a second surgical debridement to remove necrotic tissue from the infraorbital region. No antivenom was administered to the patient. The patient fully recovered with no permanent eye damage and was discharged on day 21. With a follow-up for a skin graft two weeks after discharge.

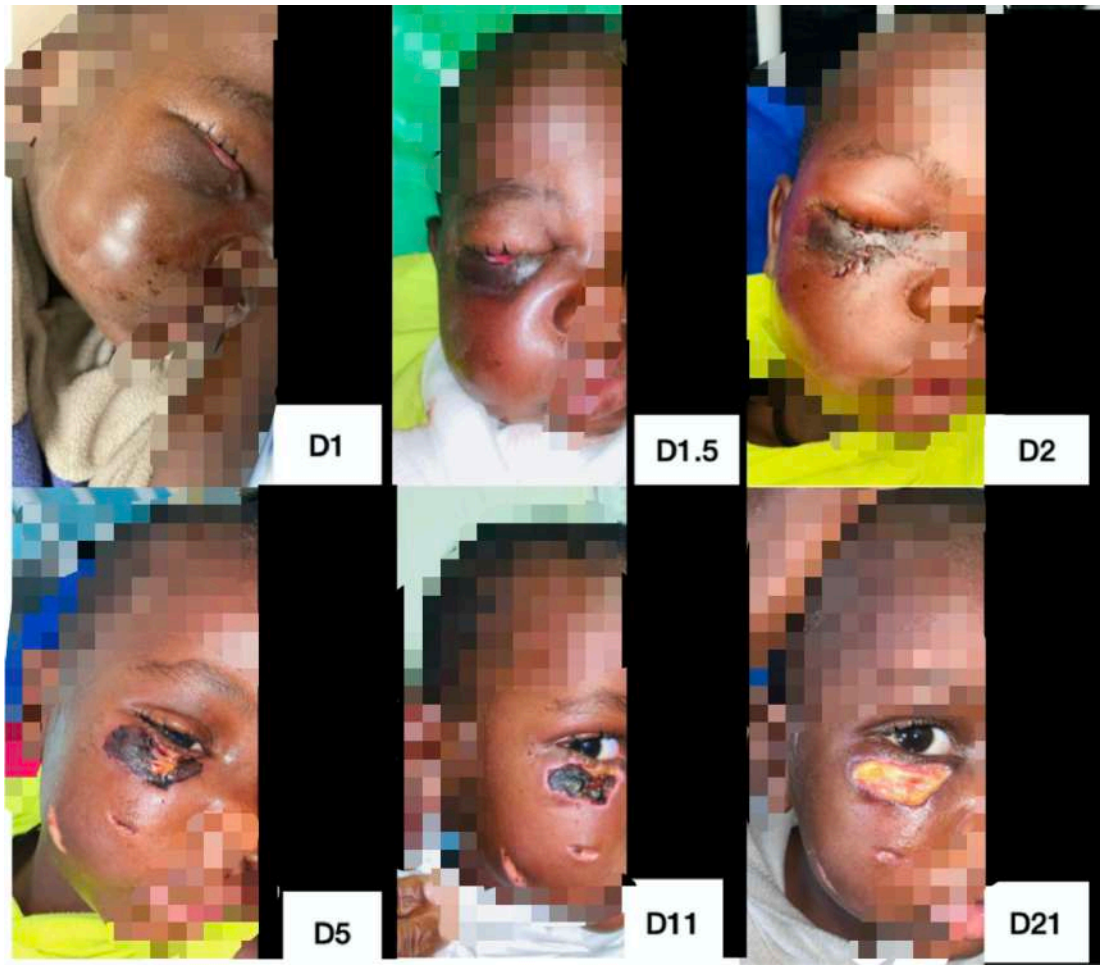


Figure 25: Case 19 Images of patient face.
A typical snakebite wound on the face. D1 illustrated the development of facial oedema. D1.5 represented the progression of facial swelling over a 12-hours period following the bite. D2 patients swelling greatly exacerbated, affecting both eyes. D5 following surgical fasciotomy and debridement. D11 the swelling in the face has completely subsided. D21 following surgical scalp removal and a second debridement procedure.

Table 22: Case 19 patient laboratory profile

Normal values	Day 1	Day 3	Day 4	Day 9
WBC (6.0 – 17.0 x 10^9/L)	17.5	6.0	8.9	8.5
RBC (3.9 – 5.3 x 10^{12}/L)	5.0	4.2	3.8	4.5
Hb (11.5 – 13.5 g/dL)	12.4	10.7	9.4	11.4
HCT (31.0 – 39.0 %)	37.9	35.6	31.3	35.9
PLT (173.0 – 360.0 × 10^9/L)	334.0	277.0	290.0	366.0
Neutrophils (1.5 – 8.5 × 10^9/L)	16.3	4.8	6.7	3.0
Lymphocytes (3.0 – 9.5 × 10^9/L)	0.6	1.1	1.6	4.9
Monocytes (0.1 – 1.1 × 10^9/L)	0.6	0.2	0.6	0.4
Eosinophils (0.1 – 0.7 × 10^9/L)	0.0	0.0	0.0	0.1
INR (0.8 – 1.3)	-	-	-	-
PT (10.2 – 13.2 s)	-	-	-	-
Urea (1.7 – 8.3 mmol/L)	3.4	5.5	5.2	7.7
Creatinine (26.5 – 88.4 mmol/L)	45.0	45.0	40.0	43.0
Albumin (36.0 – 51.0 g/L)	41.0	32.0	31.0	-
T-Bili (0.0 – 20.5 μmol/L)	7.0	6.0	8.0	-
ALP (11.0 – 302.0 IU/L)	319.0	248.0	192.0	-
GGT (6.0 – 16.0 IU/L)	10.0	8.0	8.0	-
ALT (11.0 – 39.0 IU/L)	42.0	45.0	46.0	-
AST (15.0 – 60.0 IU/L)	90.0	116.0	94.0	-
LDH (140.0 – 304.0 IU/L)	566.0	410.0	414.0	-
CK (49.0 – 397.0 IU/L)	-	-	-	-
CK-MB (0.0 – 8.0 ng/mL)	-	-	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

Case 20: A 13-year-old female was bitten on the right middle finger by *N. n. nigricincta* around 23h00 while sleeping on the floor in a shack. The incident occurred on a farm 30 km from Outjo. In an attempt to prevent the snake's venom from

spreading to the rest of the body, a family member cut the primary proper palmar digital artery that supplies blood to that finger (cutting accidentally too deep). The patient was admitted to the local hospital and later transferred to KISH, WHK seven hours prior to the incident. On examination the patient's right middle finger and hand at whole were swollen upon examination, necessitating an urgent surgical fasciotomy and debridement on day one.

From day one to day three, no laboratory tests were performed on the patient. On day four, the laboratory revealed (Table 23) that patients had a high WBC of 119.7 x 10^9/L, a high neutrophil count of 16.9 x 10^9/L, and a high platelet count of 421.0 x 109/L. The levels of RBC, Hb, HCT, INR, urea, creatinine, albumin, T-Bili, ALT, and AST were all within normal limits. PT 15.3 s, ALP 649.0 IU/L, and LDH 283.0 IU/L were also all elevated in the patient. On day seven RBC dropped to 3.7 x 10^{12}/L, Hb dropped to 10.7 x 10^9/L, and HCT also dropped to 30.8 %. No CK, CK-MB, d-dimer, fibrinogen, peripheral, or retics smears were performed on any of the days the patient was hospitalised. No antivenom was administered to the patient. As the finger became increasingly necrotic, amputation was the only option (Figure 25, D13 & D21). Patient was discharged on day 22.

