LOCAL PRODUCTION OF SCORPION & SNAKES ANTIVENOMS

21- 22 NOV 2022

Khider Elshareef Hall
University of Khartoum
Nile Avenue, Khartoum, Sudan

RECOMMENDATIONS

WORKSHOP TEAM

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PRESENTATIONS

WELCOME MESSAGE

ON behalf of the scientific organising committee, we would like to greet you heartly at the University of Khartoum and to thank you for attending and participating in the **Local Production of Scorpion and Snakes Antivenoms Workshop** held at Khider Elshareef Hall during the period from 20-21 November 2022.

Prof. Osheik Abu Asha Seidi Osheik

Dean, Deanship of Scientific Research

Dr. Rania Mohamed Hassan Baleela

Director, Toxic Organisms Research Centre

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RATIONALE

Snake bites and scorpion stings' victims are on the rise. The recent increase can be attributed to several causes including climate change, civil wars and displacement of people, founding effects, over hunting for commercial purposes and gold mining. On top of all of this, the imported antivenoms are not effective. Therefore it is high time to gather stakeholders to discuss the what is needed to produce antivenoms locally. Toxic Organisms Research Centre (TORC) affiliates will conduct the sought research to establish a local production line in partnership with the relevant authorities under the umbrella of the Deanship of Scientific Research at the University of Khartoum.

INVITEES

- Ministry of Higher Education and Scientific Research
- Federal Ministry of Health
- Khartoum State Ministry of Health
- The National Laboratory for Public Health
- National Medicines and Poisons Board
- National Medical Supplies Fund
- Central Bank of Sudan
- The Intergovernmental Authority on Development (IGAD)
- World Health Organization (WHO)
- United Nations Environment Programme (UNEP)
- United Nations Development Programme (UNDP)
- United Nations Children's Fund (UNCEF)
- United Nations Educational, Scientific and Cultural Organization (UNESCO)
- Islamic World Educational, Scientific and Cultural Organization (ICESCO)
- Higher Council of Environment and Urban Promotion
- National Center for Research
- Central Veterinary Research Laboratories
- Institute of Endemic Diseases, U. of K.
- Camel Research Centre, U. of K.
- Mycetoma Research Center, U. of K.
- Sudanese Red Crescent
- DIGITECH
- Bee Development & Housing
- President: Sudanese Banks Union
- AmiPharma Labs Co. LTD
- Bash Pharma Co. LTD
- Wildlife Protection Police
- Civil Defense Forces
- Association of African Universities
- Association of Arab Universities
- Zadna International Co.ltd for Investment, Social Responsibility Officer
- Mr. Osama Dawood
- Mr. Wagdi Merghani
- Mr. Mowaia Alberair
- Mr. Mohamed Ahmed Albaragoob
- Mr. Almahi Haj Ali
- Mr. Ashraf SidAhmed AlCardinal
- Mr. Osama SidAhmed AlCardinal
- Media (SUNA, Newspapers, Radio channels, TV channels, freelancers)

SCIENTIFIC PROGRAMME TIMETABLE

Day One: Sunday November 20th 2022

Time	Activity
8:00- 9:00 am	Registration
9:00-9:05 am	Welcome and Opening Remarks, TORC
9:05-9:10 am	Welcome Address by Dean, Faculty of Science
9:10-9:15 am	Welcome Address by Dean, Scientific Research Deanship
9:25- 9:30	Welcome Address by Vice Chancellor, University of Khartoum
9:30- 9:35	Welcome Address by H. E. Minister of Khartoum State Ministry of Health

SCIENTIFIC PROGRAMME TIMETABLE

Day One: Sunday November 20th 2022

Time	Activity
Section 1: Basic Biology	
9:40-10:00 (20 minutes)	Dr. Manal Siyam (SNHM): Scorpions of Sudan: species, toxicity and geographical distribution
10:00-10:20 (20 minutes)	Dr. Sara Saeed (SNHM): Snakes of Sudan: species, toxicity and geographical distribution
10:20-10:40 (20 minutes)	Dr. Huda Khalid (Dept. of Zoology, UofK): Antivenoms currently in use and their effectiveness
10:40-11:00 (20 minutes)	Discussion
11:00-11:30 (30 minutes)	Break
Section 2: Clinical Toxinology	
11:30-11:50 (20 minutes)	Prof. Osheik AbuAsha Seidi (Faculty of Medicine, UofK): Clinical manifestations of scorpions' and snakes' toxins in adults
11:50-12:10 (20 minutes)	Prof. Eisa El-Amin (Department of Pediatrics, National Ribat University): Clinical manifestations of scorpions' and snakes' toxins in children
12:10-12:30 (20 minutes)	Dr. Rania M. H. Baleela (TORC): Introduction to the Toxic Organisms Research Centre
12:30-13:00 (30 minutes)	Discussion
13:00- 13:30	Lunch

SCIENTIFIC PROGRAMME TIMETABLE

Day Two: Monday November 21th 2022

Time	Activity
Section 1: Antivenom Production	
9:00- 9:10 (10 minutes)	Recap
9:10-9:30 (20 minutes)	Dr. Khairallah Saeed (Department of Pharmacology & Toxicology, Faculty of Veterinary Medicine, UofK): Local Production of Scorpions' Antivenoms
9:30-9:50 (20 minutes)	Dr. Huda Khalid (Dept. of Zoology, Faculty of Science, UofK): Local production of snakes' antivenoms
9:50-10:10 (20 minutes)	Dr. Rania M. H. Baleela (TORC): Next-Generation antivenoms
10:10-10:30 (20 minutes)	Prof. Muntasir Ibrahim (IEND): Affected populations
10:30-11:00 (30 minutes)	Break
Section 2: Future Plans	
11:00-11:20 (20 minutes)	Prof. Ahmed Musa (IEND): Clinical and toxicological trials
11:20 - 11:40 (20 minutes)	Prof. Osheik AbuAsha Seidi, Faculty of Medicine, UofK: Networking and collaborations
11:40- 11:55 (15 minutes)	Transportation to Sudan Natural History Museum (SNHM)
11:55-13:45 (110 minutes)	Sudan Natural History Museum (SNHM) Visit + Discussion
13:45-14:15 (30 minutes)	Lunch

SCIENTIFIC PROGRAMME TIMETABLE

Day Two: Monday November 21th 2022

Time	Activity
Section 3: Closing Session	
14:15-14:25 (10 minutes)	Dr Hisham Elhag Ahmed Khartoum Medicines Information Centre
14:25- 14:35 (10 minutes)	Dr. Fatima Alzahraa Adil (PashPharma) : Role of Sudanese pharmaceutical companies in production of local antivenoms
14:35- 14:45 (10 minutes)	Prof. Hassan Hussain (Faculty of Medical Laboratory Sciences, UofK.): Budget and instrumentation
14:45-15:05 (20 minutes)	Final Discussion and Recommendations
Refreshments	

Presentations

Edited by Rania Baleela

Scorpions of Sudan: Species, Toxicity & Geographical Distribution

Dr. Manal Siyam

Sudan Natural History Museum & Toxic Organisms Research Centre, Faculty of Science, University of Khartoum
manal.siyam@gmail.com

Why?

" To reflect the high threat to human life due to increased numbers of venomous scorpions in association with different ecological factors and the insufficient medical facilities, community awareness and supportive care in Sudan"

Introduction

- Scorpions are arachnids.
- It lives in hot or temperate places and usually hides in the cracks of the land and also lives in old and abandoned houses.
- Scorpions are different species and each type has a suitable environment and food.
- Its density increases during the summer seasons, when the heat intensifies, in autumn during the River Nile floods and in mating season in spring.

There are 17 (15 from Family Buthidae , 2 from Family Scorpionidae) species of scorpions in Sudan, 4 of which are deadly species whose sting may cause death, especially among children and the elderly if medical treatment is not carried out quickly.

Geographical Distribution

High Toxicity Scorpions

Parabuthus abyssinicus

- **Khartoum State**
- **Kassala State**
- **Red Sea State**

Leiurus quinquestriatus

- **Northern State**
- **River Nile State**
- **Khartoum State**
- **North Darfur State**
- **Kassala State**
- **White Nile State**

Androctonus amoureuxi
Androctonus austuralis

- **Northern State**
- **River Nile State**
- **Khartoum State**
- **North Darfur State**
- **North Kordofan State**

Medium Toxicity Scorpions

Buthacus leptochelys

- Northern State
- White Nile State
- Red Sea State

Hottentota minax

- Gezira State
- Kassala State

Hottentota niloticus

- River Nile State
- Khartoum State
- Sennar State
- South Kordofan State

Low Toxicity Scorpions

Pandinurus sudanicus

- North Kordofan State
- South Kordofan State
- Blue Nile State

Orthochirus olivaceus

- Northern State
- River Nile State
- Kassala State

Compsobuthus werneri

- Northern State
- Khartoum State
- Kassala State
- North Kordofan State
- Red Sea State
- White Nile State

Toxicity:

Scorpion Sting Symptoms

- Pain, which can be intense
- Numbness and tingling
- Slight swelling
- Warmth
- Difficulty breathing
- Muscle twitching
- Unusual head, neck and eye movements

- Drooling
- Sweating
- Nausea and vomiting
- High blood pressure (hypertension)
- Accelerated heart rate (tachycardia)
- Restlessness or excitability, or inconsolable crying in children

Analysis of the current situation of the spread of scorpions

During years from 2018 to 2021

- **There has been an increase in the density of scorpions in three states, which has increased the rate of stings, injuries and deaths, especially for children:**

States

- Northern State
- River Nile State
- Khartoum State

Reason

- A notable fact here is that scorpions can give birth repeatedly to several broods after one mating which is called "iteroparity".
- In Buthidae, the number of broods can be 4 to 5 separated by 2 or 3 months. The Number of young per brood differs between different species;

1. Reproduction seasons

- *Androctonus* sp. (45-80)
- *Leirus sp.* (21-43)
- *Parabuthus* sp. (40-95)

(A greater number of females in the sex ratio)

2. Conservation Behavior of species

- It means "the reproductive success of an individual".
- The reproductive of scorpions begins by spring (March) until Autumn.
- When the scorpion feels in danger to loss or extinction, it increases the production of offspring.
- The species can genetically developed and reproduce more aggressive, bigger species.

3. Mining Activities

Environmental systems are impacted by "Mining" in a range of positive and negative, and direct and indirect ways. Changing topography of some regions by mining, lead scorpions to escape from mining areas to a safer place .

- **Northern State**
- **River Nile State**

4. Random/ illegal Collection of Scorpions

Collection of thousands of scorpions cause an increase in reproductivity and aggression of new scorpion members to protect the species as a behavioral reaction. And so, all areas in these states considered infested with scorpions and sounded the alarm.

- **Northern State**
- **River Nile State**
- **Khartoum State**

Fieldwork in Northern State (El-Madiqeen area)

Abu Sara

We found a density of highly venomous scorpions

Androctonus amoreuxi

Leiurus quinquestriatus

Fieldwork outcomes

- **The areas in Northern State and Nile River are among the areas infested with scorpions due to the increase in mining activities and previous random collection of scorpions.**
- **Lack of health centers and medical staff.**
- **lack of Antivenoms in large quantities.**

Possible disasters that can happen in increase / decrease in the number of scorpions

In the case of high density of scorpions

- Increase in the rate of stings and injuries, which may lead to an increase in the death rate. .
- The state's inability to provide the appropriate amount of scorpion antivenoms in the affected areas on a regular basis and to store them properly.
- Due to the great need, antivenoms of low efficiency manufactured for species found in other countries (VINS) are imported at prices that suit the state budget.
- The reproduction of more compatible, virulent and higher venomous species to preserve the species.
- Increase of size (El- Manaseer).
- Rare Mutations: (Wadi Halfa – Dongola).

In the case of low density of scorpions

- ❑ **Increasing of agricultural pests and consequently damage to agricultural crops.**
- ❑ **Increase in Soilures numbers.**

Community awareness

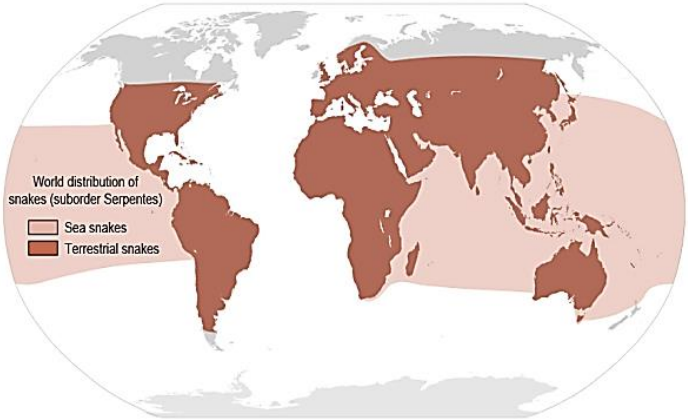
Recommendations

- ❑ Creation of a committee to control the random collection of scorpions and the environmental survey of areas in the various states of Sudan.
- ❑ Adding scorpions among the endangered animals in the Hunting and National Parks Protection Law of 1986 - General Directorate for Wildlife Protection - Ministry of Interior.
- ❑ Building a breeding centers for scorpions and snakes scientifically (in the case of investing in them and exporting them abroad for economic benefit)
- ❑ Providing an appropriate amount of scorpion and snake antivenoms in endemic areas in the states.
- ❑ Communicating with the Ministry of Minerals and the Geological Research Authority regarding indiscriminate mining operations in the regions of the northern state.

Snakes of Sudan: Species, Toxicity & Geographical Distribution

Dr. Sara A.K. Saeed

Sudan Natural History Museum & Toxic Organisms Research Centre, Faculty of Science, University of Khartoum



There are more than 3000 species of snakes on the planet, and about 600 species are venomous.

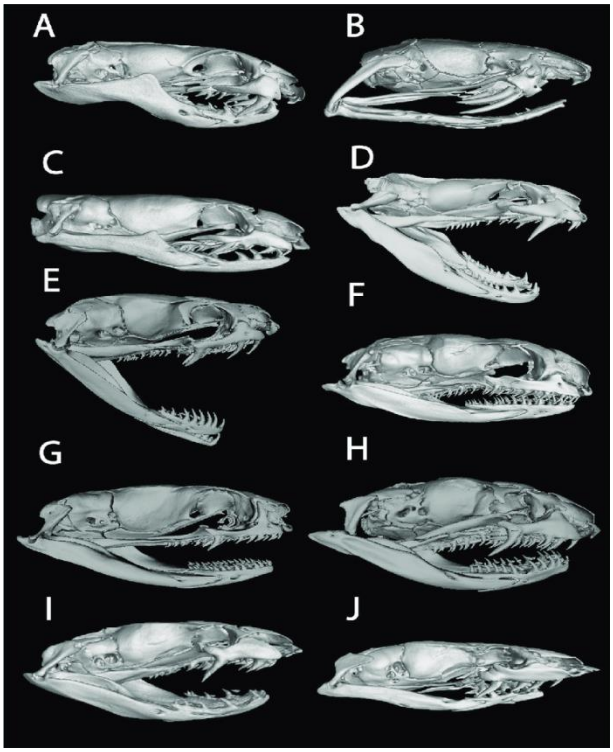
Venomous Snakes & their venom apparatus

Viperidae

Elapidae

Colubridae

Atractaspididae



Snake venom

- **Snake venoms are complex mixtures of enzymes and proteins of various sizes, amines, lipids, nucleosides, and carbohydrates. Venoms also contain various metal ions.**
- **Venom composition varies widely between species and even within the same species.**
- **Other factors, such as environmental conditions, age, sex or type of prey available, can also affect venom composition**
- **All the snake venoms have proteolytic effect**
- **Neurotoxic venom is considered as deadliest one, that it can kill within 30 minutes.**

Types of snake venom

- **Myotoxic**
- **Neurotoxic**
- **Cytotoxic**
- **Hemotoxic**

From a medical perspective, the venomous snakes of Africa can be divided into five categories:

Category 1: Snakes that bite frequently, and are associated with serious or life- threatening envenoming.