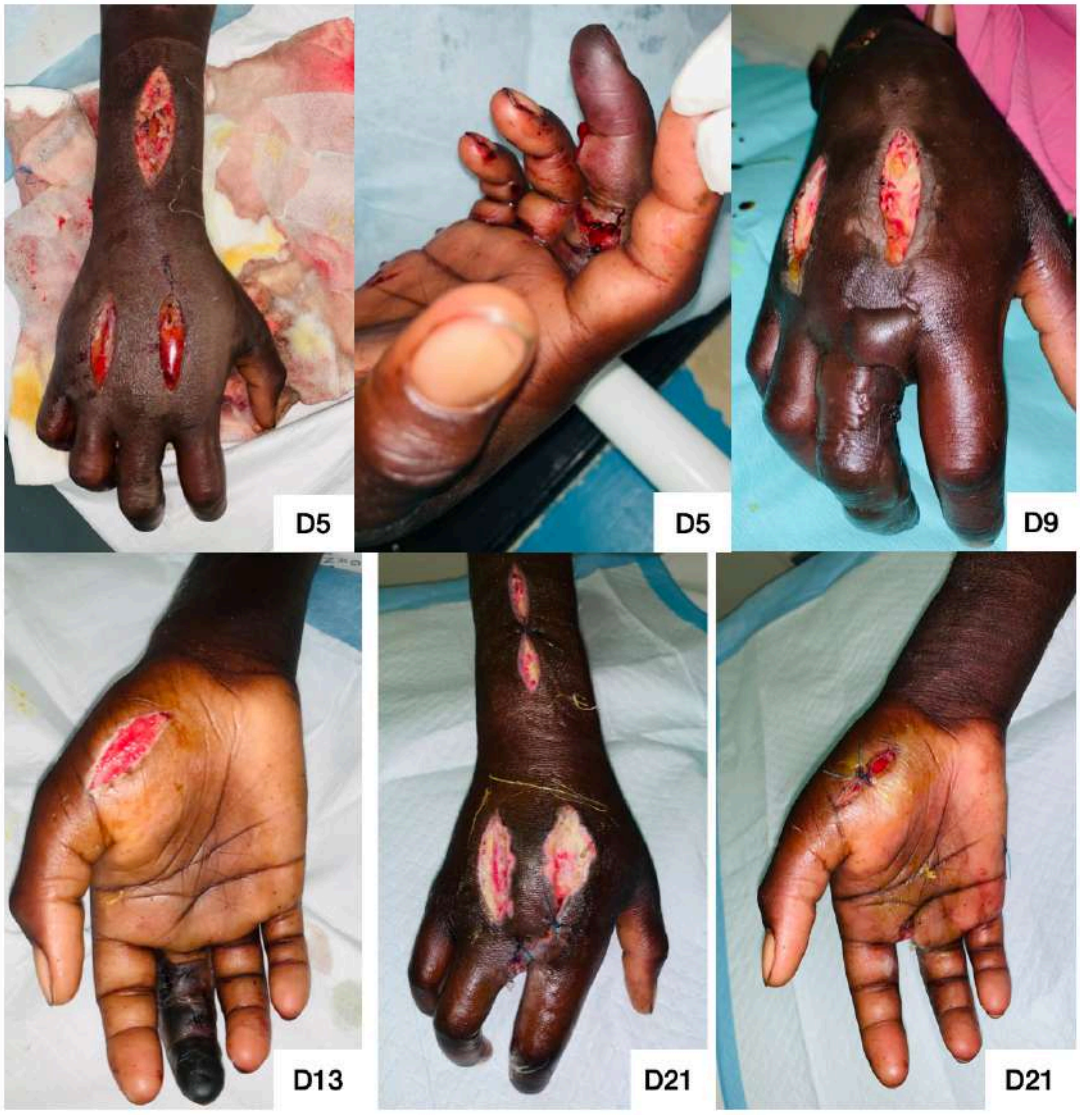


Figure 26: Case 20 Images of patient snakebite wounds.
The progression of a patient's snakebite wound. D5 following surgical fasciotomy and debridement. The D9 image depicts the formation of blisters on the hand. D13 denotes the spread of necrosis to the entire right middle finger. D21 images taken after the amputation procedure.

Table 23: Case 20 patient laboratory profile

Normal values	**Day 4**	**Day 7**
WBC (3.4 – 8.9 x 10^9/L)	19.7	10.7
RBC (3.9 – 5.3 x 10^{12}/L)	4.5	3.7
Hb (11.5 – 15.5 g/dL)	13.9	11.1
HCT (36.9 – 49.1 %)	39.3	30.8
PLT (171 – 388 × 10^9/L)	421.0	388.0
Neutrophils (1.5 – 8.0 × 10^9/L)	16.9	7.6

Normal values	Day 4	Day 7
Lymphocytes (1.5 – 6.5 × 10^9/L)	1.9	2.1
Monocytes (0.0 – 0.4 × 10^9/L)	0.9	0.8
Eosinophils (0.0 – 0.5 × 10^9/L)	0.0	0.1
INR (0.8 – 1.3)	1.3	-
PT (10.2 – 13.2 s)	15.3	-
Urea (2.1 – 7.1 mmol/L)	4.0	3.7
Creatinine (26.5 – 88.4 mmol/L)	62.0	53.0
Albumin (31.0 – 48.0 g/L)	45.0	-
T-Bili (0.0 – 20.5 μmol/L)	3.0	-
ALP (83.0 – 382.0 IU/L)	649.0	-
GGT (7.0 – 50.0 IU/L)	-	-
ALT (7.0 – 35.0 IU/L)	20.0	-
AST (15.0 – 41.0 IU/L)	36.0	-
LDH (98.0 – 192.0 IU/L)	283.0	-
CK (49.0 – 397.0 IU/L)	-	-
CK-MB (0.0 – 4.8 ng/mL)	-	-
D-dimer (0.0 - 230.0 ng/mL)	-	-

WBC = white blood cell count; RBC = red blood cell; Hb = haemoglobin; HCT = haematocrit; PLT = platelet count; INR = international normalised ratio; PT = prothrombin time; T-Bili = total bilirubin; ALP = alkaline phosphatase; GGT = gamma – glutamyl transferase; ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase; CK = creatine kinase; CK-MB = creatine kinase myocardial band.

4.7. Systemic envenomation

4.7.1. Clinical manifestation

The study results revealed that 30 % (6) of the patients showed persistent symptoms of haemolysis, 45 % (9) of patients did not have a test performed to confirm the diagnosis of haemolysis, and 25 % (5) of the patients did not have any signs of haemolysis. Anaemia was discovered in 30 % (6) of the patients, 55 % (11) were not anaemic, and 15 % (3) of patients' laboratory results were unavailable to confirm the diagnosis of anaemia. The results also revealed that about 15 % (3) of the patients displayed symptoms of abnormal coagulation in the extrinsic coagulation pathway (all

had elevated PT and INR), and 30 % (6) of the patients did not have laboratory results to validate their diagnosis for disturbed coagulation. Rhabdomyolysis was observed in 35 % (7) of the patients, while 35 % (7) of the patients did not have the necessary laboratory results needed to rule out rhabdomyolysis. Only two patients did not have the required laboratory results to rule out the possibility of renal injury, however one patient had confirmed kidney damage. Of the patients bitten by *N. n. nigricincta* snakes 20 % (4) had liver damage, and 45 % (9) of the patients had insufficient information to establish the liver damage diagnosis.

Patients who were bitten by *N. n. nigricincta* snake had clinical pathological characteristics, with rhabdomyolysis being the highest accounting for 58 % (7) of the patients as presented in Figure 27. Table 24 indicated the different cases that affected pathologically. Neurotoxicity was observed in 50 % (10) patients, 40 % (8) were bitten by *N. n. nigricincta* and 10 % (2) were patients bitten by *B. a. arietans*.

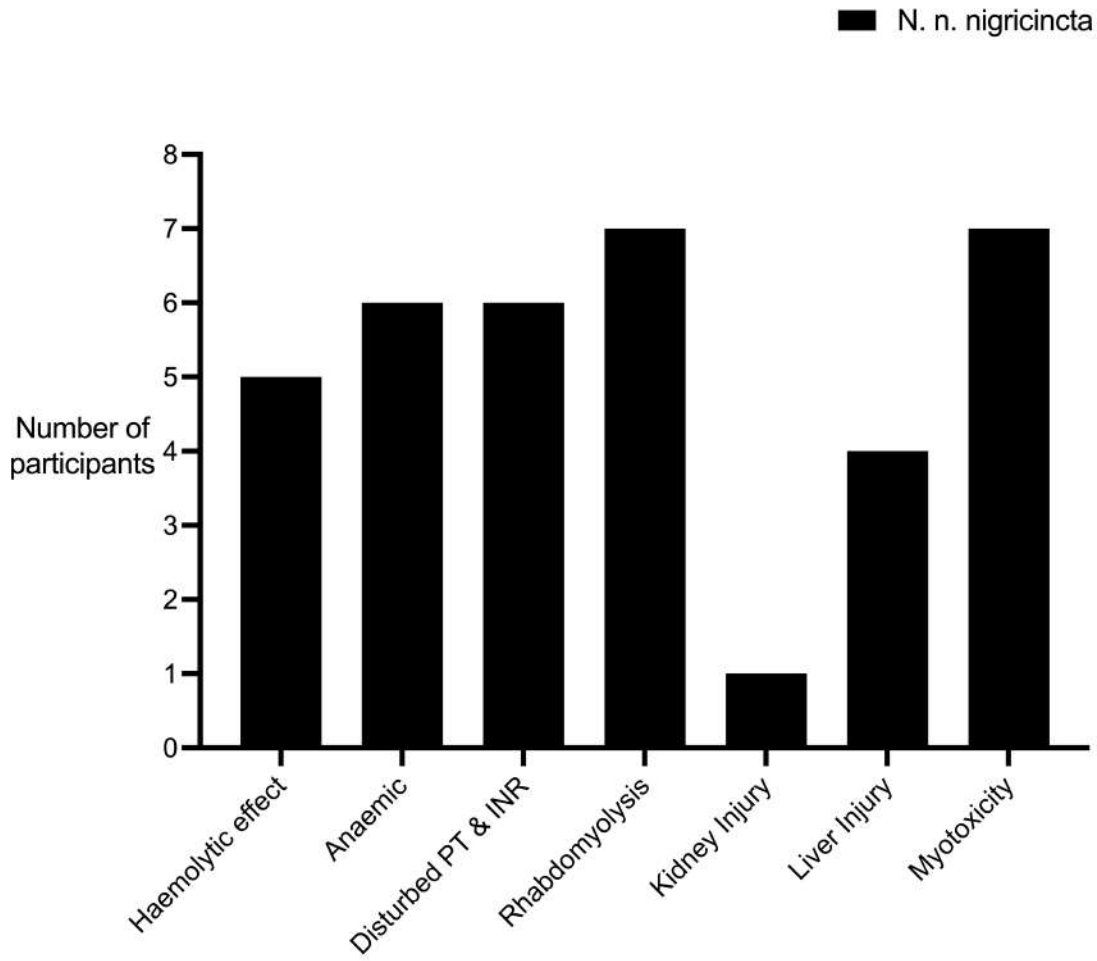


Figure 27: Clinical pathological features inflicted by *N. n. nigricincta* snakes