Category 2: Snakes that bite frequently, but rarely cause serious or life-threatening envenoming.

Category 3: Snakes that bite rarely, but are capable of causing severe or lifethreatening envenoming.

Category 4: Snakes that bite rarely, and have not caused significant envenoming.

Category 5: Other potentially venomous snakes which have not caused documented bites

Venomous snakes of medical importance in Sudan

Viperidae

Cerastes cerastes
(North Sudan)

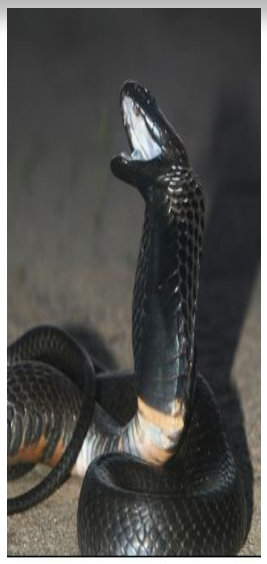
Echis pyramidum
(Very common)

Bitis arietans
(common except in North Sudan)

Cerastes vipera
(Northern Sudan)

Snake-Woman
Miss Intisar Salih

Elapidae



Naja nigricollis
West and South Sudan

Naja haje
Eastern Sudan

Naja nubiae
North, central and western Sudan

Antivenoms currently in use and their effectiveness

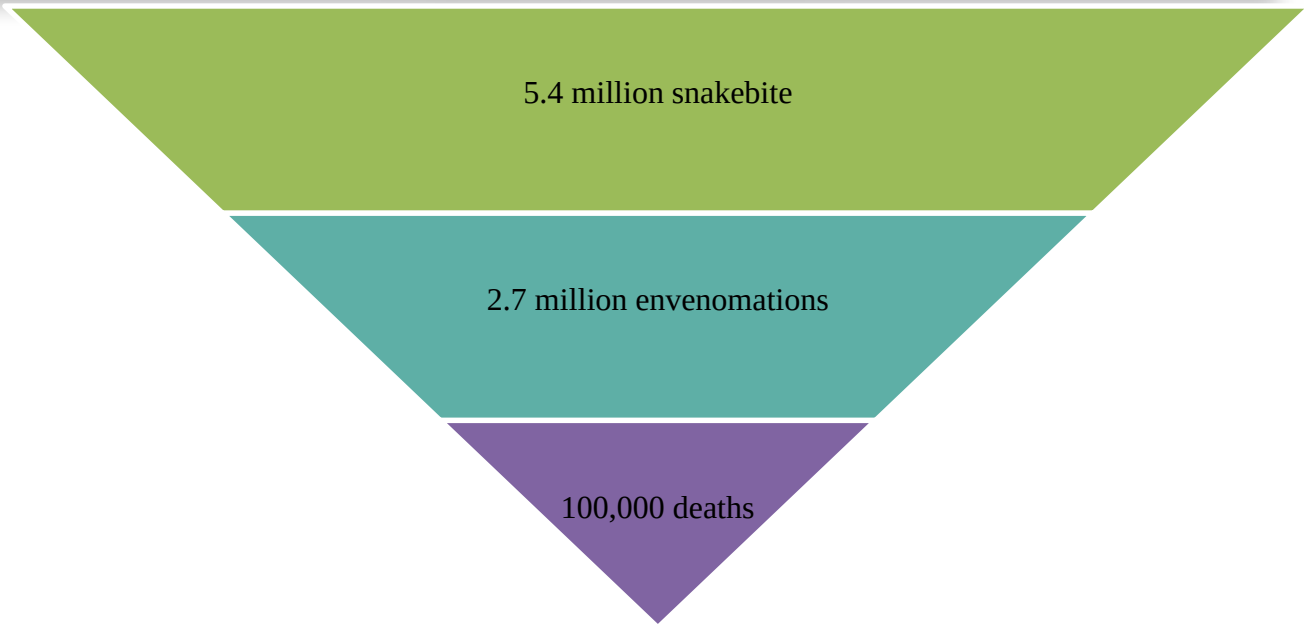
Dr. Huda Khalid

Department of Zoology & Toxic Organisms Research Centre, Faculty of Science, University of Khartoum

Introduction

- Snakebite envenoming is a major health hazard in the rural tropics and subtropics.
- It has been given little attention by national and international health authorities.
- Added to the WHO's list of **neglected disease in 2009** and formally listed as a **high priority neglected tropical disease in June 2017.**

The global burden of snakebite

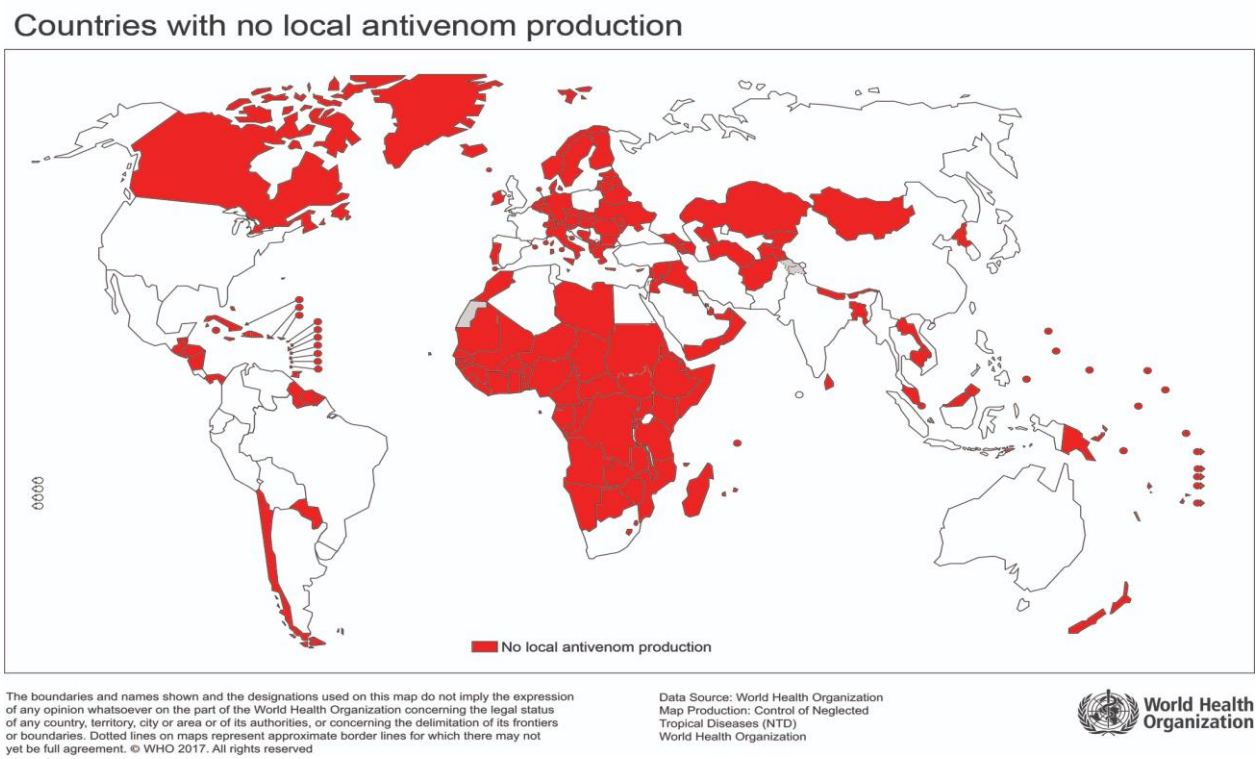


Situation in Sudan

Bitten patients may die shortly after hospital admission due to the **delay in transporting** patients to hospitals.
Poor medical care specially in remote areas.
Antivenom is very **expensive and rarely available**.
Non specific antivenoms have been used in Sudan.
Cold chain is not available in many rural areas.

WHO

Countries with no local antivenom production



Antivenoms used Sudan

India	Egypt
☐	☐
☐ Raised against Indian venoms	☐ Geographically relevant
☐ Misleading information	☐ Provided as liquid
☐ Therapeutic effects were unproved	☐

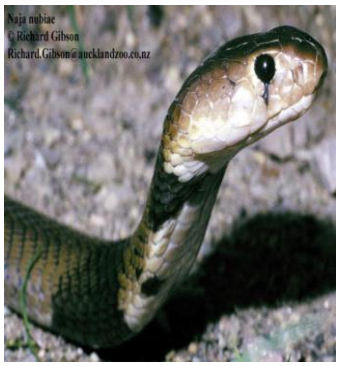
Marketing Indian antivenoms in Africa may lead to disastrous outcomes.

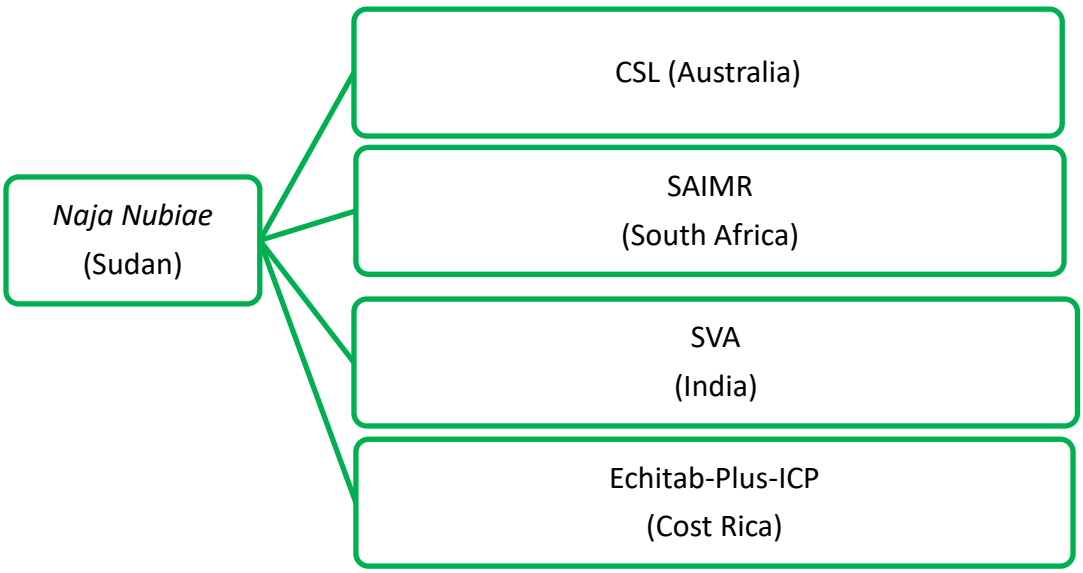
In Ghana, the Indian Asna Antivenom (Bharat Serum and Vaccines Ltd) was found ineffective against *E. Ocellatus* with a mortality rate of **12.1%**, compared to **1.8%** for FAV-AfriqueTM antivenom (Aventis Pasteur) (Visser et al, 2008).

In West Africa, Preclinical and antivenomics analysis approved the effectiveness of geographically appropriate antivenoms against the venoms of *E. ocellatus* and related species' in Sub-Saharan Africa but not against Asian *Echis carinatus* venom. (Abdulrazag G Habib and David A Warrel , 2013)

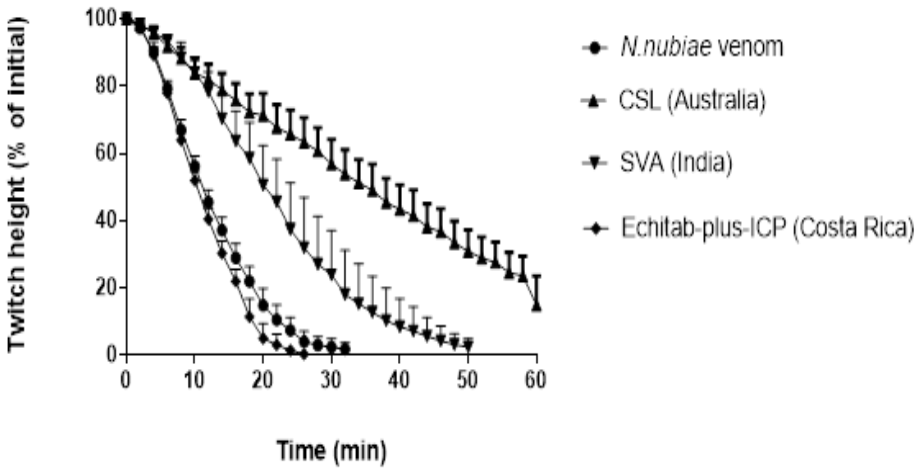
Testing the effectiveness of antivenoms

1. Faculty of Science, U. of K.
2. Institute of Endemic Diseases, U. of K.
3.Monash University, Australia





The effect of antivenoms on *N. nubiae* venom



The effect of *N. nubiae* venom on nerve-mediated twitches in **the chick isolated biventer cervicis nerve-muscle preparation,** without antivenom , with CSL antivenom,with SVA antivenom ,or Echitab-Plus-ICP antivenom.

Recommendations

1- Use specific antivenom from the region.
2- New products must be tested before use.
3- Produce antivenom specific for Sudan.

Regional antivenoms

National antivenom and Vaccine Production Centre (KSA)

Inoserp™ MENA)
North African and Middle East

Vacsera (EgyVac)
Egypt

Approach to Adult Patients with Scorpions and Snakes Envenomation

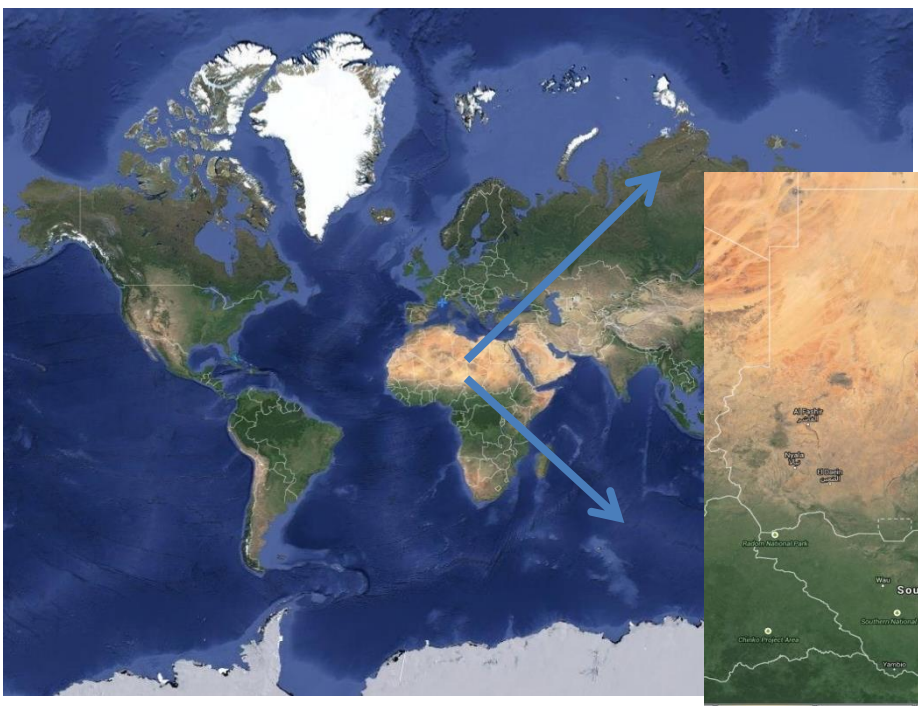
Prof Osheik Abu'Asha Seidi

MRCP(UK), ABIM, CCST (UK), FRCPG, FRCPE, FRCP, FAAN

Dean, Deanship of Scientific Research, University of Khartoum

Outlines of the Talk

- The magnitude of the Problem
- Scorpion stings in Adults
- Snake bites in Adults
- Prevention of Envomation
- Use of Antivenoms
- Future approach to management of risks



Scorpion Stings

- The history
- Clinical Examination
- Clinical Evolutions
- Important Flag Features
- Complications
- Management

Scorpions

- In many tropical and subtropical regions of the world scorpions-crab like arachnids- are the most important venomous animals after snakes
- Scorpions are eight-legged arthropods; order Scorpionida and class Arachnida.
- The terminal segment, called the telson (bulb containing a pair of venom secreting salivary glands), contains two venom glands connecting with the curved needle-sharp sting that is used either for defense or to obtain food
- The length of adult scorpions varies from under 2 cm to about 20 cm but the length does not relate to its toxicity (some of the most dangerous scorpions are only 2–4 cm long)

Composition of The scorpion Venom

It is s a mixture of various active substances:

Mainly polypeptides and enzymes.