Table 24: Patients systemic results

Systemic signs	Case 1	Case 5	Case 8	Case 9	Case 13	Case 15	Case 17	Case 19	Case 20
Anaemia	•	•				•	•		•
Haemolysis	•			•	•	•	•		
Rhabdomyolysis	•		•	•	•	•	•	•	
Myotoxicity	•		•	•	•	•	•	•	
Kidney damage						•			
Liver damage	•		•	•	•			•	

4.8. Treatment of Snakebites

Intravenous fluids, pain medication, analgesics, SAIMR polyvalent antivenom, antibiotics and limb elevation were used to treat snakebites in this study. Antibiotics (Clindamycin, Augmentin, Ceftriaxone, Cloxacillin, and Cefuroxime) on the other hand, were only given to patients who've had cuts or necrosis. In contrast, only three (15 %) patients received antivenom, one for *N. n. nigricincta* bites and two for *B. a. arietans* bites, although the majority of snakebites observed in the study cause significant injuries.

A significant number of patients with snakebite injuries from *N. n. nigricincta* and *B. a. arietans* required surgical intervention, with 45 % (9) fasciotomy, 60 % (12) debridement, and 20 % (4) skin graft procedures being performed on the patients. For the purpose of relieving intracompartmental pressure, approximately 58 % (7) of patients bitten by *N. n. nigricincta* underwent fasciotomy, whereas only 25 % (2) of patients were bitten by *B. a. arietans* required fasciotomy (Figure 27). Debridement of necrotic tissue was performed on 9 of the patients bitten by *N. n. nigricincta* and 3 of the patients bitten by *B. a. arietans* in this study.

Table 25 Surgical interventions in the patients

	N. n. nigricincta n, (%)	*B. a. arietans* n, (%)
Fasciotomy	7 (58)	2 (25)
Debridement	9 (75)	3 (38)
Skin graft	3 (25)	1 (13)

4.9. Patients Functional Outcomes

The average length of stay in the hospital for snakebite patients was 18 ± 14 days, with one day being the shortest hospitalisation stay and 43 days being the longest hospitalisation stay. Complete recovery was observed in 55 % (11) patients, with no damage other than scarring of the skin. The study indicated that 30 % (6) of the patients were discharged with muscle weakness, and 15 % (3) patients had limb amputations. Two of the three amputees were bitten by *N. n. nigricincta* snakes, and only one was bitten by *B. a. arietans* (Figure 28). Of the patients 42 % (5) of patients who were bitten by the *N. n. nigricincta* snake recovered fully, whereas 75 % (6) patients who were bitten by the *B. a. arietans* snake recovered fully.

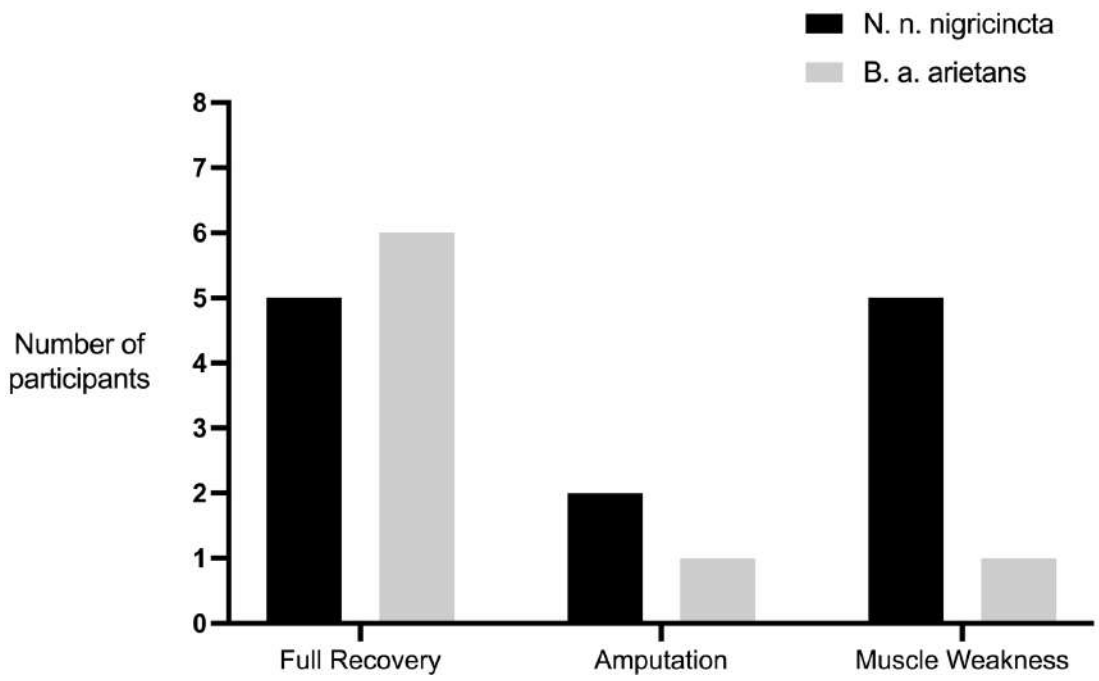


Figure 28: Patients functional outcome

CHAPTER 5

5. Discussion

5.1. An Overview

Snakebite is a major public health issue that disproportionately affects remote and rural communities (7). It is frequently overlooked and understudied, leading to a dearth of information on the pathology caused by snakebite, effective treatment procedures, the availability specialists that treat snakebites, and the availability of antivenom (7). Namibia is a sparsely populated country with a high incidence of snakebite, particularly those caused by the *N. n. nigricincta* and *B. a. arietans* (6,19,20). This study was carried out in Windhoek (WHK), focusing on patients who were presented to Katutura Intermediate State Hospital (KISH) and Windhoek Central (WCH) after being bitten by *N. n. nigricincta* and *B. a. arietans* snakes. The study assessed the clinicopathological in terms of signs, symptoms and laboratory aspects in order to determine any organ damage caused by the venom toxins of *N. n. nigricincta* and *B. a. arietans* bites.

5.2. Patient's Natural History

The study included 20 snakebite patients, 18 of whom had symptoms consistent with envenomation (swelling, redness, bruising, blistering around the bite site, etc.) and two who had dry bites. Dry bites happen when a poisonous snake bites a person and the person exhibits no clinical signs of envenomation, neither local nor systemic (7). This may be the result of mechanical inefficiency or the snake's ability to regulate the release of its venom. The *N. n. nigricincta* snakes was the most frequently encountered snake in this study, accounting for 60 % of bites. *N. n. nigricincta* snake prefer to disguise themselves among trees and in the ground (20). *N. n. nigricincta* snakes in

this study were more likely to appear in people's homes, where they targeted patients mostly while they were sleeping. *B. a. arietans* snakes, on the other hand, are typically found in the patient's yard, and patients are generally bitten when walking around or playing in the yard. This is because *N. n. nigricincta* snakes have a tendency to attack people at night, probably because they are attracted to the odour of perspiration, may feel threatened when in contact with a human, or may mistake humans for food (16,45,66).

The epidemiological characteristic in this investigation revealed that males got bitten more frequently than females, and the majority of the patients (65 %) who were bitten were children between the ages of 0 – 15 years. This is consistent with previous studies, which could be due to children being less aware of their surroundings than adults, whereas adults can usually detect danger from a distance (7,10,15,34,38,55).

In this study, the majority of snakebites happened on farms, with the most of bites occurring on the hands and feet. Additionally, this was consistent with other studies that indicated farm workers to be more susceptible to snakebites, with most bites occurring on the hand, leg, or foot as a result of herding cattle or resting under a tree (7,11,33,34,55). Children commonly reach out to play with or to try and kill the snakes, completely unaware of the danger they are exposing themselves to and the risk that the snakes may possess. Adults usually aim to kill the snake, and do not wear protective gear when working/walking in the fields.

The season for most of the snakebites in this study happened during summer months, which runs from October to March in Namibia. This study was comparative to others studies that indicated that snakebites happen in the warmer and wet months of the year (5,7,15,30,40,76). Seasonal transition to warmer climate conditions has enabled snake species to expand their range into more favourable habitats in quest of food (11,34).