- Venom consists of:

(1) neurotoxin, which acts on the respiratory, vasomotor centres, nerve terminals and end plates of both striated and non-striated muscles

(2) haemolysins, agglutinin haemorrhagins, leukocytolysins coaggulins, lecithin, cholesterine,cardio-toxins, nephrotoxins, hyaluronidases, 11 phosphodiesterases, phopholipases, glycosaminoglycans, histamine, tryptophan and cytokine releasers.

- A number of free amino acids and serotonin are isolated from the venom

The neurotoxins are the most important

Action of The scorpion Venom

Causes massive release of endogenous catecholamines into the circulation due to delayed activation of sodium neuronal channels by the venom

The main molecular targets of scorpion neurotoxins are the voltage gated sodium channels and potassium channels including calcium activated potassium channels.

- Iberiotoxin and tamulotoxin content of the scorpion (Mesobuthus tamulus) venom are the only selective inhibitors of potassium channel

The toxicity of scorpion venom is worse than that of the snakes but only a small quantity is injected

Clinical features of Scorpion Stings

- Venom is deposited deep to subcutaneous tissue after sting; almost complete absorption of the venom from sting site would occur in 7–8 hours (70% of maximum concentration of venom in the blood reached within 15 minutes of sting)
- The severity of envenoming is related to age (high fatality is seen in children and 50% mortality in less than 4 years old in the past), size of scorpion and the season of sting

Local Reaction

- Severe excruciating local pain is the only clinical manifestation seen in 35% of cases ,radiating along the corresponding dermatomes.
- Local signs such as swelling, redness, heat and regional lymph node involvement are never extensive.
- Stings typically do not produce a visible skin lesion, although on rare occasion a small red mark is noted
- Local oedema, urticaria, fasciculations and spasm of underlying muscles are rarely seen at the site of sting due to persistent stimulation of pain receptors and the liberated serotonin.
- Positive tap test is present (on tapping increase in paresthesia occurs) in some patients
- Due to pain there is transient bradycardia, transient rise in blood pressure and sweating with warm extremities
- Most scorpion stings are minor, producing severe local pain and paraesthesias without systemic involvement (benign or dry sting)

Systemic Effects of Scorpion Venom

- Scorpion venom delays the closing of neuronal sodium channels resulting in “autonomic storm” owing to sudden outpouring of endogenous catecholamines into the circulation
- Systemic symptoms may develop within minutes but may be delayed as much as 24 hours
- Features of autonomic nervous system excitation are transient cholinergic and prolonged adrenergic stimulation
- Initial parasympathetic excitation is characterized by - vomiting once or twice, - profuse sweating (skin diarrhoea for 3–17 hours) - ice cold extremities, - hypersalivation and -thick mucus secretion due to stimulation of bronchial mucus glands, - lacrimation, -pin-point pupils, -diarrhoea, -abdominal distension, -priapism, -bradycardia and hypotension
- Prolonged massive release of catecholamines, as in pheochromocytoma, later produces - restlessness, -piloerection, -marked tachycardia, -mydriasis, -hyperglycaemia, -hypertension, -toxic myocarditis, -cardiac failure and pulmonary oedema

Use of Antivenoms in Scorpion Stings

- When to use antivenoms ?
- When NOT to use?
- Types antivenoms and Doses
- Side effects and complications
- Other medications:
  - Tetanus Vaccination/ Antiserum
  - Antihistamines
  - Steroids
  - Anti-emetics
  - Antibiotics- No routinely

Clinical grading of Scorpion Envenomation

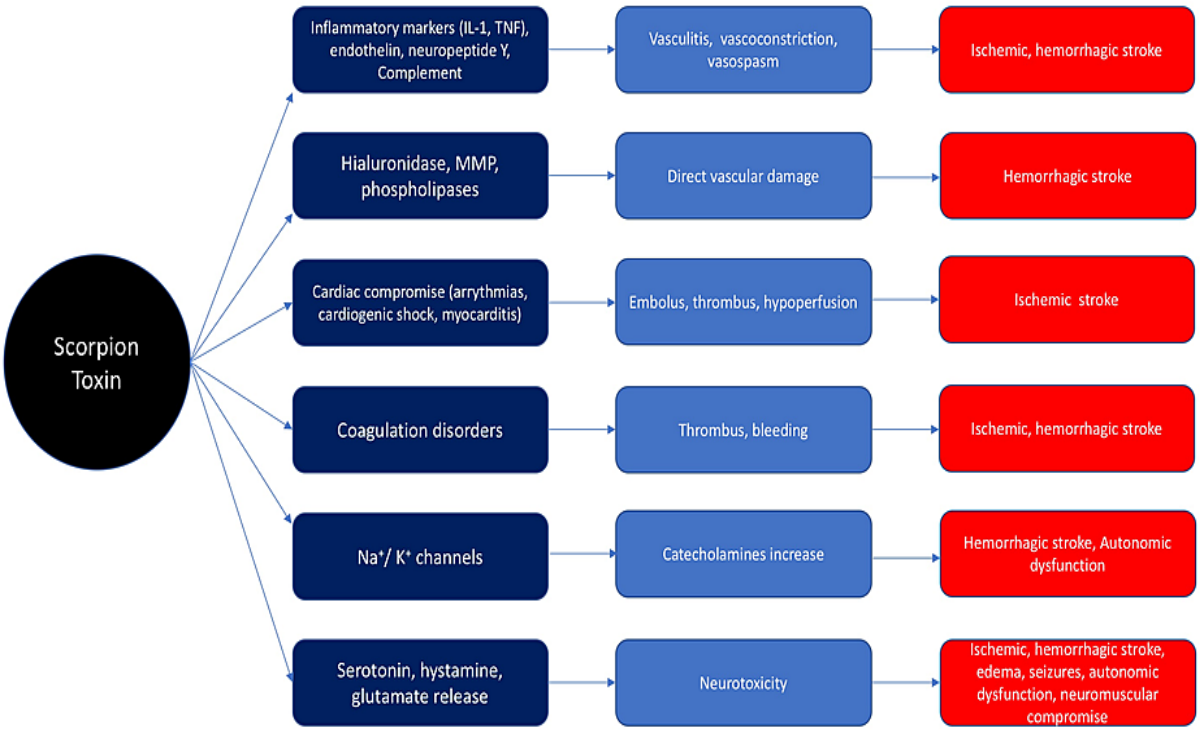
- **Grade 1:**

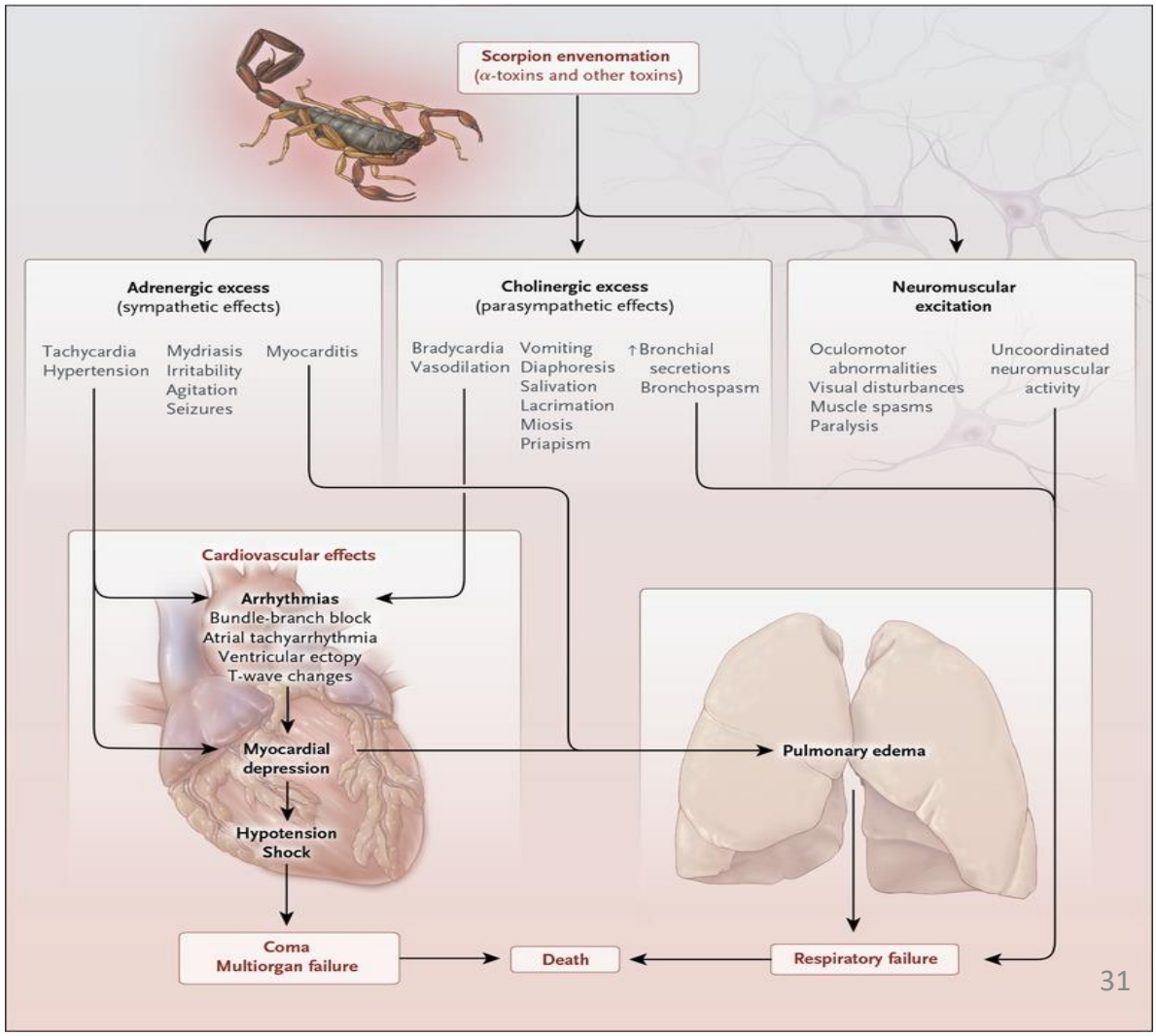
  Severe excruciating local pain radiating along corresponding dermatomes, mild local edema at the site of sting without systemic involvement.
- **Grade 2:**

  Features of autonomic storm characterized by parasympathetic and sympathetic stimulation.
- **Grade 3:**

  Cold extremities, tachycardia, hypotension or hypertension with pulmonary edema.
- **Grade 4:**

  Tachycardia, hypotension with or without pulmonary edema with warm extremities (warm shock).


Scorpion Toxin
Inflammatory markers (IL-1, TNF), endothelin, neuropeptide Y, Complement
Vasculitis, vascoconstriction, vasospasm
Ischemic, hemorrhagic stroke
Hialuronidase, MMP, phospholipases
Direct vascular damage
Hemorrhagic stroke
Cardiac compromise (arrythmias, cardiogenic shock, myocarditis)
Embolus, thrombus, hypoperfusion
Ischemic stroke
Coagulation disorders
Thrombus, bleeding
Ischemic, hemorrhagic stroke
Na+/ K+ channels
Catecholamines increase
Hemorrhagic stroke, Autonomic dysfunction
Serotonin, hystamine, glutamate release
Neurotoxicity
Ischemic, hemorrhagic stroke, edema, seizures, autonomic dysfunction, neuromuscular compromise


Scorpion envenomation
(α-toxins and other toxins)
Adrenergic excess
(sympathetic effects)
Tachycardia
Hypertension
Mydriasis
Irritability
Agitation
Seizures
Myocarditis
Cholinergic excess
(parasympathetic effects)
Bradycardia
Vasodilation
Vomiting
Diaphoresis
Salivation
Lacrimation
Miosis
Priapism
↑Bronchial secretions
Bronchospasm
Neuromuscular excitation
Oculomotor abnormalities
Visual disturbances
Muscle spasms
Paralysis
Uncoordinated neuromuscular activity
Cardiovascular effects
Arrhythmias
Bundle-branch block
Atrial tachyarrhythmia
Ventricular ectopy
T-wave changes
Myocardial depression
Hypotension
Shock
Pulmonary edema
Coma
Multiorgan failure
Death
Respiratory failure

Management of Scorpion Envenomation

- No scorpion sting should be taken as benign unless observed for 24 hours irrespective of species involved.
- On the basis of pathophysiology, therapeutic effort should be directed against the venom, overstimulated autonomic nervous system and correction of hypovolemia.
- **Local treatment:**
  - Mild pain -ice packs over the site of sting.
  - Severe excruciating local pain -lignocaine (without adrenaline in digital block)
  - Oral diazepam and nonsteroidal anti-inflammatory drugs (NSAIDs) with lignocaine block can give prolonged relief from pain.
  - Incision at the site of sting or tourniquet application is **NOT** advisable at all
  - Patients suspected of envenomation should be hospitalized for at least 12 hours and observed for cardiovascular and neurological sequelae

Treatment of Systemic Effects

- Pulmonary oedema is the most important cause of mortality and should be treated with propped up position, nasal oxygen,intravenous loop diuretics and prazosin
- Inotropic support with dopamine and dobutamine 5–15 mg/kg per minute is advocated for 36–48 hours in warm hypotensive shock patients.

The Use Scorpion antivenom

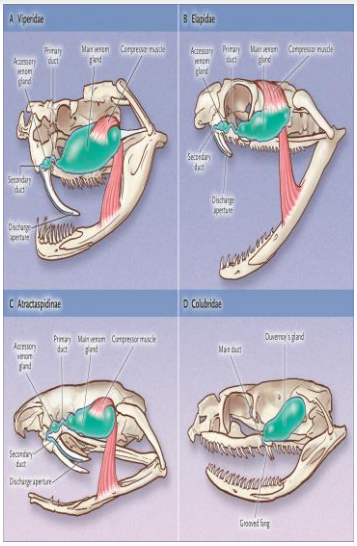
- Scorpion antivenom is effective if a victim is brought at an early stage of scorpion sting (in a stage of acetyl choline excess) ongoing cholinergic phenomenon is suggestive of free circulating
- Intravenous administration of antivenom rapidly reverses systemic toxicity features but not pain and paresthesia.
- No test dose is required as there are high circulating catecholamines and anaphylaxis is very rare.
- Addition of SAV to prazosin enhances recovery time and shortens hospital stay in patients with grade 2–4 Mesobuthus tamulus envenomation in India (Needs studies in Sudan)
- Many use Steroids routinely- controversial issue!

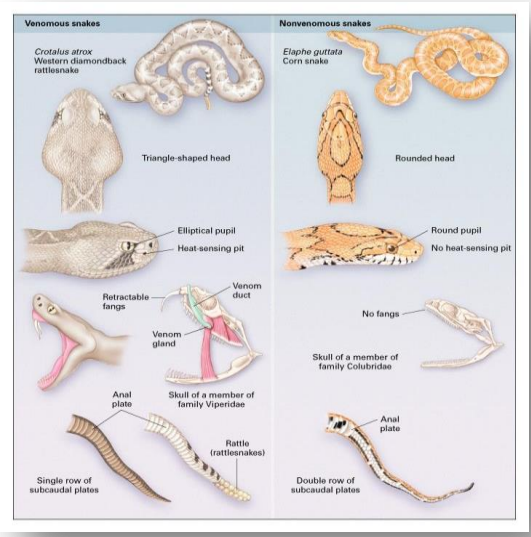
TABLE 1. MAJOR VENOMOUS SNAKES OF THE WORLD.

FAMILY	SUBFAMILY	DISTRIBUTION AND EXAMPLES	COMMENTS
Viperidae	Crotalinae (pit vipers)	North America: crotalus and sistrurus species (rattlesnake), agkistrodon species (cottonmouth, copperhead) Central and South America: crotalus species (rattlesnake), agkistrodon species (copperhead), bothrops species (fer-de-lance), *Lachesis muta* (bushmaster)	Heat-sensing foramen "pit" between each eye and nostril; elliptical pupils; retractable, canalized fangs
Viperidae	Viperinae (true vipers)	Africa, Europe, Middle East: *Bitis arietans* (puff adder), *B. gabonica* (Gaboon viper), *B. nasicornus* (rhinoceros-horned viper), echis species (saw-scaled viper), cerastes species (horned or desert vipers), vipera species (vipers) Indian subcontinent and Southeast Asia: *Daboia russelli* (Russell's viper)	No heat-sensing pit
Elapidae		Tropical and warm temperate zones: naja species (cobras), dendroaspis species (mambas), bungarus species (kraits), micrurus, calliophis, and maticora species (coral snakes), and most venomous snakes of Australia	Short, fixed fangs; venom injected by succession of chewing movements
Hydrophidae	Hydrophinae (true sea snakes)	Indopacific region: *Pelamis platurus* (pelagic sea snake)	Fangs similar to those of elapidae; highly neurotoxic venom; rarely bite humans

Snake Bites

- The history
- Clinical Examination
- Clinical Evolutions
- Important Flag Features
- Complications
- Management



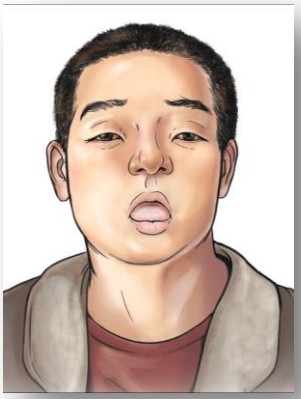


Composition of Snake venom

- Modern techniques of “venomics” (proteomics as applied to venoms) such as high performance liquid chromatography, SDS-PAGE, and mass spectrometry are revealing the enormous complexity of snake venoms (Warrell et al., 2013).
- More than 90% of snake venom (dry weight) is protein.
- Each venom contains more than a hundred different proteins: enzymes (constituting 80-90 % of viperid and 25- 70 % of elapid venoms), non-enzymatic polypeptide toxins, and non-toxic proteins such as nerve growth factor.
- Nonprotein ingredients include carbohydrates and metals (often part of glycoprotein metalloprotein enzymes), lipids, free amino acids, nucleosides, and biogenic amines such as serotonin and acetylcholine

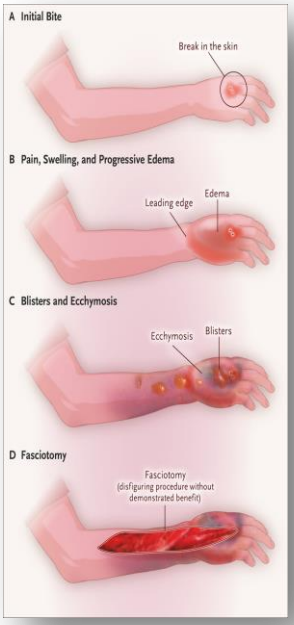
Clinical Features of Snake Envenomation

- Vary between different types of snakes and with same Genera
- Local knowledge and ideally predator's identification help in management- but difficult
- Local manifestations
- Systemic:
  - Neurotoxicity
  - Cardiovascular
  - Nephrotoxicity
  - Haemotoxicity/ Coagulopathies



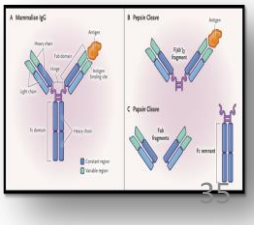
Outlines of Management

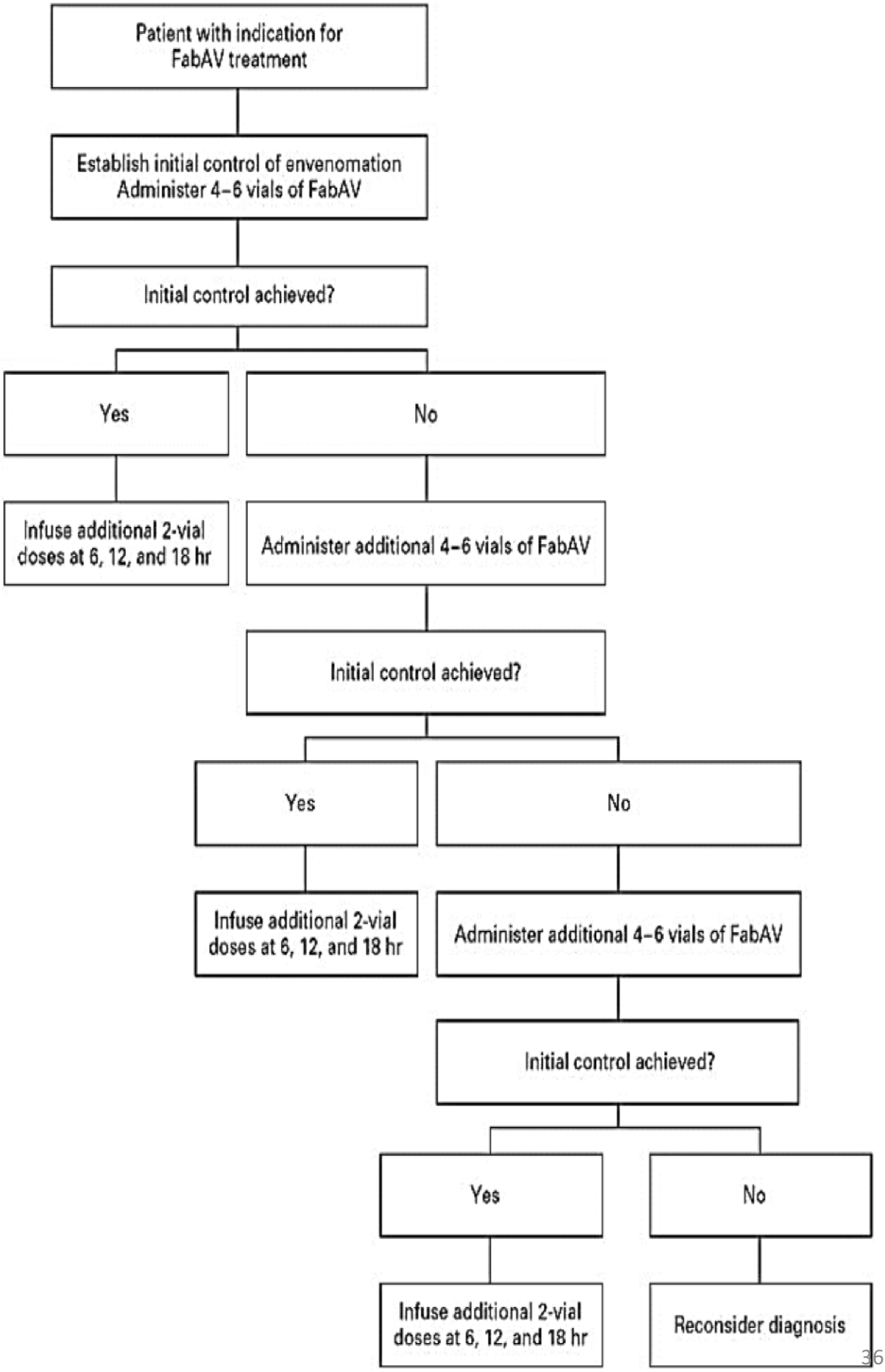
- **Pre-Hospital Care:**
  - Remove risk
  - Identify / catch , kill offender
  - Reassure/ immobilize site of bite/ gentle bandage
  - Anticipate swelling: remove rings etc
  - Native remedies delay care and may cause damage: scarification, sucking ..
  - Take to medical care ASAP
- **Hospital Care**
  - General Support: stable and critical care
  - Anti-venom
  - Anti Tetanus serum/ vaccination/ antibiotics
  - Treat complications: release incisions
  - ICU: ventilation, inotropes, Dialysis, ….



Use of Antivenoms in Snake Bites

- When to use antivenoms
- When NOT to use
- Types antivenoms and Doses
- Side effects and complications





https://www.nejm.org/doi/pdf/10.1056/NEJMra2105228?articleTools=true

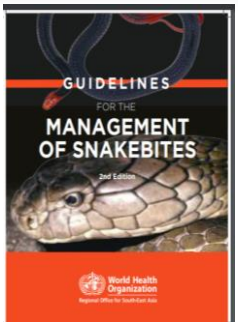
Recommendations

- Bites by small snakes should not be ignored or dismissed. They should be taken just as seriously as bites by large snakes of the same species
- Design and manufacture of antivenoms should take account of geographical and ontogenic variation in venom composition within individual species
- We work together to investigate this problem
- We work together to produce locally Antivenoms of high quality in good quantities to safe lives
- All sincere efforts are welcome

With Africa for Africa

Biological Means

Raising Awareness



Prevention of Envomation

- Not all stings and bites are poisonous
- Mild clinical syndromes are more common
- When to suspect stings or bites if no clear incident identified by the patient?

Improving Services in Remote Areas Sudan

The Future and Dreams for Sudan

- Comprehensive Project of the Study of Scorpions and Snakes in Sudan
- Isolation and Characterization of Faul and their Venoms
- Development of local Antivenoms using cutting edge technologies
- Educate the public and healthy professional about the
- Develop Network for Fast access to medical care for victims of stings and bites
- Provide effective antivenom to remote parts of the country , times e.g. using Drones and mixing specific antivenoms

The Future

Home - Canva

Figure

Caption

Figure 1. Buthus mariefranceae, from south of Morocco. Photo by Arie van der Meijden.

This figure was uploaded by Miquel A. Arnedo

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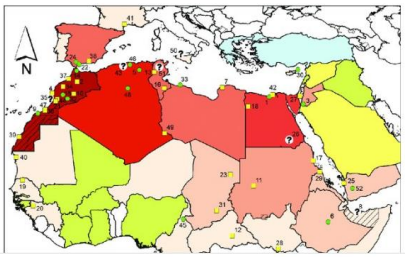
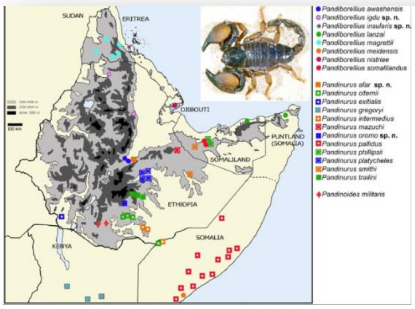


Figure

Caption

Figure 2. Map of Buthus species distribution, and the known number of species by country. Also depicted are the species' type localities (numbers according to the species' Catalogue and Table 2) where known or the best possible approximation. Actual distribution within each country can be much smaller, but detailed distri bution information is unknown for … Read more

This figure was uploaded by Miquel A. Arnedo



Figure

Caption

Figure 396: Map showing confirmed Horn of Africa distrib recently verified localities of Pandinoides militaris in Ethiopia ution of Pandiborellius and Pandinurus. There are only two Oromia State, Sidamo Province marked (Yabello, 4°50.574'N e Borena, Goba village, 04°51'48"N 39°18'35"E, 750m a.s.l., n of genus Pandinoides. For complete distrib … Read more

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Figure

Caption

Figures 1-9: Spiniform setation of tarsomeres of right legs I-IV, ventral or retrolateral aspect. Figures 1-4: Pandiborellius awashensis, female paratype. Figures 5-9: Pandinurus trailini, male topotype. Abbreviations: vm, ventral medial; vst, ventral subterminal; vt, ventral terminal; pd, pro-lateral distal; pt, prolateral terminal; pst, prolater al subterminal; rm, retrolateral … Read more

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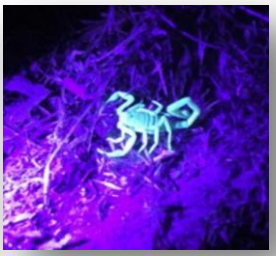
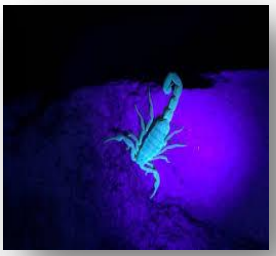
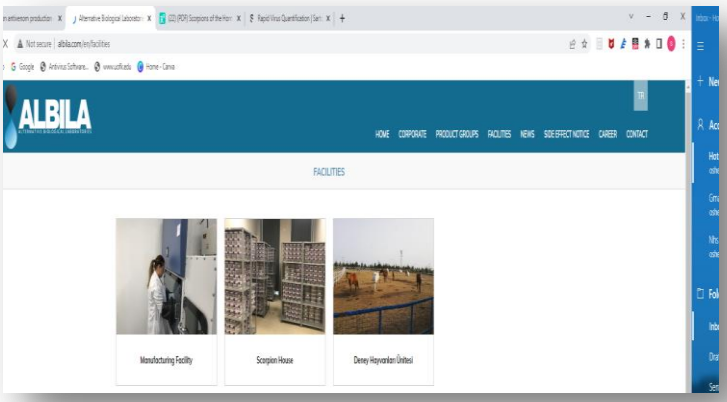
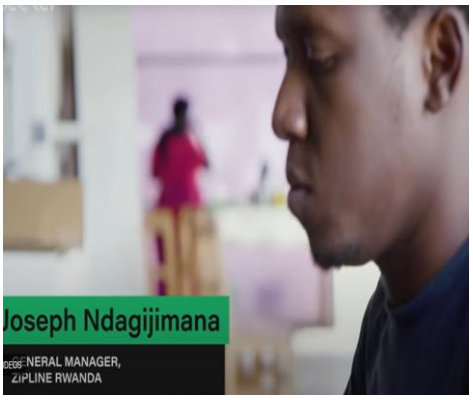
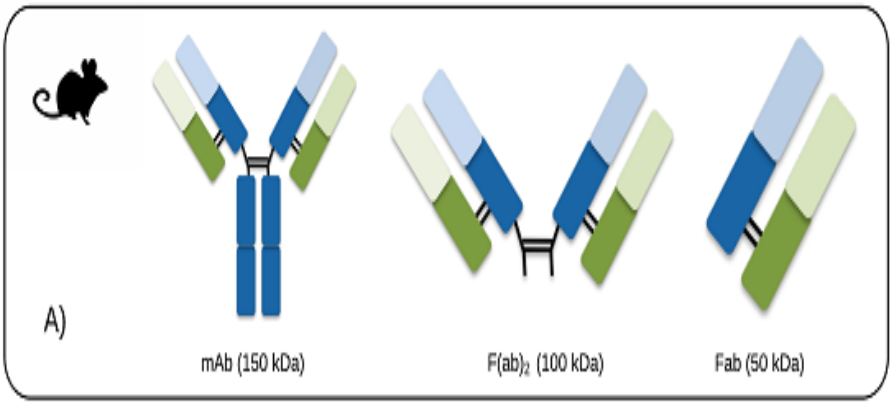