Furthermore, this could also be because of the harvesting of the agricultural crops, which causes there to be longer grass everywhere during this time of year, which in turn attracts rats and mice for snakes to prey (7,11). As a result, snakes may enter people's homes in search of food and shelter.

In this investigation, Kunene region recorded the highest number of snakebite incidents, with bites from only the *N. n. nigricincta* snake. This is because Namibia's wildlife park (Etosha National Park) is located in the Kunene region, which offers favourable climates, trees, and long grass for the habitat of *N. n. nigricincta* snake (16). It is also a remote region that is predominately made up of farms, allowing for the cultivation of plants, which increases the population of rodents, which snakes prey on. Omaheke and Erongo regions had the lowest incidence, with both regions only recording *B. a. arietans* bites. Since, *B. a. arietans* have a sandy (light brown) colouring (15), they prefer habitats where they can blend in with their surroundings and sneak up on their prey. Both of these Omaheke and Erongo regions are dry and sand, ideal for *B. a. arietans* because their environment is slightly cooler, desert like, savanna and open grasslands (12,15).

This study revealed that the majority of these snakebites occurred on farms located in remote areas, it took most patients an average of 1 – 4.5 hours and 1.4 – 22.8 hours to get to the primary health care centres and referral hospital (KISH and WCH), respectively. Not only are patients delayed in receiving treatment because they live on farms, but also because their initial local hospitals/ health centres may lack capacity in treating snakebites, such as they lacked antivenom, requisite equipment and competence to treat snakebites, necessitating the transfer to WHK for better health care. Although snakebites are considered a medical emergency in Namibia and transport to WHK's referral hospitals from primary health care centre is readily

available, patients may still experience delays in treatment. This could be due to a lack of transportation in remote areas, the fact that some patients do not seek treatment immediately after getting bitten by a snake, or the distance between the patient's primary health care centre and WHK's referral hospitals. Consequently, patients develop severe oedema often due to the huge significant time difference between the time of the bite and the time the patient's received assistance at WHK's referral hospitals. This was consistent with a study done in South Africa that also found factors that contributed to treatment delays such as rural communities that lack access to transportation, as well as problems with patient transferring from referring health facilities (77).

5.3. Local Effects on Snakebite Patients

This study found that several people (80 %) had local symptoms such as discomfort, oedema, necrosis and blistering, which were consistent with previous research that indicated that *N. n. nigricincta* and *B. a. arietans* cause tissue damage, intense pain, swelling, blistering and necrosis (1,7,10,15,16). Three of the patients received traditional medication/therapy, which included application methylated spirits to the patient's bite site (case 2), drinking petrol (case 9), application both methylated spirits and petrol to the bite site (case 11), and finally case 20, who reported that incisions were made at the bite site that were so deep that they severed the artery supplying blood to the finger. Although traditional methods are known to aggravate the patient's condition and are strongly discouraged from use, many people still use them before seeking medical attention (2,7,10,19,77).

The venom from *N. n. nigricincta* and *B. a. arietans*, contains hyaluronidase, phospholipase A, and polypeptide toxins that increase permeability, was found to

cause necrosis, which was consistent to this study findings indicating that patients developed necrosis after the bite (45,48). This study highlighted that surgical intervention was essential because patients required debridement to remove necrotic tissue and aid wound healing. Approximately 60 % of patients underwent surgical debridement in order to facilitate wound healing which is a common practice according to the guideline on snakebite management in Namibia (19). Furthermore, fasciotomy was performed on patients with significant oedema, with 45 % of patients in this study undergoing fasciotomy to relieve pressure; however, not all patients with significant oedema underwent fasciotomy. The fasciotomy procedure was solely determined by the physician on call, and there was no pressure measurement to confirm the treatment. As a consequence, patients had intolerable levels of pain, and their rate of recovery was extremely slow (longer hospital stays). The findings of this study were inconsistent with previous studies, which typically performed compartment pressure measurements before performing fasciotomies (7,10,53,78). Ultimately, only 20 % underwent skin grafting following surgical debridement and fasciotomy.

5.4. Systemic Effects from Snake Envenomation

In this study bites from *B. a. arietans* showed no signs of biological systemic damage, except for mild neurotoxicity. This study finding is different from other studies that illustrated bites from *B. a. arietans* may cause haemolytic anaemia, change in coagulation, and organ damage (kidney, liver and heart) (4,8,19,24,76,77). This may be due to the fact that the study had a relatively small sample size, which shows that this may have been a factor contributing to no evidence of systemic effect.

In this investigation, neurological symptoms were present in 50 % of the patients; however, these symptoms were all relatively mild. The most prevalent neurological symptoms were drowsiness and limb weakness in this study. Furthermore, this study findings showed that neurological symptoms were present in 60 % of cases involving *N. n. nigricincta* bites, while only 25 % of cases involving *B. a. arietans* bites exhibited neurological symptoms. This investigation results were compatible with previous studies that reported that *N. n. nigricincta* and *B. a. arietans* bites have been shown to cause neurotoxic symptoms such as collapse (hypotension, shock), nausea, vomiting, diarrhoea, severe headaches, drowsiness, heaviness of the eyelids, and ptosis, all of which are among the most common symptoms associated with systemic envenomation, however the effects are frequently mild (1,7,10,15,19).

Six (case 1, 5, 9, 15, 17, and 20) of 12 patients bitten by *N. n. nigricincta* snake in this study had anaemia, and six (case 1, 9, 13, 15, 17, and 20) of the patient's developed haemolysis due to the venom toxins from *N. n. nigricincta* snake. Furthermore, these findings revealed that only five patients were confirmed to have haemolytic anaemia (case 1, 9, 15, 17, and 20). This was consistent with other studies that reported that venom toxins from elapid species such as spitting cobras may cause haemolytic anaemia (4,7,10,24).

Patients in this study (cases 1, 5, and 8) exhibited prolonged prothrombin times and high international normalized ratios, indicating that their blood was not clotting normally. However, because fibrinogen, activated partial thromboplastin clotting time (PTT), and d-dimer were not conducted, it is hard to determine that the three patients had a coagulation disorder. Serine proteinase (SVSPs) has been shown to affect coagulation, platelet aggregation, fibrinolysis, the complementary system, and the immune system in both elapid and viper snakebites (26,45,79,80). Typically, elevated

INR are also associated with liver illness, warfarin medication, or depletion as a result of consumptive coagulopathy, acute bleeding, or major transfusion (64). Platelet count for case 1 and case 8 were within the normal range, but Case 5 exhibited thrombocytosis, which could have been caused by an infection. In conclusion, venom indicated extrinsic pathway activation in patients, demonstrating that PT and INR alone cannot be utilised as a reliable predictor to determine affected coagulation of hemotoxic envenomation in the patients. However, this result finding is different from other studies that illustrated that both *N. n. nigricincta and B. a. arietans* have venom that is known to be cytotoxic and hemotoxic, causing severe haemostasis disruption, tissue damage, intense pain, swelling, and necrosis (15,16).

Similarly, to a study by Saaiman et al. (20), these findings revealed that 58 % of the patients who had rhabdomyolysis (case 1, 8, 9, 13, 15, 17, & 19), were bitten by a *N. n. nigricincta* snake. Rhabdomyolysis is a common complication of snake envenomation that causes damaged or injured skeletal muscle to dissolve quickly (7–10,20,58).

These findings indicated that one patient (case 15) had a verified kidney damage following a *N. n. nigricincta* snakebite. Despite the fact that rhabdomyolysis is a frequent cause of kidney disease (65), this investigation recorded no evidence to rule out the potential that any further patients acquired kidney injury. However, the fact that no urine output test was performed on any of the remaining patients in this study to confirm the diagnosis, their glomerular filtration rates (GFRs) were within normal limits. These findings are consistent with previous research, which found that patients who were bitten by elapid or viper snakes may or may not have kidney damage (7,8,10,19).

Two of the patients bitten by *N. n. nigricincta* in this study (case 8 and case 9) had evidence of elevated LDH, AST, and creatinine kinase myocardial band (CK-MB) levels indicating muscle damage to the heart. This was consistent with previous research indicating that snake venom containing phospholipase A2s (svPLA2s) causes cardiotoxicity in both elapid and viper snakebites (45). However, there was no sufficient data to validate the potential.

Liver damage was established in 20 % of patients (case 1, 8, 13 and 19) bitten by *N. n. nigricincta* snakes in this study. The liver impairment was diagnosed as a result of elevated ALT, AST, and bilirubin levels, as well as a low albumin level (62).

Despite the severe injuries sustained by patients only 15 % of the patients received antivenom, two (case 2 and case 3) bitten by *B. a. arietans* and one bitten by *N. n. nigricincta* (case 9). Antivenom is not readily available in Namibia, especially at community health centres, because it is expensive and must be stored at specific temperatures. As a result, medical practitioners have resorted to procedures other than antivenom to treat snakebites, including surgical treatment, elevating the injured limb, etc (19).