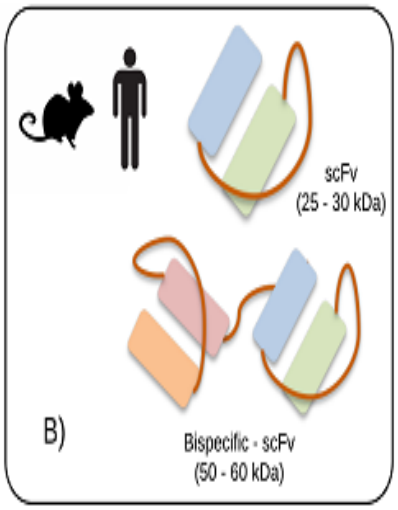


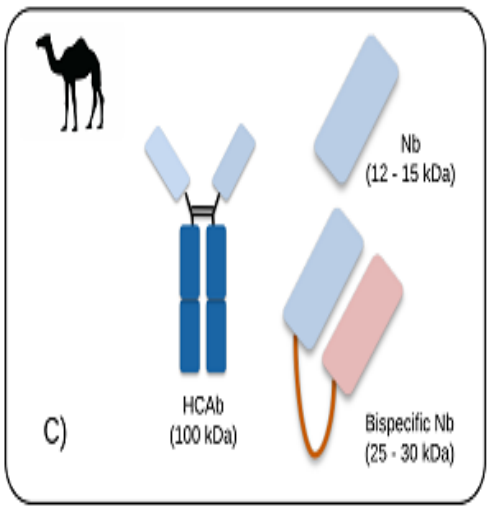
Production of Scorpion and Snake Antivenoms

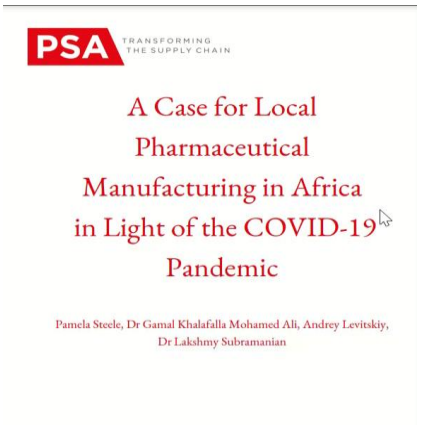


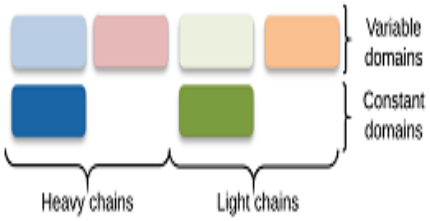












Clinical manifestations of scorpions' and snakes' toxins in children

Prof. Eisa Osman El-Amin Abdalla, MBBS, DTCH, MRCP,FRCP, FRCPCH

Department of Pediatrics, National Ribat University

Phylum Arthropoda

Invertebrate, articulate-legged animals
At least 1 billion species
Most successful life forms on earth
3 Subphyla
- Chilicerates (spiders, scorpions, ticks)
- Uniramia (centipedes, millipedes, insects)
- Crustacea (crabs, lobster, shrimp)
- *Vachon - Vedantu*

Envenomations

Arthropods
- Insects (Hymenoptera)
- Spiders (Arachnid)
- Scorpions (Arachnid

Reptiles
- Pit Vipers (Crotalidae)
- Cobras (Elapidae)
- Coral Snakes (Elapidae)

Venomous Marine Life

Dangerous species (Toxicon news letters)

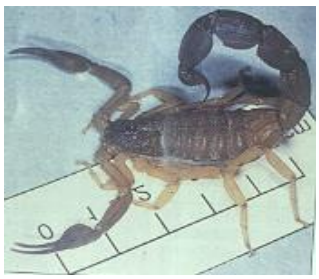
- More than a billion species
- 15 dangerous
- Cosmopolitan
- Most ancient
- Survived atomic explosions

Scorpion UV fluorescence is well known, but we haven't seen many pictures that show this unique quality. Photo by Kenton Elliott

Leiurus quenquestriatus
Androctonus crassicauda
Buthus and para-Buthus
Titus serrulitis

Sudanese species (Mohamed Telmasani)

1. ***Androctonus*** **(Hemprich& Ehrenburg)**
   - Western
   - Brown yellow
   - High toxicity



2. ***Androctonus crassicauda***
   - North / East
   - Dark brown to black. Greenish legs and tail
   - Highly toxic

3. ***Androctonus australis***
   - North, Centre and West
   - Brown to yellow
   - Less toxic

4. ***Buthus*** **(Leach)**
   - West starting from Omdurman
   - Yellow to brown
   - Highly toxic

5. ***Parabuthus***
   - All Sudan except desert
   - Yellow darkens to brown
   - Less toxic

6. Leiurus quinquestriatus

- All over Sudan, Mostly the North
- Light yellow to orange. Caudal ventral segments more dark
- The most dangerous sp.(similar to Titus of Argentina)

- ***Leiurus & Androctonus***

also prevalent in:

- The Gulf
- Iran
- Turkey
- Palastine
- Tunisia

The Venom

- Polypeptide
- Neurotoxic / Cardio toxic
- Autonomic storm
- Catecholamines
- Hyperglycaemia
- Electrolytes disturbances
- Others

Habitat

The start

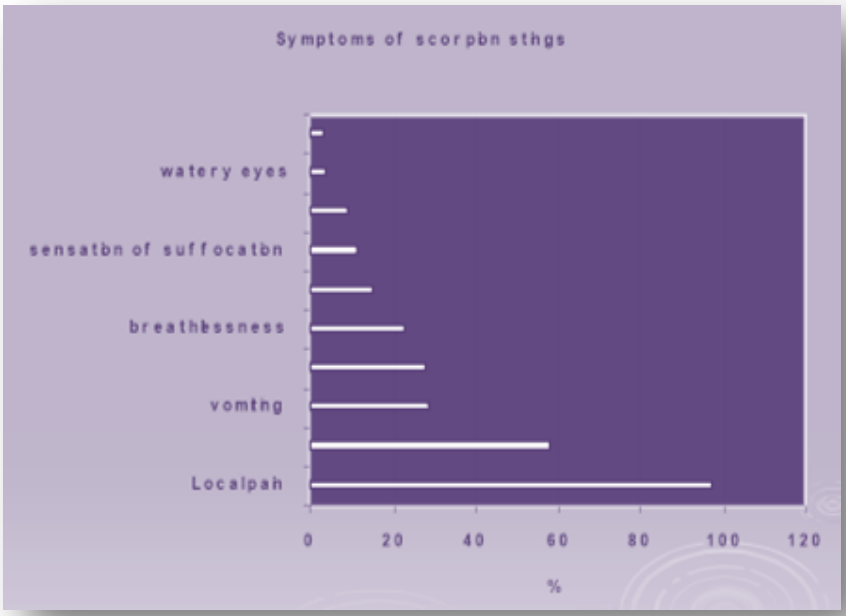
- In Madina Munawara (1987)
- High mortality
- No clinical information
- No protocols for management
- Wrong information in textbooks

Very high mortality

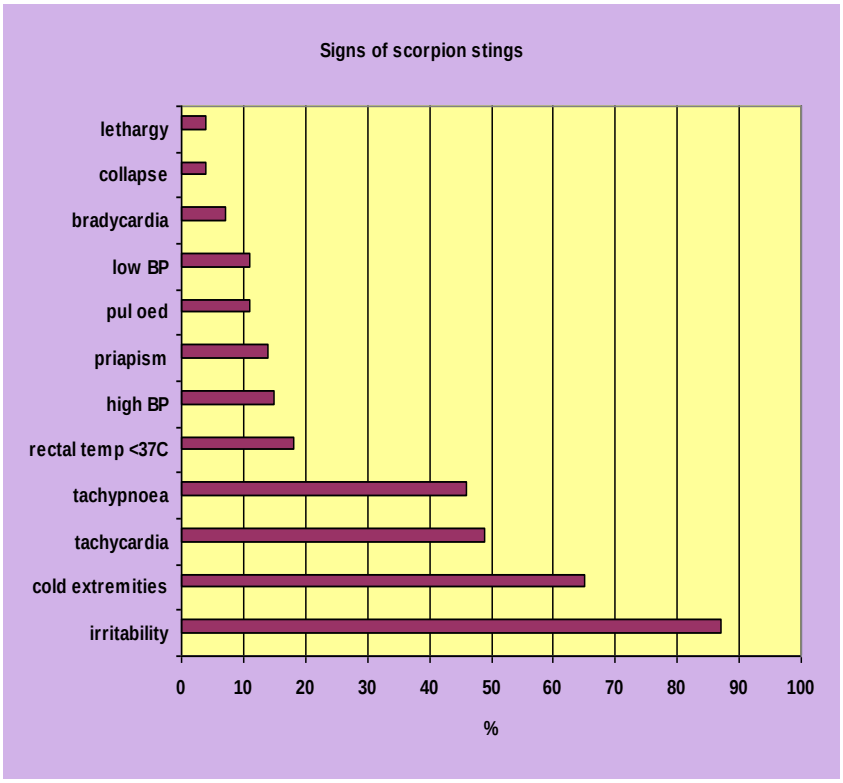
Year	1986	1987	1988
Total admit	4470	4632	4550
Scorpion admit	172	156	145
Total death	56	35	41
Scorpion death	11	9	4
Case fatality (%)	6.39	4.59	2.6

E.O. El-Amin, A. Elidrissy, H.S. hamid, O.M. Sultan & R.A. Safar: Scorpion stings, a management problem. Annals of Tropical Pediatrics. 1991; 11:143-8

Eisa Osman El-Amin: Issues in the management of scorpion sting in children. Toxicon. 1992; 30:111-15



Eisa Osman El-Amin: Issues in the management of scorpion sting in children. Toxicon. 1992; 30:111-15



Clinical categories

Asymptomatic	152
Symptomatic but not serious	24
Mild shock	10
Profound shock	6
Pulmonary oedema	3
Shock and pulm Oedema	11

. E.O. El-Amin,O.M. Sultan, M.S. AL-Magamci & A. Elidrissy: Serotherapy in the management of scorpion sting. Annals of Tropical Pediatrics. 1994; (14) 21-24.

Scorpion stings: Pathophysiology and treatment

Year	1986	1987	1988
OPD		221	163
Inpt	172	196	150
Shock	22	25	20
P. Oed	15	12	13
Death	11	9	4

E.O.El-Amin and R.Berair: Scorpion stings: Pathophysiology and treatment. Review Article French Archives of Paediatrics.1995; 2:766-73

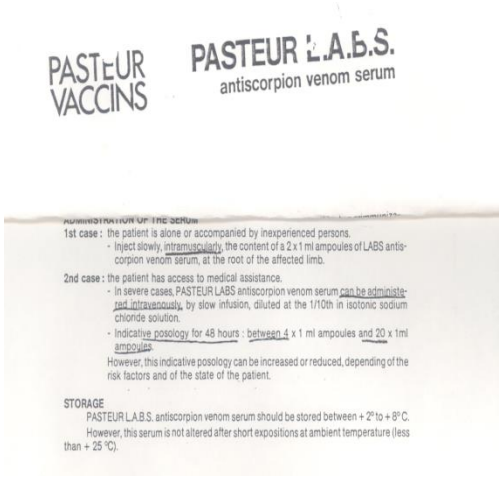
Laboratory work

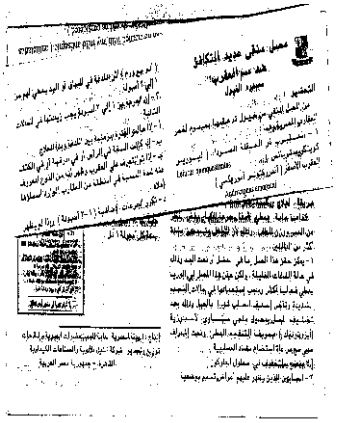
- Normal haematological indices
- Normal electrolytes (Ca)
- Normal urea / creatinine
- No bleeding diathesis
- Blood sugar

Eisa O. El-Amin and Miraj UL-Din Khan: Haematological and biochemical findings in scorpion-stung children. Annals of Saud Medicine 991:11:625-7

The antivenom

- Useful / harmful
- Suitable/ unsuitable
- Adequate/ inadequate





Neutralization Potency studies

- Nonspecific Unsuitable antivenom
- Inadequate
- Mohamed Ismael Hamid, King Khalid Uni, KSA

Critical clinical observations

- Plasma infusion harmful
- Hydration
- Barbiturates
- Narcotics

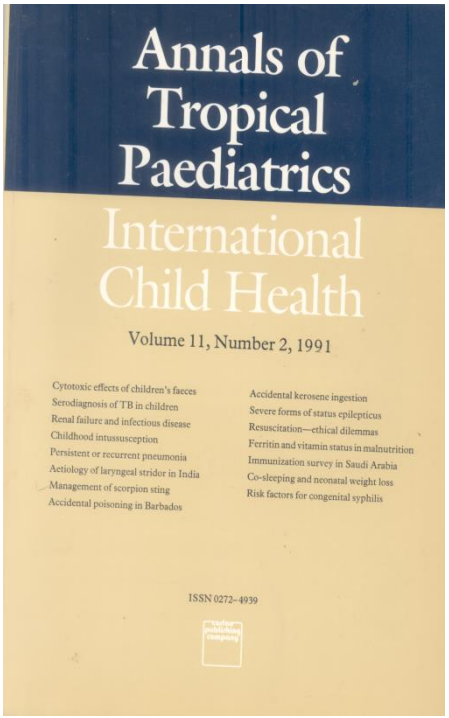
E.O. El-Amin: The Clinical management of scorpion sting in (Children- (leading article). Qatar Medical Journal. 2003;Vol 12 (1): 11-14

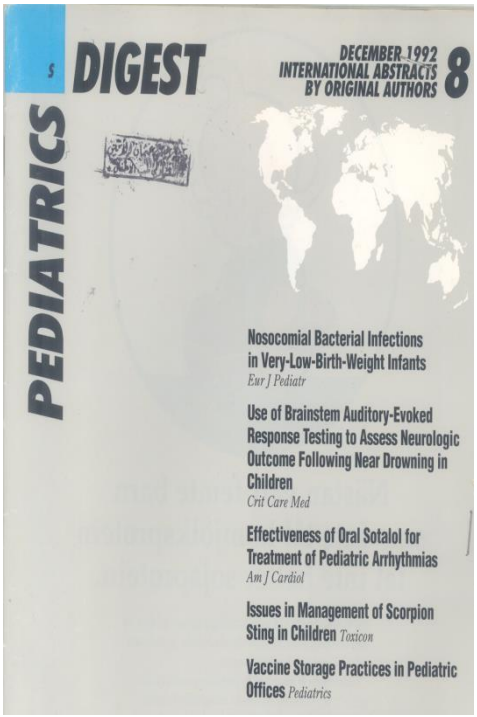
Drugs and scorpionism

- Local anaethetics
- Sedation - Chloropromazine/ Promethazine
- Anticonvulsants - Dizepam
- Cardiotonics - Dobutamine
- Diuretics
- Antihypertensives - Nifidapine

==========

- Atropine
- Antihistamines
- Steroids





Prevention

- Domestic garbage
- Building and ruins remains
- Sleep away from walls
- Check bedding before sleep
- Shoes outdoors
- Bare footing evenings and dark
- Insecticides useless

Our protocol of Almadina adopted in KSA

GUIDELINES FOR THE MANAGEMENT OF SCORPION STING

CONFIRMED SCORPION STING

ADULTS

CHILDREN

Did you notice any systemic manifestation?

No

Observe for 8 hours. Did you notice any systemic manifestation?

Yes

No

Yes

Discharge

At the onset of the systemic manifestation proceed as follows:

GIVE SCORPION ANTIVENOM

A. crassicauda

L. quinquestriatus

The two most dangerous scorpions in Saudi Arabia and two of the most toxic in the world.

Polyvalent Scorpion Antivenom

5 x 1 ml ampoules polyvalent scorpion antivenom diluted in a 20-50 ml half normal saline, given i.v. over a period of 20 minutes. If systemic manifestation still exists, the same dose is to be repeated every 2 hours up to 4 doses, then keep under observation for at least 24hr, after recovery.

Please note that the Antivenom dose is based mainly on titration of the symptoms until clinical manifestation disappears.

Laboratory Procedure and Expected Results

Some or all of these changes can be seen in the victims

WBC ↑	Na+ & Ca ↓
Blood glucose ↑	K ↑
CPK ↑	Blood gases (acidosis)
LDH ↑	ECG changes
Amylase ↑	X ray changes

Cause of death: cardiac failure, circulatory collapse, or respiratory failure

Adjunctive Therapy to Support Vital Functions

Severe pain
0.5 ml (max.) of 1% xylocaine, infiltrated at the site of the sting.

Vomiting
Chlorepromazine 0.5-1 mg/kg i.m. repeated if necessary.

Convulsion
Diazepam i.v. slowly.

Pulmonary Oedema
O_2, furosemide and fluid restriction.

Dyspnea
IPPV

Hyperthermia
Acetaminophen suppository

Hypertension
Hydralazine or Nifedipin.

Acidosis
Correct blood gases and electrolytes

Shock
c.v.p. line with 0.5 N saline to keep value at 8-12 cm H_2O and maintain blood pressure at a level to perfuse vital organs. (Systolic B.P. between 60-70 mm Hg in children).

Contraindicated Drugs (don't use!)

Barbiturates, Morphine or pithidine, Beta Blockers

For further information

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P.O. Box 22490, Riyadh 11426, KSA
(011-4029) ext. 3626/3603
fax: 011-4938
e-mail: nangic@ngha.org.

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Dr. Mohammed Abd Allah Ebrahim, Bsc pharm Sci, PhD
(011-4088-ext. 3221/3463, pager 8338)

Reviewed by: Prof. Mohammed Ismail Hamad, Bsc pharm Sci, Drug Anal. D, Chem Pathol D. PhD

Introduction to the Toxic Organisms Research Centre (TORC)

Dr. Rania Mohamed Hassan Baleela , MSc, PhD, DLSHTM
Director, TORC & Department of Zoology, Faculty of Science, University of Khartoum
RSTMH Ambassador (2020- 2023)


Albarajob Khaleel Harbi
Faisal Ibrahim Ali daughter
Waleed Osman
Mohamed Atif
Mawahib Hasabo
Sawsan Mujahid
Aisha Hassan
Children Death in Manaseer
Cemetery Photo credit @ Abuhaneen

Photos credit @ Abuhaneen

TORC Path Timeline

I read a message conveying the death of 68 children

Approached U. of K. VC to take an action

Here we are looking forward to produce local antivenoms

2019

I made a Facebook call to scientists & the 1st scientific research group was established

2020

2021

TORC final approved by the U. of K. Council

2022

2019 -present

Surveys, raising awareness, education mapping

About TORC

Sudan is a vast country with diverse climatic regions. Ranging from the desert climate in the north to the rich savannah in the south, these climates provides appropriate environments for the presence of different types of organisms, including poisonous and venomous ones.

https://science.uofk.edu/en/departments/toxic-organisms-research-centre-torc

About TORC

Sudan is a vast country with diverse climatic regions. Ranging from the desert climate in the north to the rich savannah in the south, these climates provides appropriate environments for the presence of different types of organisms, including poisonous and venomous ones.

TORC

Vision

A center specialized in studying & classifying toxic organisms in Sudan, extracting their venoms & toxins, studying them & producing antivenoms locally.

Mission

To contribute to Sudanese citizens protection against the dangers of toxins and venoms and to promote sustainable development through scientific research and distinguished community partnership.

OBJECTIVES

- Training
- Scientific research
- Community service

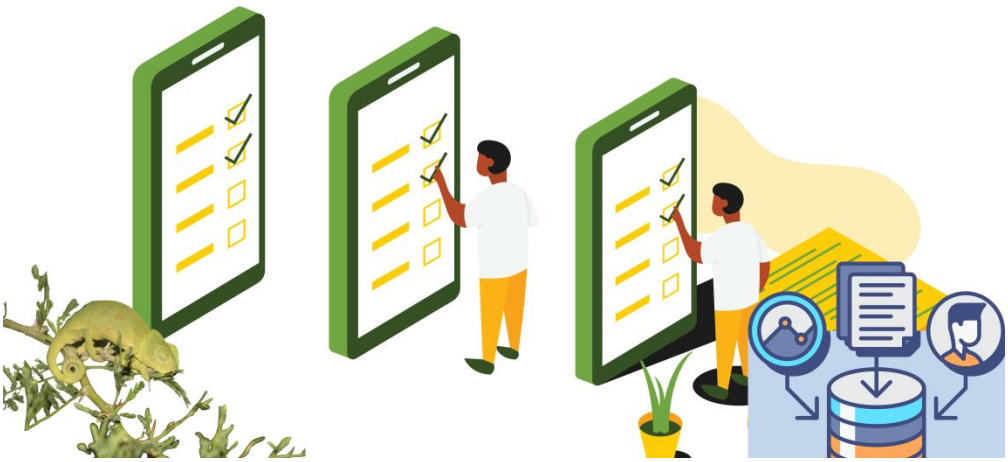
SCIENTIFIC UNITS

- Taxonomy and Environmental Studies Unit
- Biotoxicology Unit
- Toxicogenomics and Bioinformatics Unit
- Nanotoxicology & Natural Antidotes Unit

SERVICE UNITS

- Experimental animals' house and plant nursery unit
- Information, Awareness, Guidance and E-Services Unit

We do physical and online surveys



We Raise Awareness & Educate Local Communities

A'agri

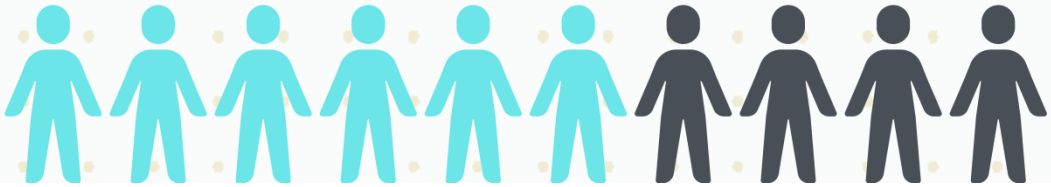
Tundi-Felo

Solub

Tondi-Hibais

We Provide Scientific Information to Decision-Makers & Authorities

A community of volunteers are helping us out



We know the geographical distribution of snakes and scorpions in Sudan

Bitis arietan Puff Adder

Causus rismus Green night adder

Echis ocellatus Saw Scaled Viper

Atractaspis microlepidota

Cerastes vipera Sahara Sand Viper

Naja haje Egyptian cobra

Echis pyramidum Saw Scaled Viper

Naja nubiae Nubian Spitting Cobra

Leiurusquinquestriatus

Parabuthusabyssinicus

Androctonusamoureuxi

Hottentota

Buthacus leptochelys

Pandinurus sudanicus

Local Production of Scorpions Antivenom

Dr. Khairalla Mohamed Saeed Khairalla

Faculty of Veterinary Medicine, Department of Pharmacology & Toxicology

Humble Trial

- The Idea came to mind During the Harsh, Drastic Autumn of 2014
- Many People died in Western Omdurman because of Scorpions' sting Specially children and elderly people.

Leiurus quinquestriatus (Deathstalker)

The most dominant scorpion species which cause that tragedy was The Yellow Scorpion

- The antivenom is imported from abroad.
- Too Expensive.

- We wondered if there was locally produced Antivenom ?
- The Answer was
- Nothing,

- No Data, No Records, No Trials.
- The Emerging Question is
- Is it Possible???

- A complementary MVPT Dissertation was proposed to try that.
- Facilities were not all on Hand
- We started with the Simplest and BASIC idea of producing Antibodies.
- Injection of Ag in a lab. Animal to enhance immunity to produce Abs .

1) Collection of Scorpions

- Nearly 150 or more scorpions were collected from Jebel El Awlia and Hagar El Asal
- Identification and taxonomy was done in the Faculty of Science – Department of Zoology and SNHM.
- Deathstalkers were selected.
- Kept in SNHM.

2) Extraction & Preparation of Venom

The Electric Shock Technique was used for venom extraction (milking)

2) Extraction & Preparation of Venom

Then the collected venom was purified, lyophilized and kept freezed.

3) Determination of LD50

No attempts were done for that while a published article cited the LD_{50} of *Leiurus quinquestriatus* in mammals is: 0.16-0.50 mg/kg

(Lucian K. Ross, 2008)

4) Immunization of Rabbits

- Many pilot trials were made under the range of LD_{50}
- Three satisfactory sub LD_{50} doses which gave tangible results were chosen
- GA lowest dose, GB medium dose and GC highest dose.

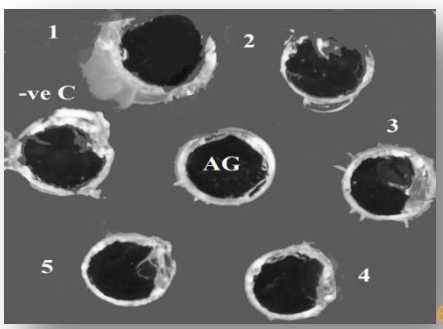
Day	Injected volume (ml) I/V
1	**0.1**
2	**0.2**
3	**0.4**
4	**0.6**
5	**0.8**
6	**1.0**
17	**1.5 (1st booster dose)**
30	**1.5 (2nd booster dose)**
37	**1.5 (3rd booster dose)**

5) Collection of Sera

- Sera were collected in days 21, 30 and 42
- Labeled and kept freezed

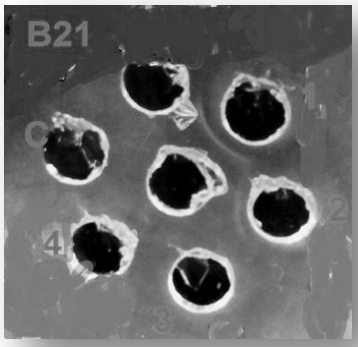
6) Detection of Antibodies in Sera

- Also the simplest method of detecting Ag/Ab reaction was used.
- The Agar Gel Immunodifusion (AGID).

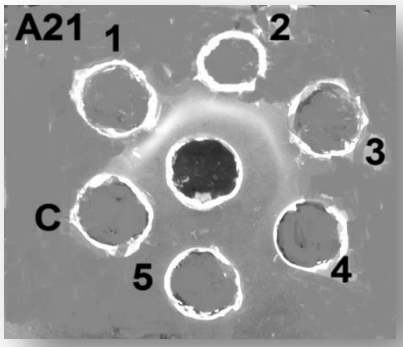


6) Detection of Antibodies in Sera

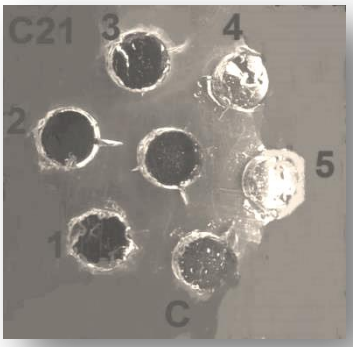
3/5 = 60%



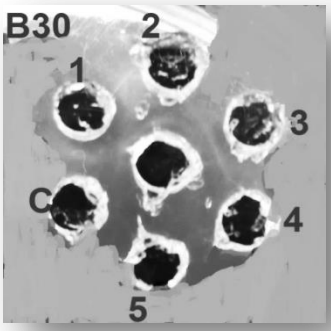
4/5 = 80%



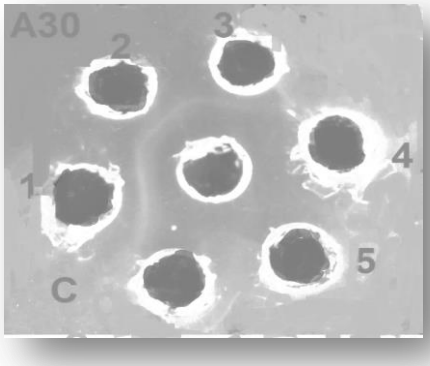
2/5 = 40%



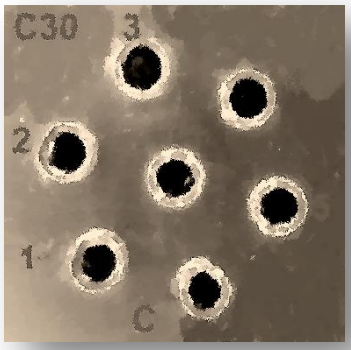
3/5 = 60%

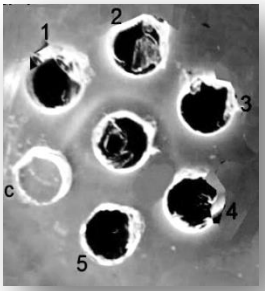


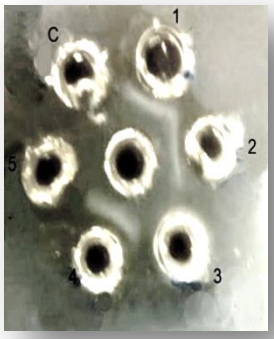
3/5 = 60%



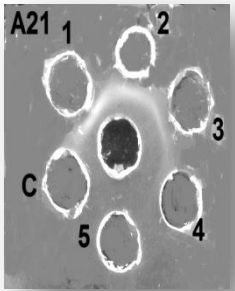
1/5 = 20%

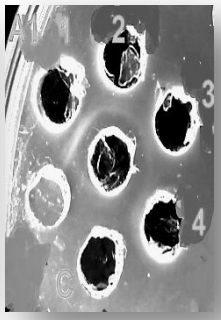




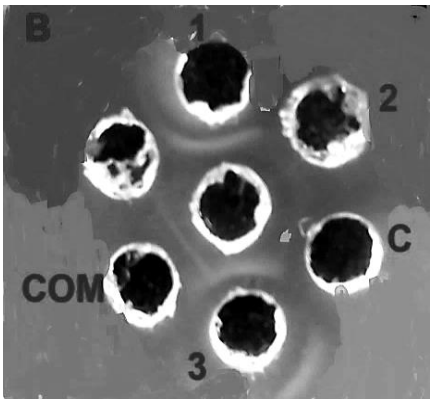


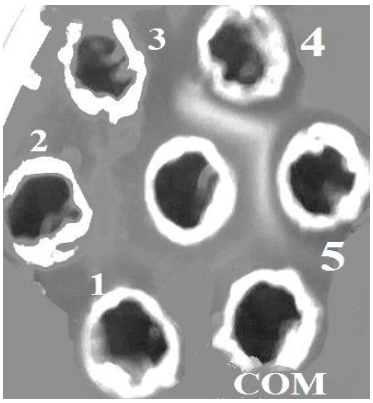
After 2nd Booster dose





After double fold dilution of anti-sera





When Compared with the Commercial Antivenom

Conclusion

1. **The question was answered successfully:** "It is possible to Produce local Antivenom"
2. The most potent activity was obtain with the lowest dose 0.09 mg/kg either after the 1st or 2nd booster doses even if were double diluted.