5.4.1. Case Discussions on Systemic Envenomation

Case one showed signs of haemolytic anaemia, rhabdomyolysis, myotoxicity, and liver damage. Cases 5, 6, and 12 all had thrombocytosis, with the exception of Case 5, which was also anaemic. Case eight displayed signs of rhabdomyolysis, myotoxicity, and organ damage (heart and liver). Case nine also showed signs of rhabdomyolysis, myotoxicity, haemolysis, and hart damage. Cases 13 and 19 showed signs of rhabdomyolysis, myotoxicity, and liver damage, but Case 13 also showed signs of haemolysis. Case 15 displayed symptoms of rhabdomyolysis, myotoxicity,

thrombocytopenia, haemolytic anaemia, and kidney damage. Case 17 was experiencing from rhabdomyolysis, myotoxicity, and haemolytic anaemia.

5.5. Overall Shortcoming and Strength of this Study

Snakebite registry was not reliable, as some of the patients were not recorded in the book. The sample sizes for the two species were not equal, which could have resulted in skewed findings indicating that the *N. n. nigricincta* bites caused more systemic envenomation; therefore, a larger sample size would have been preferable. Since there was no standardised treatment in this study, each patient was treated according to the doctor on call, which was a significant study limitation resulting in some patients missing some laboratory measures that the clinical assessor did not request them. These laboratory measures that were missing would have been relevant in ruling out systemic envenomation for some of the patients. Hence, making it difficult to determine whether or not the snake venom toxin had altered the patient's system. However, the mechanism of systemic damage of snakebite toxins is not fully understood for snakebites (1,3,4,7,10). For the first time a clinical pathological study of bites from *N. n. nigricincta and B. a. arietans* has been conducted in Namibia. Providing better understanding of patient's treatment and clinical outcome associated with bites of *N. n. nigricincta and B. a. arietans* in Namibia.

CHAPTER 6

6. Conclusion

Snakebite injury is common in Namibia, especially of those of *N. n. nigricincta* and *B. a. arietans*. Snakebite treatment and diagnosis from bites of *N. n. nigricincta* and *B. a. arietans* in Namibia are not insurmountable challenges when clinical examiners adhere to the standards provided (Namibian standards for Medical Management of Snakebite Victims), and adequate resources are available to treat patients. This study revealed that children are the most affected population in Namibia, particularly those who live on farms, and sleep on the floors of shacks. In this study finding *N. n. nigricincta* and *B. a. arietans* bites produced cytotoxicity, and neurotoxic effects and were well-documented. Nevertheless, the investigation of hemotoxins and cardiotoxins yielded unclear results because the majority of patients did not have the relevant laboratory results to draw those conclusions. *N. n. nigricincta* bites in this study indicated that the venom had an adverse effect on the patient's biological systems both locally and systemically. The bites from the *B. a. arietans*, on the other hand, caused predominantly local effects, although some patients experienced neurological problems, and no major clinical pathology was detected on the patients. No known infection occurred from snakebite wounds, most healed well but left some patients with some disabilities such as muscle weakness and amputations based on this study finding. Patient's mobility and function was restored, maintained, and improved thanks to a collaborative effort between the medical professionals and the physiotherapy intervention in this study. However, patients are not mentally ready to see the damage inflicted by *N. n. nigricincta* and *B. a. arietans* snakebites, and there is no collaboration between medical professionals and social workers or psychologists. As a result, patients experienced severe psychological distress as a result of viewing

the wounds. By comparison, patients bitten by *B. a. arietans* have better prognosis and outcomes in this study over those bitten by *N. n. nigricincta*.

CHAPTER 7

7. Recommendations

- Further studies with a larger sample size are required to determine which regions account more for which snake species (*N. n. nigricincta* and *B. a. arietans*) in Namibia, as well as to determine more evidence of systemic pathology especially bites from *B. a. arietans*.
- Wound treatment techniques for *N. n. nigricincta* and *B. a. arietans* snakebites require improvement.
- Teaching medical and occupational students about snakebite management protocols by incorporating it into medical school's curriculum, such as pathology modules.
- Provide training classes for medical professionals on how to properly treat *N. n. nigricincta* and *B. a. arietans* snakebites, especially those in local clinics and hospitals.
- Educate communities on proper snakebite prevention practices (such as decluttering the homestead, storing food in appropriate closed containers, avoiding sleeping on the floor or raising the bed above floor level, using mosquito nets and completely tucking it under the sleeping mat when sleeping on the floor, using light and properly looking around the room before tucking the children in to sleep, watching the children while they play outside, etc.).
- Community members should be educated on proper first aid practices, including what they should and should not do in the event of a snakebite.
- Establish strict rules to use striker needles in order to test the severity of compartment syndrome prior to performing fasciotomy on patients. This aids

in avoiding unnecessary fasciotomies, which can result in wound complications such as scarring.

- There is a need for emergency service in remote areas.
- The Ministry of Health and Social Service should look into the need to fund the production of *N. n. nigricincta* snake antivenom in Namibia, which is desperately needed given that the majority of the bites in this study were from *N. n. nigricincta*, which accounted for the severe damage done to the patients.

Reference

1. World Health Organization. WHO launches a strategy to cut snakebite deaths and disabilities in half? [Internet]. 2019 [cited 2020 Mar 10]. Available from: https://www.msf.org/who-launches-strategy-cut-snakebitedeaths-and-disabilities-half.
2. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, et al. The global burden of snakebite: A literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Medicine. 2008;5(11):1591–604.
3. World Health Organization. Snakebite envenoming: a strategy for prevention and control. 2019; 392:29–30.
4. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nature reviews Disease primers. 2017;3(1):1-21.
5. Halilu S, Iliyasu G, Hamza M, Chippaux JP, Kuznik A, Habib AG. Snakebite burden in Sub-Saharan Africa: estimates from 41 countries. Toxicon [Internet]. 2019;159(September 2018):1–4. Available from: https://doi.org/10.1016/j.toxicon.2018.12.002.
6. Hunter CJ, Piechazek KH, Nyarang'o PM, Rennie T. Snakebite envenoming. Vol. 393, The Lancet. Lancet Publishing Group; 2019. p. 129–31.
7. World Health Organization. Snake management in Africa. 2010 [cited 2021 Jun 30]. Available from: https://doi.org/10.1007/s40475-020-00198-y.
8. Knudsen C, Jürgensen JA, Føns S, Haack AM, Friis RU, Dam SH, Bush SP, White J, Laustsen AH. Snakebite envenoming diagnosis and diagnostics. Frontiers in Immunology. 2021;12:1268.
9. Pogribny A, Moreno-Walton LA. Snake Envenomation. In Prepare for the Pediatric Emergency Medicine Board Examination 2020 (pp. 635-641). Springer, Cham.
10. WHO Regional Office for Africa. Guidelines for the prevention and clinical management of snakebite in Africa. World Health Organization. Regional Office for Africa. 2010;1–145. Available from: https://apps.who.int/iris/handle/10665/204458.

11. Warrell DA. WHO/SEARO Guidelines for the clinical management of snake bites in the Southeast Asian region. Southeast Asian J Trop Med Public Health. 1999;30 Suppl 1:1–85.
12. Hauptfleisch ML, Sikongo IN, Theart F. A spatial and temporal assessment of human-snake encounters in urban and peri-urban areas of Windhoek, Namibia. Urban Ecosystems. 2021;24(1):165-73.
13. World Health Organization. Governing Body matters: Key issues arising out of the Seventy-first World Health Assembly and the 142nd and 143rd Sessions of the WHO Executive Board. World Health Organization. Regional Office for South-East Asia; 2018.
14. Koh DC, Armugam A, Jeyaseelan K. Snake venom components and their applications in biomedicine. Cellular and Molecular Life Sciences CMLS. 2006;63(24):3030-41.
15. Muller GJ, Modler H, Wium CA, Marks CJ, Veale DJ. Snake bite in southern Africa: diagnosis and management. CME: Your SA Journal of CPD. 2012;30(10):362-82.
16. Kandiwa E, Mushonga B, Samkange A, Fabiano E. Quantitative characterization of the hemorrhagic, necrotic, coagulation-altering properties and edema-forming effects of zebra snake (Naja nigricincta nigricincta) venom. Journal of Toxicology. 2018;2018, 6940798.
17. Gutiérrez JM. Preclinical assessment of the neutralizing efficacy of snake antivenoms in Latin America and the Caribbean: A review. Toxicon. 2018;146:138-50.
18. Del Brutto OH, Del Brutto VJ. Neurological complications of venomous snake bites: a review. Acta Neurologica Scandinavica. 2012;125(6):363-72.
19. Buys PJC, Saaiman EL. Medical Management of the Snakebite Victims Namibia. Hilos Tensados. 2019;1:1–476.
20. Saaiman EL, Buys PJ. Spitting cobra (Naja nigricincta nigricincta) bites complicated by rhabdomyolysis, possible intravascular haemolysis, and coagulopathy. South African Medical Journal. 2019;109(10):736-40.
21. Ayello EA, Baranoski S. Nursing2014 survey results: Wound care and prevention. Nursing2020. 2014;44(4):32-40.