Recommendations

1. **This trial must be developed in order to produced the antivenom commercially.**
2. **The urgent situation of the scorpions' sting requires immediate production with this traditional techniques until become ready for the Next Generation ones.**
3. **Use large animals such as horses or goats to obtain large volume of serum.**
4. **Use of the common known adjuvants to enhance immunity in order to produce high titer of Abs.**
5. **So all needed facilities must be provided for this target.**

Local production of snakes' antivenoms

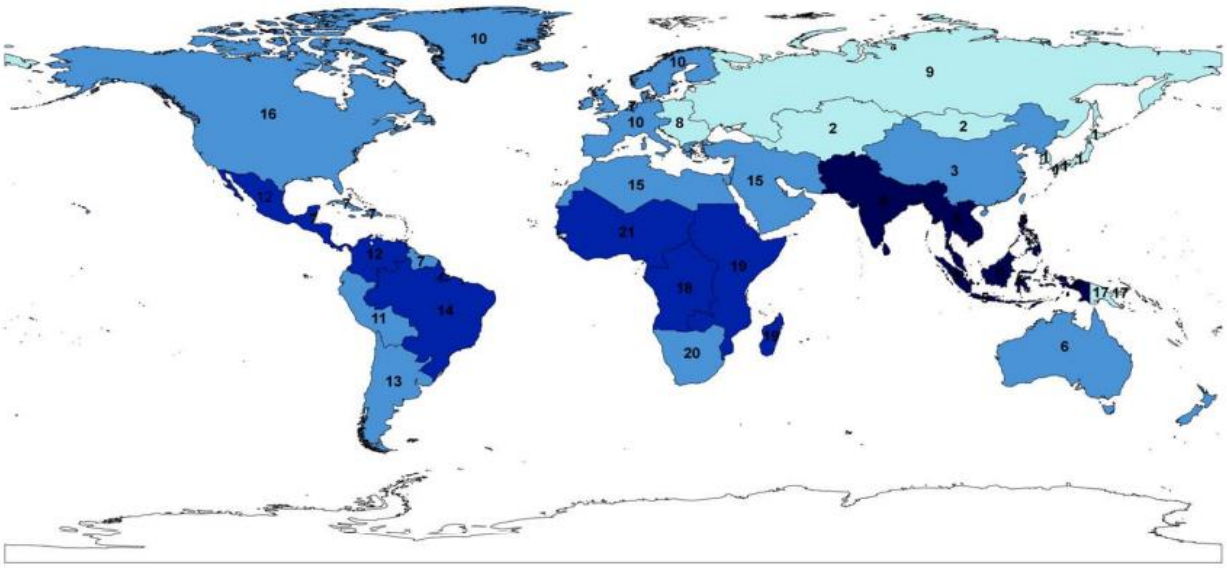
Dr. Huda Khalid

Department of Zoology & Toxic Organisms Research Centre, Faculty of Science, University of Khartoum

The effect of antivenoms on *N. nubiae* venom

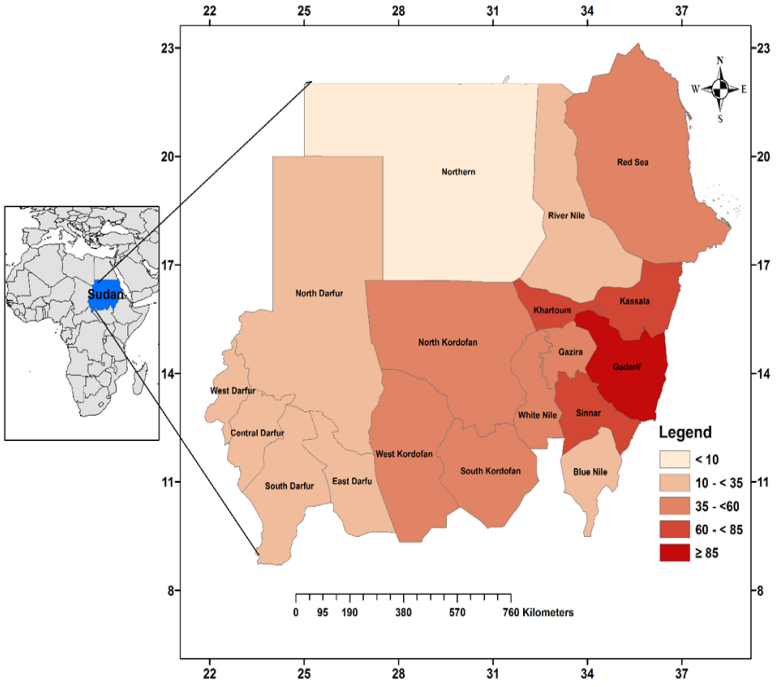
- High quality snake antivenoms are the only effective treatment to prevent most of the venomous effects of snake bites.
- The high cost of antivenom therapy stay the most important challenge to many sub-Saharan developing countries (one vial cost 50$- 150$).
- In Sudan, snake antivenom research is lacking in spite of the high burden of snakebite envenoming.

Estimation of the global burden of Snakebite



Hospital based statistics of snakebite

an average of 13 000 cases/year



Gadarif

Kassala

Khartoum

The only mean to resolve this problem is to establish national or regional antivenom using immunization mixture of the medically important species in that area.

Antivenom production in Sudan

1. **Faculty of Science, University of Khartoum**
2. **Institute of Endemic Diseases, University of Khartoum**
3. **Monash University, Australia.**

Immunization protocol

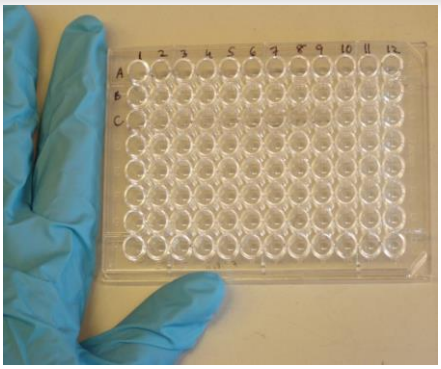
Goats were immunized using the low dose, low volume multi-site protocol

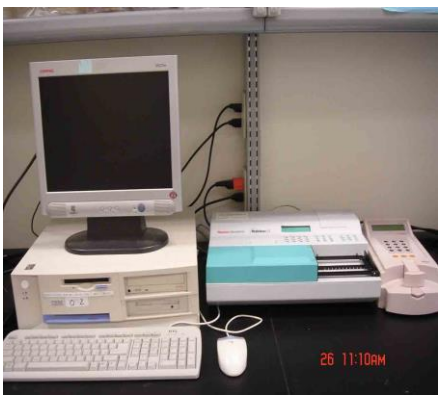
Blood samples were collected from the jugular vein.

Serum samples were kept at
-20° C

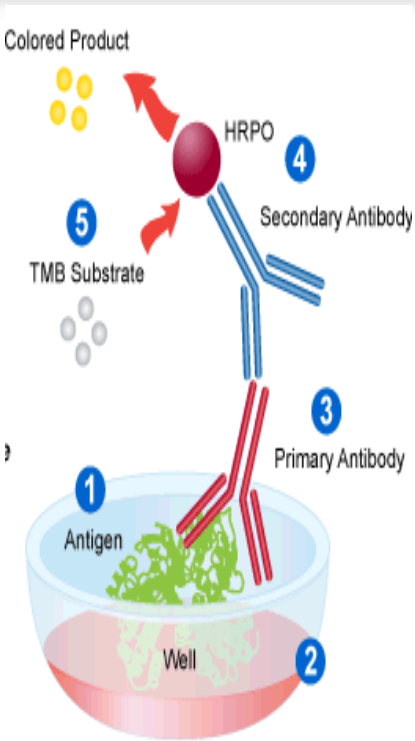
Immunization of goats

Measurement of antibodies in the immunized goat sera

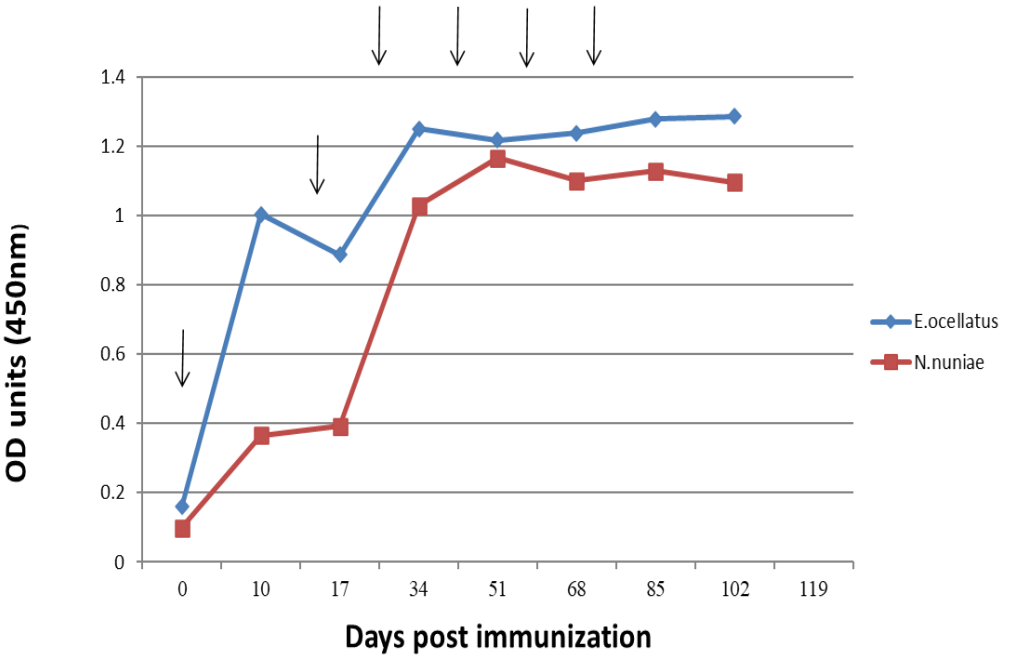




ELISA

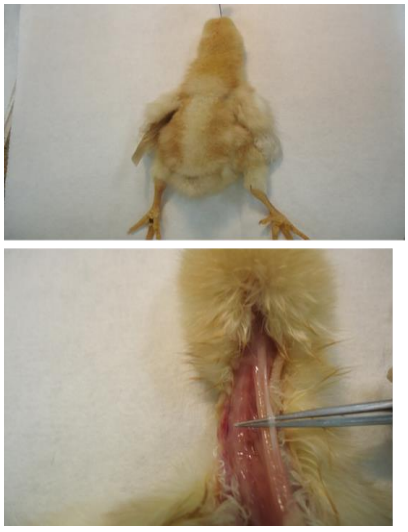


ELISA

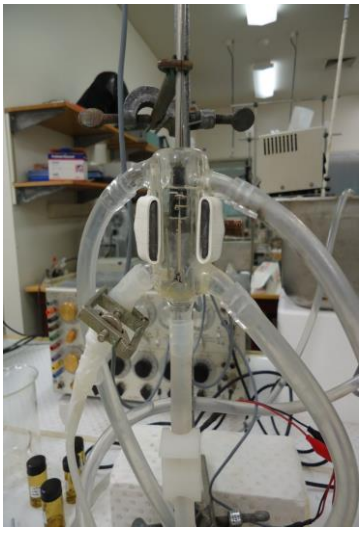


ELISA titers of the goats immunized with *E. ocellatus* and *N. nubiae* venoms.

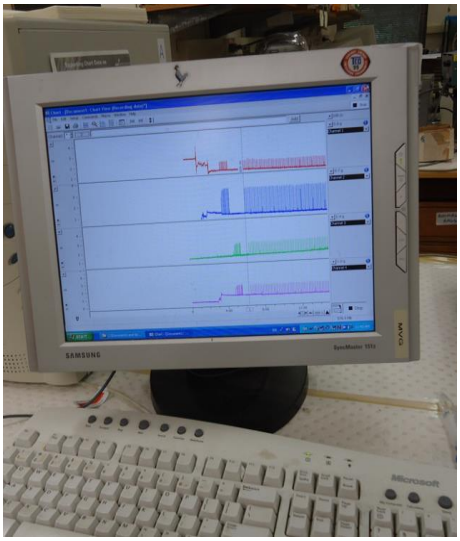
Neurotoxicity



Chicks aged between 4 - 10 days were killed by CO2

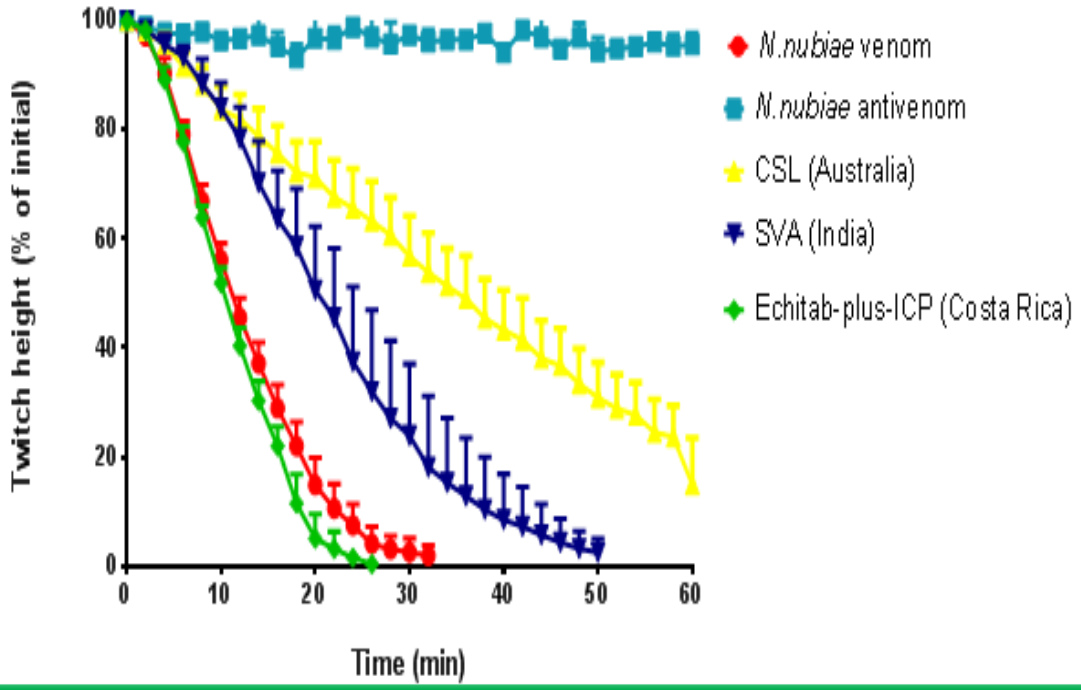


Mounted in 5 ml organ baths containing krebs solution.



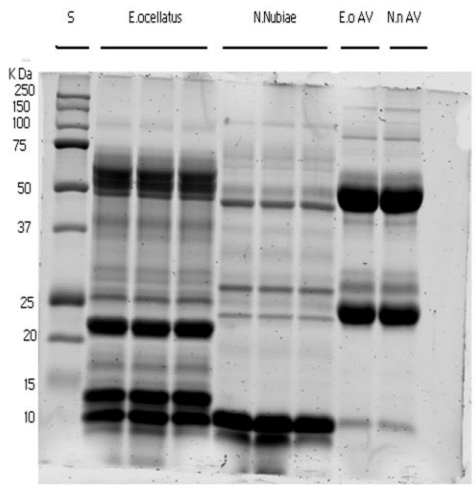
T90 values were calculated.