22. Dissanayake DA, Sosai C, Weerawardane M, Priyadharshanie JW, Rajapakse RP, Kularatne SA. Description of the histological features in wounds of snake bite aetiology. Adv Surg Sci. 2017;5(7):57-60.
23. Republic of Namibia Ministry of Health and Social Services. Namibia Standard Treatment Guidelines, First Edition. 2011;891.
24. Johnson CA. Management of snakebite. Vol. 44, American Family Physician. 1991. 174–180 p.
25. Antivenom-Southafrica-Savp-Polyvalentsnake Pdf [package insert]. South African Vaccine Producers (PTY) LTD. Gauteng; 2006 [cited 2020 Feb 10]. Available from: http://www.antivenoms.toxinfo.med.tum.de/resources/antivenom_southafrica-savp-polyvalentsnake_2011-07-04.pdf.
26. Gutiérrez JM, Lomonte B, Leon G, Alape-Giron A, Flores-Diaz M, Sanz L, Angulo Y, Calvete JJ. Snake venomics and antivenomics: Proteomic tools in the design and control of antivenoms for the treatment of snakebite envenoming. Journal of proteomics. 2009;72(2):165-82.
27. Gutiérrez JM, Theakston RD, Warrell DA. Confronting the neglected problem of snake bite envenoming: the need for a global partnership. PLoS medicine. 2006;3(6):150.
28. Chanhome L, Cox MJ, Wilde H, Jintakoon P, Chaiyabutr N, Sitprija V. Venomous snakebite in Thailand I: medically important snakes. Military medicine. 1998;163(5):310-7.
29. Xiao H, Pan H, Liao K, Yang M, Huang C. Snake venom PLA2, a promising target for broad-spectrum antivenom drug development. BioMed research international. 2017;2017.
30. Lancet T. Snake-bite envenoming: a priority neglected tropical disease. Lancet (London, England). 2017;390(10089):2.
31. Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease. Journal of Venomous Animals and Toxins including Tropical Diseases. 2017;23(1):1-2.
32. Murugan A, Ahmed S, Gani M. A retrospective study of snake bite envenomation in a tertiary care teaching hospital in Southern India. International Journal of Research in Medical Sciences. 2015;3(9):2419–24.

33. Habibid AG, Musa BM, Iliyasuid G, Hamza M, Kuznik A, Chippauxid JP. Challenges and prospects of snake antivenom supply in Sub-Saharan Africa. PLoS Neglected Tropical Diseases. 2020;14(8):1–10.
34. Alirol E, Sharma SK, Bawaskar HS, Kuch U, Chappuis F. Snake bite in south asia: A review. PLoS Neglected Tropical Diseases. 2010;4(1).
35. Tilbury CR. Observations on the bite of the Mozambique spitting cobra (Naja mossambica mossambica). South African Medical Journal. 1982;61(9):308-13.
36. Isbister GK, Silva A. Addressing the global challenge of snake envenoming. The Lancet. 2018;392(10148):619-20.
37. Longbottom J. Correspondence Snakebite envenoming. 2016;391(18):1–2.
38. Omogbai EK, Nworgu ZA, Imhafidon MA, Ikpeme AA, Ojo DO, Nwako CN. Snake bites in Nigeria: A study of the prevalence and treatment in Benin City. Tropical Journal of Pharmaceutical Research. 2002;1(1):39-44.
39. Progga NI, Rezoana N, Hossain MS, Islam RU, Andersson K. A CNN Based Model for Venomous and Non-venomous Snake Classification. In: Communications in Computer and Information Science. Springer Science and Business Media Deutschland GmbH; 2021. p. 216–31.
40. Bauchot R, editor. Snakes: a natural history. Sterling Publishing Company, Inc.; 2006.
41. Fatah C. Pathophysiological and Pharmacological Effects of Snake Venom Components: Molecular Targets. Journal of Clinical Toxicology. 2014;04(02).
42. Goswami PK, Samant MA, Srivastava RS. Snake venom, anti-snake venom & potential of snake venom. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;6(5):4-7
43. Ferraz CR, Arrahman A, Xie C, Casewell NR, Lewis RJ, Kool J, Cardoso FC. Multifunctional toxins in snake venoms and therapeutic implications: from pain to hemorrhage and necrosis. Frontiers in ecology and evolution. 2019;7:218.
44. Tasoulis T, Isbister GK. A review and database of snake venom proteomes. Toxins. 2017;9(9):290.
45. Katali O, Shipingana L, Nyarangó P, Pääkkönen M, Haindongo E, Rennie T, James P, Eriksson J, Hunter CJ. Protein identification of venoms of the

African spitting cobras, Naja mossambica and Naja nigricincta nigricincta. Toxins. 2020;12(8):520.

46. Kelwick R, Desanlis I, Wheeler GN, Edwards DR. The ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs) family. Genome Biology. 2015;16(1).
47. Wang Y, Pereira EF, Maus AD, Ostlie NS, Navaneetham D, Lei S, Albuquerque EX, Conti-Fine BM. Human bronchial epithelial and endothelial cells express α7 nicotinic acetylcholine receptors. Molecular Pharmacology. 2001;60(6):1201-9.
48. Laden A, Duterte T, Flament F. The Market of Snake Antivenoms [presentation transcript]. 2001;1–9. https://slideplayer.com/slide/10157305/.
49. Xiong S, Huang C. Synergistic strategies of predominant toxins in snake venoms. Toxicology letters. 2018;287:142-54.
50. Gutiérrez JM, Rucavado A, Escalante T, Díaz C. Haemorrhage induced by snake venom metalloproteinases: Biochemical and biophysical mechanisms involved in microvessel damage. Toxicon. 2005;45(8):997–1011.
51. de Paula RC, Castro HC, Rodrigues CR, Melo PA, Fuly AL. Structural and pharmacological features of phospholipases A2 from snake venoms. Protein and Peptide Letters. 2009;16(8):899-907.
52. Warrell DA, Greenwood BM, Davidson NM, Ormerod LD, Prentice CR. Necrosis, haemorrhage and complement depletion following bites by the spitting cobra (Naja nigricollis). QJM: An International Journal of Medicine. 1976;45(1):1-22.
53. Cumpston KL. Is there a role for fasciotomy in Crotalinae envenomations in North America?. Clinical Toxicology. 2011;49(5):351-65.
54. Isbister GK, Brown SGA, Page CB, McCoubrie DL, Greene SL, Buckley NA. Snakebite in Australia: A practical approach to diagnosis and treatment. Medical Journal of Australia. 2013;199(11):763–8.
55. Blaylock RS. The identification and syndromic management of snakebite in South Africa. South African Family Practice. 2005;47(9):48–53.
56. Osei-Bimpong A, McLean R, Bhonda E, Lewis SM. The use of the white cell count and haemoglobin in combination as an effective screen to predict

the normality of the full blood count. International journal of laboratory hematology. 2012;34(1):91-7.

57. Leach M. Interpretation of the full blood count in systemic disease--a guide for the physician. JR Coll Physicians Edinb. 2014;44(1):36-41.
58. Frare BT, Silva Resende YK, Dornelas BD, Jorge MT, Souza Ricarte VA, Alves LM, Izidoro LF. Clinical, laboratory, and therapeutic aspects of Crotalus durissus (South American rattlesnake) victims: A literature review. BioMed research international. 2019;2019.
59. Beldon P. Basic science of wound healing. Surgery (Oxford). 2010;28(9):409-12.
60. Walters MC, Abelson HT. Interpretation of the complete blood count. Pediatric Clinics. 1996;43(3):599-622.
61. Vieth JT, Lane DR. Anemia. Emergency Medicine Clinics. 2014;32(3):613-28.
62. Levick C. How to interpret liver function tests. South Sudan Medical Journal. 2017;10(2):40-3.
63. Walters MC, Abelson HT. Interpretation of the complete blood count. Pediatric Clinics. 1996;43(3):599-622.
64. Bennett JS. Blood coagulation and coagulation tests. Medical Clinics of North America. 1984;68(3):557-76.
65. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. Critical care. 2016;20(1):1-3.
66. Bittenbinder MA, Zdenek CN, Op den Brouw B, Youngman NJ, Dobson JS, Naude A, Vonk FJ, Fry BG. Coagulotoxic cobras: Clinical implications of strong anticoagulant actions of African spitting Naja venoms that are not neutralised by antivenom but are by LY315920 (Varespladib). Toxins. 2018;10(12):516.
67. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood, The Journal of the American Society of Hematology. 2009;113(13):2878-87.
68. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. Journal of Intensive Care. 2014;2(1):1-8.

69. Patel ND. Differential diagnosis of acute liver failure in India. Annals of hepatology. 2006;5(3):150-6.
70. Dart RC, McNally J. Efficacy, safety, and use of snake antivenoms in the United States. Annals of emergency medicine. 2001;37(2):181-8.
71. Tan NH, Tan CH. Cytotoxicity of snake venoms and toxins: mechanisms and applications. Arcadius V. Krivoshein YNU, editor. Snake Venoms and Envenomation: Modern Trends and Future Prospects. Medicine and Biology Research Developments. New York: Nova Science Publishers. 2016:215-54.
72. Chippaux JP. Guidelines for the production, control and regulation of snake antivenom immunoglobulins. Biologie aujourd'hui. 2010;204(1):87-91.
73. Harrison RA, Oluoch GO, Ainsworth S, Alsolaiss J, Bolton F, Arias AS, Gutiérrez JM, Rowley P, Kalya S, Ozwara H, Casewell NR. Preclinical antivenom-efficacy testing reveals potentially disturbing deficiencies of snakebite treatment capability in East Africa. PLoS neglected tropical diseases. 2017;11(10):e0005969.
74. de Oliveira PR, de França FS, Boas IM, da Rocha MM, Sant'Anna SS, de Lourdes Bastos M, Tambourgi DV. Snake venoms from Angola: Intra-specific variations and immunogenicity. Toxicon. 2018;148:85-94.
75. Parker-Cote J, Meggs WJ. First aid and pre-hospital management of venomous snakebites. Tropical medicine and infectious disease. 2018;3(2):45.
76. Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: treatment modalities and outcomes. South African Medical Journal. 2009;99(11).
77. Kim YH, Choi JH, Kim J, Chung YK. Fasciotomy in compartment syndrome from snakebite. Archives of plastic surgery. 2019 Jan;46(1):69.
78. Goswami PK, Samant MA, Srivastava RS. Snake venom, anti-snake venom & potential of snake venom. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;6(5):4-7.
79. Kerkkamp H, Bagowski C, Kool J, van Soolingen B, Vonk FJ, Vlecken D. Whole snake venoms: Cytotoxic, anti-metastatic and antiangiogenic properties. Toxicon. 2018;150:39-49.

80. Cunniff C, Byrne JLB, Hudgins LM, Moeschler JB, Olney AH, Pauli RM, et al. Informed consent for medical photographs. Genetics in Medicine. 2000;2(6):353–5.

ANNEXURE A: Informed Consent Form

Patient Name:_____ Date: _____ Case No: _____

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT: Clinicopathological study of snakebite injury resulting from *Naja nigricincta nigricincta* (Zebra spitting cobra) and *Bitis arietans* (Puff adder)

PRINCIPAL INVESTIGATOR: Katrina Niiteta

CONTACT NUMBER: +264812535833

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Ministry of Health and Social Service Ethics Committee for ethical approval and permission to collect data, and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and Namibian National Research Ethics Guidelines.

1. **What is this research study all about?**

a) *Where will the study be conducted; are there other sites; total number of participants to be recruited at your site and altogether.*

The study is a quantitative descriptive cross-sectional study, which will be conducted at Katutura Intermediate State Hospital and Central Hospital in Windhoek, Namibia. The sample size for this study will be all patients bitten by zebra spitting cobra and puff adder.

b) *Explain in participant friendly language what your project aims to do and why you are doing it?*

The aim of the study is to observe and describe the snakebite wound, and to monitor how patients are being treated resulting from the zebra spitting cobra and puff adder bites at Katutura Intermediate State Hospital and Windhoek Central Hospital. And to come up with a functional outcome protocol on how to care for snakebite by looking at their wounds, signs of organ damage and how their treated.

c) *Explain all procedures.*

Upon admission the research team will be recording all the data, this will include laboratory measurements and vital signs already done by the medical physician, the history of the snakebite, and photographs of the snakebite wound will be taken (upon consent). The research team will describe the wound overtime. Moreover, notified of new findings and subsequently will be followed until the patient is discharged.

d) *Explain any randomization process that may occur.*

N/A

e) *Explain the use of any medication, if applicable.*

N/A

2. Why have you been invited to participate?

a) Explain this question clearly.

You have been invited to participate in this study because you are a patient presenting at Katutura Intermediate State Hospital or Windhoek Central Hospital, who have been bitten by a snake (Zebra spitting cobra or Puff Adder). Consequently, you fall under our study population.

3. What will your responsibilities be?

a) *Explain this question clearly.*

To provide information regarding the history of the snakebite and identification of the snake, to sign both consents/assent (informed consent to participate in the study and patient medical photographs consent), and to be photographed at the site of the bite.

b) Explain the duration the participant is expected to participate in the study (i.e. 2 hours, 4 days, etc.)

From the day upon admission, to discharge day.

4. Will you benefit from taking part in this research?

a) Explain all benefits objectively. If there are no personal benefits, then indicate who is likely to benefit from this research e.g., future patients.

There is no direct benefit or remuneration to the participants, it will provide future information that might help improve medical personnel on how to treat snakebites better.

5. Are there in risks involved in your taking part in this research?

a) Identify any risks objectively.

There are no risks, or harm done to the participants. It is an observational study.

6. If you do not agree to take part, what alternatives do you have?

b) Clearly indicate in broad terms what alternative treatment is available and where it can be accessed, if applicable.

You will still get treatment, even if do not agree to take part in this study. The study is voluntary, and participants have the right withdraw at any given time.

7. Who will have access to your medical records? (Where applicable)

a) Explain that the information collected will be treated as confidential and protected. If it is used in a publication or thesis, the identity of the participant will remain anonymous. Clearly indicate who will have access to the information.

Confidentially and anonymity will strictly be adhered to, hence no names and patients face (during photography) will be used in this study, unless patient is bitten on the facial area. All patient data collected will be filed and kept in a locked cupboard, in a locked office situated at the University of Namibia, only principal investigator and research team will have access. For thesis and publication, no names or patient faces (during photography) will be used, unless bites are on the face.

8. What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?

a) Clarify issues related to insurance cover if applicable. If any pharmaceutical agents are involved will compensation be according to ABPI guidelines? (Association of British Pharmaceutical Industry compensation guidelines for research related injury which is regarded as the international gold standard). If yes, please include the details here. If no, then explain what compensation will be available and under what conditions.

It is very unlikely that there will be any injury, as the study is observational. But in cases that you become ill or uncomfortable while taking part in the study a physician/nurse will be available immediately for necessary medical treatment.

9. Will you be paid to take part in this study and are there any costs involved?

There will not be any form of payments and costs involved.

10. Is there anything else that you should know or do?

a) *You should inform your family practitioner or usual doctor that you are taking part in a research study. (Include if applicable)*

b) *You should also inform your medical insurance company that you are participating in a research study. (Include if applicable)*

c) *You can contact* ***Katrina Niiteta*** *at tel:* **+264812535833** *if you have any further queries or encounter any problems.*

d) *You can contact the Centre for Research and Publications* **at +264 061 2063061; pclaassen@unam.na** *if you have any concerns or complaints that have not been adequately addressed by the investigator.*

e) *You will receive a copy of this information and consent form for your own records.*

11. Declaration by participant

By signing below, I ……. agree to take part in a research study entitled *(***Clinicopathological study of snakebite injury resulting from *Naja nigricincta nigricincta* (Zebra spitting cobra) and *Bitis arietans* (Puff adder)***)***. **I declare that:**

a) I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

b) I have had a chance to ask questions and all my questions have been adequately answered.

c) I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.

d) I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

e) I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…… on (*date*) ……...……..

..... **.....**

Signature of participant Signature of witness

12. Declaration by investigator

I …… declare that:

- I explained the information in this document to ……
- I encouraged him/her to ask questions and took adequate time to answer them.

- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....….....…… on (*date*) ……...….

..... **.....**

Signature of investigator Signature of witness

13. Declaration by interpreter

I *(name)* declare that:

a) I assisted the investigator (*name*) ……. to

explain the information in this document to (*name of participant*)

……..…….. using the language medium of

(Oshiwambo, Damara/Nama, Oshiherero, Afrikaans, etc.)

ANNEXURE B: Medical Photography Consent/Assent Form by (81)**.**

Patient Consent for Medical Photography

Patient Name: _____ Date: _____

Case No: _____

☐ Check here if minor and unable to consent

I ……. Consent for medical photographs to be made of me or my child (or person whom I am legal guardian). I understand that the information may be used in my medical records, for purpose of medical teaching, or for publication in medical textbooks or journals as I have designated below. By consenting to these medical photographs, I understand that I will not receive payment from any party. Refusal to consent to photographs will in no way affect the medical care I will receive. If I have any questions or wish to withdraw my consent in the future I may contact: Katrina Niiteta at 0812535833.

By signing this form below, I confirm that this consent form has been explained to me in terms which I understand.

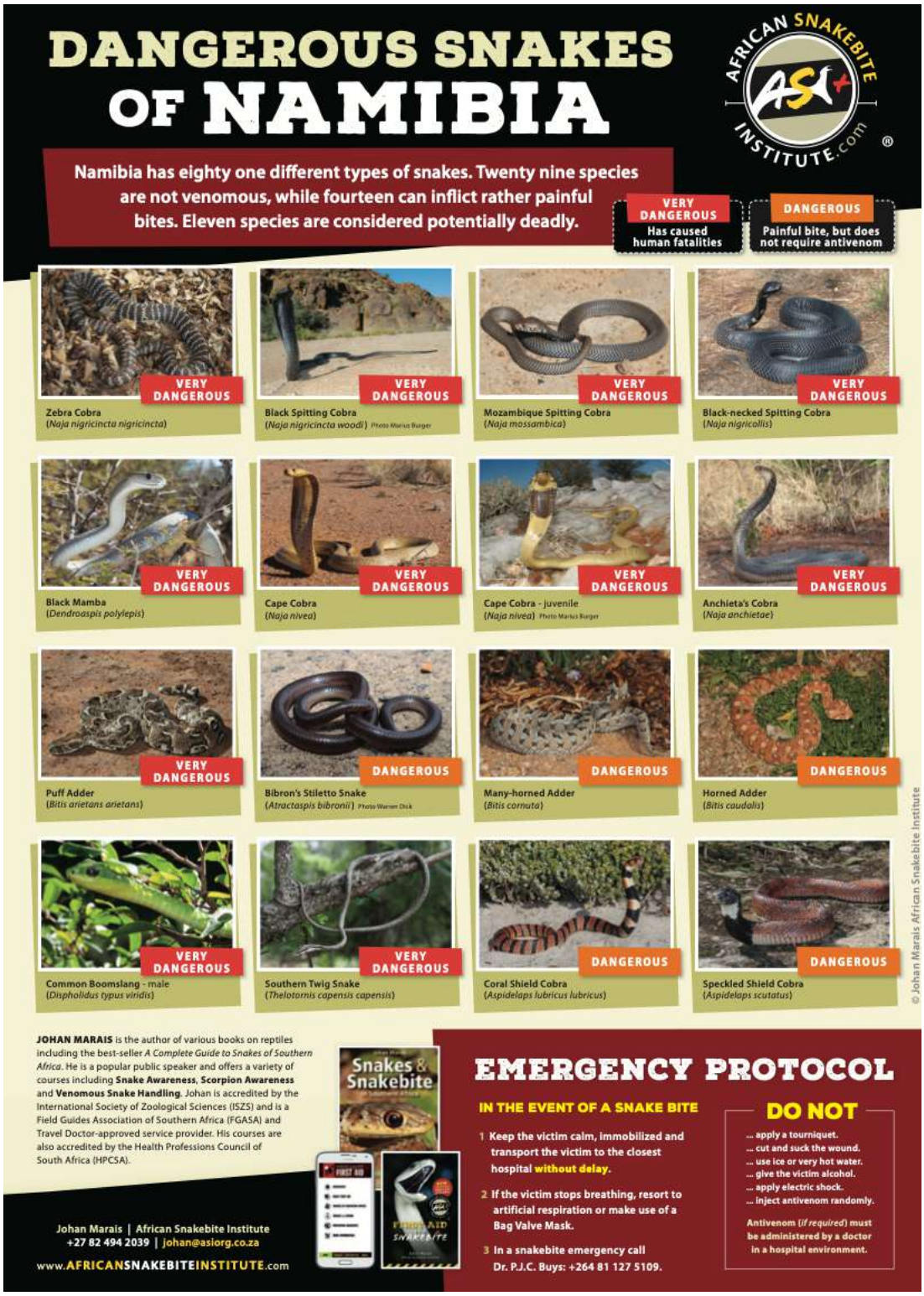
I consent for these photographs to be used in medical publication, including medical journals, textbooks, and electronic publication. I understand that the image may be seen by members of the general public, in addition to scientists and medical researchers that regularly use this publication in their professional education. Although these photographs will be used without identifying information such as my name, I understand that it is possible that someone may recognize me. I also agree for my image to be shown for teaching purposes and to be used for medical records.

Signed at (*place*) .....…..……. on (*date*) ……...……

....

Signature of participant Signature of witness

ANNEXURE C: Namibian Snake Poster



ANNEXURE D: Snakebite Data Collection

Part A (Patient History)

Name…………………………………………. Case No…………………...
Date……………………………………………...

Patient history (Time, Date, Location)

……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………
……………………………………………………………………………………………

ANNEXURE E: Snakebite Data Collection

Part B (Patient details) **Case No…….**

Personal Details

PATIENT NAME……

DATE OF BIRTH……..... SEX: M F

ADMISSION DATE…….....DEBRIMENT Yes No

If Yes Date……

PHYSICAL EXAMINATION

Bite site……...

Activity when bitten……...

Swelling stage: Mild Moderate Severe

Other symptoms…….....

Antivenom administered: Yes No

Type of snake/ description if unknown:

……

……

NEUROTOXICITY EXAMINATION

Description	**Tick type of symptoms (✓)**
Drowsiness	
Limb weakness	
Sweating	
Vomiting	
Inability to swallow saliva	
Ptosis	
Blurred or double vision	
Respiratory muscle paralysis	

ANNEXURE F: Snakebite Data Collection

Part C (Wound Clinical Report)

NAME…… **CASE NO……**

Daily Patient Wound Report

DATE	COMMENT

0	1	2	3	4	5	6	7	8	9	10

0 No pain 1 – 3 mild pain 4 – 6 moderate 7 – 10 severe pains

Grade the pain levels according to the scale above.

ANNEXURE G: Snakebite Data Collection

Part D (Laboratory Profile)

NAME…… CASE NO……

LABORATORY DAILY RESULTS

Normal Parameters	**Date**	**Date**	**Date**	**Date**	**Date**
WBC (3.4 – 8.9 x 10^9/L)					
RBC (3.9 – 5.3 x 10^{12} /L)					
Hb (11.5 – 15.5 g/dL)					
HCT (36.9 – 49.1 %)					
PLT (171 – 388 × 10^9/L)					
Neutrophils (1.5 – 8.0 × 10^9/L)					
Lymphocytes (1.5 – 6.5 × 10^9/L)					
Monocytes (0.0 – 0.4 × 10^9/L)					
Eosinophils (0.0 – 0.5 × 10^9/L)					
INR (0.8 – 1.3)					
PT (10.2 – 13.2 s)					
Urea (2.1 – 7.1 mmol/L)					
Creatinine (26.5 – 88.4 mmol/L)					
Albumin (31.0 – 48.0 g/L)					
T-Bili (0.0 – 20.5 umol/L)					
ALP (83.0 – 382.0 IU/L)					
GGT (7.0 – 50.0 IU/L)					
ALT (7.0 – 35.0 IU/L)					
AST (15.0 – 41.0 IU/L)					
LDH (98.0 – 192.0 IU/L)					
CK (49.0 – 397.0 IU/L)					
CK-MB (0.0 – 4.8 ng/mL)					
D-dimer (0.0 - 230.0 ng/mL)					

ANNEXURE H: Ethical Clearance Certificate

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: H-G /584/2020 **Date: 15 September, 2020**

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: **Clinicopathological Study Of Snakebite Injury Resulting From Zebra Spitting Cobra *(Naja Nigracincta Nigracincta)* and Puff Adder *(Bitis Arientans)***

Researcher: KATRINA NIITETA

Student Number: 201034123

Supervisor(s) *Prof Christian Hunter*

Campus: Hage Geingob Campus

Take note of the following:

(a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the HREC. An application to make amendments may be necessary.

(b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the HREC.

(c) The Principal Researcher must report issues of ethical compliance to the UREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by HREC.

(d) The HREC retains the right to:

(i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,

(ii) Request for an ethical compliance report at any point during the course of the research;

(iii) Cognizance and the observation of Namibia's Research Science and Technology Act, 2004 which makes it compulsory for Non-Namibian based researchers to obtain the compulsory Research Permit from the National Commission on Research Science and Technology (NCRST), FIRST, BEFORE the research can commence.

HREC wishes you the best in your research.

Dr. J.E. de Villiers HREC Chairperson
pp. R Verbeeck

Ms. P. Claassen: HREC Secretary

ANNEXURE I: Ministry of Health and Social Services Research Approval

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
Windhoek
Namibia

Ministerial Building
Harvey Street
Windhoek

Tel: 061 – 203 2537
Fax: 061 – 222558
E-mail: itashipu87@gmail.com

OFFICE OF THE EXECUTIVE DIRECTOR

Ref: 17/3/3/KN
Enquiries: Mr. A. Shipanga

Date: 03 December 2020

Ms. Katrina Niiteta
PO Box 469
Ondangwa
Namibia

Dear Ms. Niiteta

***Re:* Clinicopathological study of snakebite injury resulting from Zebra spitting Cobra (Naja nigracincta nigracincta) and Puff Adder (Bitis arientans).**

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;
3.2 No other data should be collected other than the data stated in the proposal;
3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
3.4 A quarterly report to be submitted to the Ministry's Research Unit;
3.5 Preliminary findings to be submitted upon completion of the study;
3.6 Final report to be submitted upon completion of the study;
3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

EXECUTIVE DIRECTOR
MINISTRY OF HEALTH AND SOCIAL SERVICES

BEN NANGOMBE
EXECUTIVE DIRECTOR

"Your Health Our Concern"