The effect N.nubiae antivenom and four other antivenoms



Characterization of the two Sudanese snakes Naja nubiae and Echis ocellatus.

SDS-PAGE

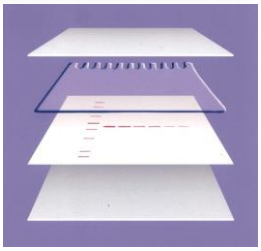


SDS-PAGE of *E. ocellatus*, *N. nubiae*, *E. ocellatus* antiserum and *N. nubiae* antiserum

Electrophoresis was preformed using 12% polyacrylamide gel.

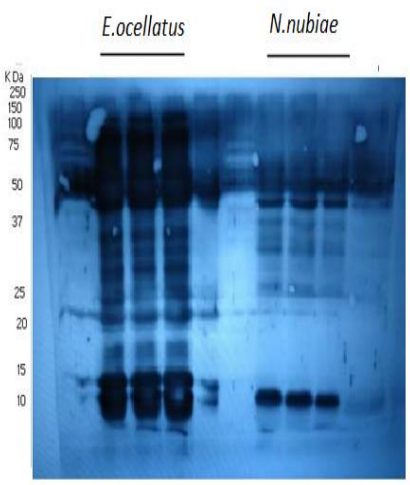
Western blotting

- 12% SDS-PAGE
- Proteins were transferred onto membrane.
- Protein were visualized using X-ray film.

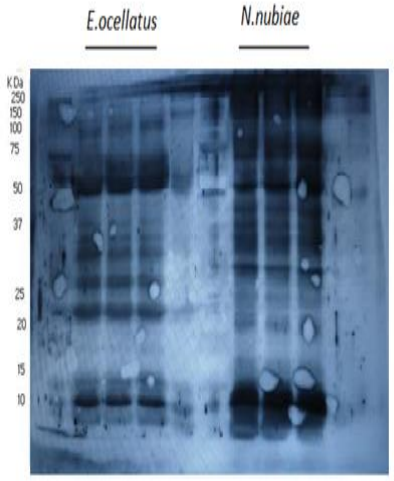


Immunoblotting of the venoms with goat's sera

***E. ocellatus* antiserum**



***N. nubiae* antiserum**

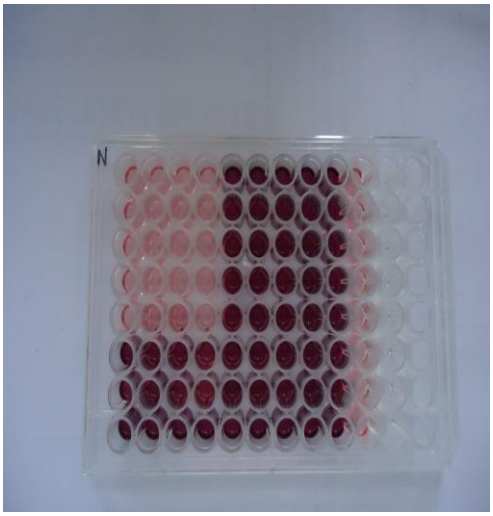


Cell cytotoxicity

MTS assay

skeletal muscles cell line L6 cells
Incubation with serially diluted

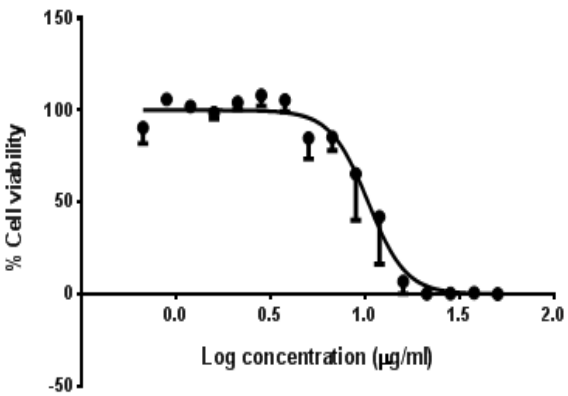
- ***E.ocellatus* venom**
- ***N.nubiae* venom**



Cytotoxicity of venoms

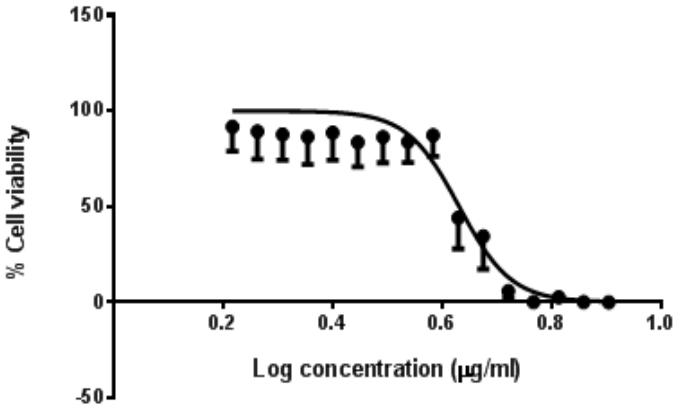
- **Data analysis:** Graphpad Prism 5 software.
- Growth curve.
- IC_{50} (Venom)

E.ocellatus venom



IC_{50} = 10.33 µg/ml

N.nubiae venom

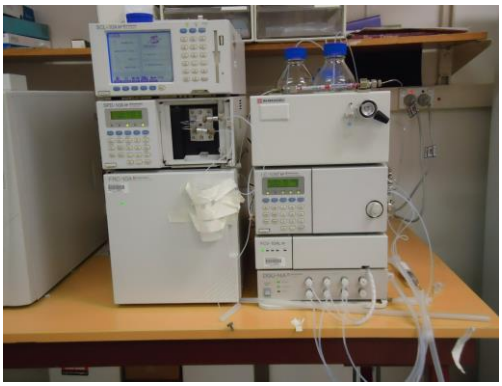


IC_{50} = 4.27 µg/ml

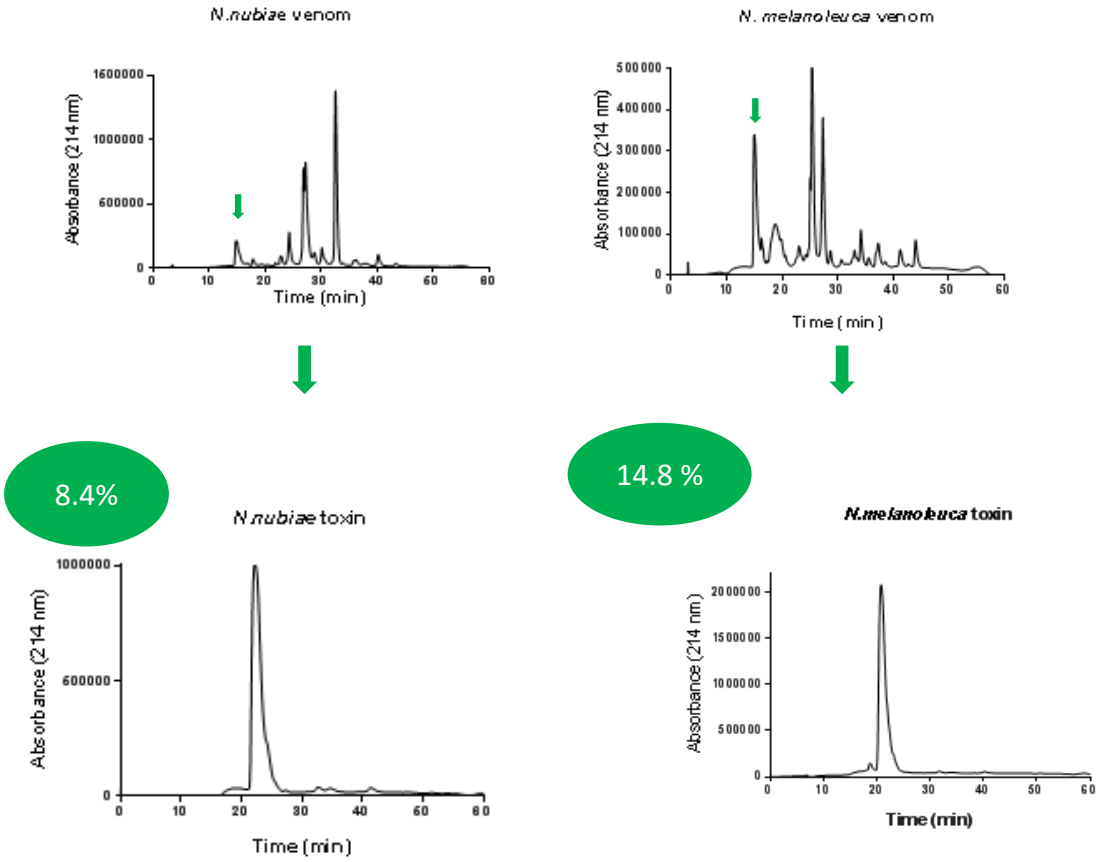
Characterization of α-neurotoxins

HPLC

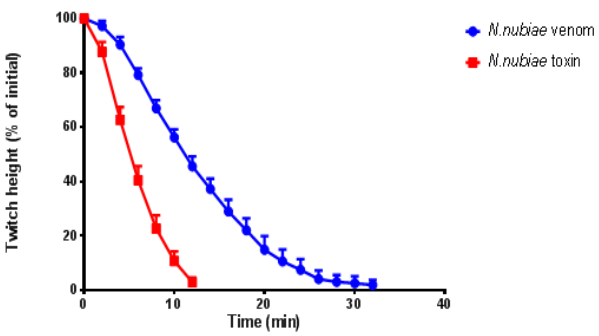
- *N. nubiae* and *N. melanoleuca* venoms were separated using RP-HPLC
- The pure toxins samples were collected.



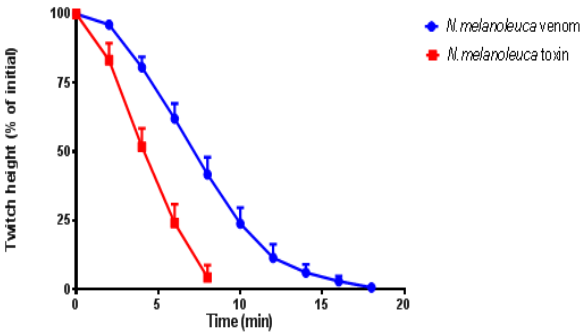
HPLC of (N. n & N. m) venoms & toxins



The effect of α-neurotoxin



- $t_{90\ venom}$ = 22.2±1.9 min
- $t_{90\ toxin}$ = 10 ± 0.6 min



- $t_{90\ venom}$ = 12.9±1.2 min
- $t_{90\ toxin}$ = 8.2 ± 0.3 min

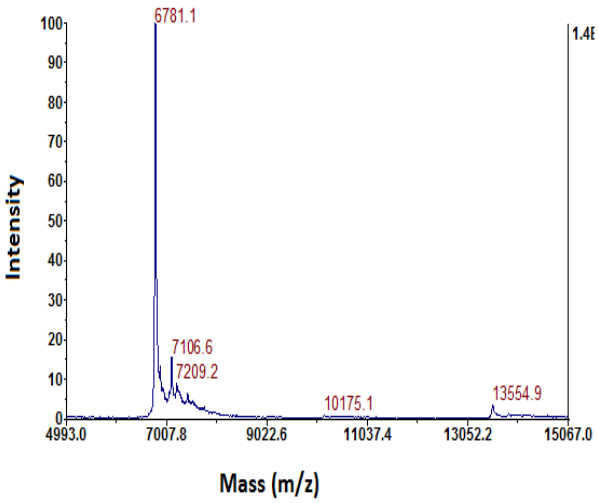
The efficacy of the purified toxin was tested using the chick biventer preparation.

Characterization of α-neurotoxins

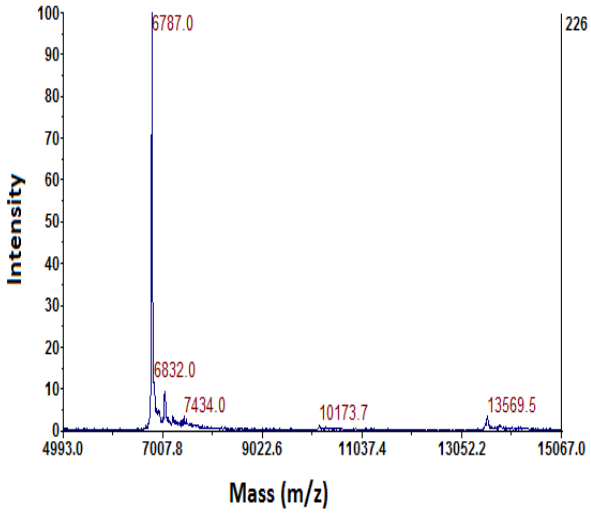
Matrix Associated Laser Desorption Time of Flight (MALDI- ToF) used to determine the molecular mass of the two toxins.

MALDI-ToF

N. nubiae
MW= 6781.1 D



N. melanoleuca
MW= 6787.0 D



Conclusion

We can do it

Next-generation antivenoms

Dr. Rania Mohamed Hassan Baleela

Department of Zoology & Toxic Organisms Research Centre, Faculty of Science, University of Khartoum

" In Sudan, the presence of venomous snakes and scorpions overlaps with the lack of access to healthcare and effective treatment."

WE NEED A SOLUTION & WE NEED IT NOW!

Photo credit @ Abuhaneen

NEXT-GEN

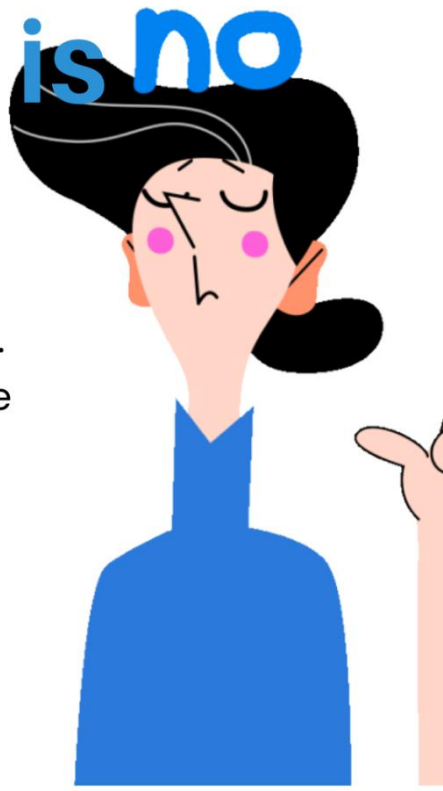
ANTIVENOMS

Rania Baleela

MSC, PHD, DLSHTM

Are existing antivenoms really as good as they could be?

The short answer is no



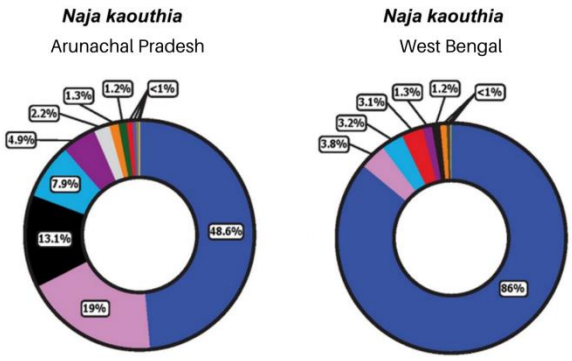
The long answer is

- They are effective in neutralizing venoms by binding to them and thus, they can be lifesaving.
- The animal-derived antibodies can cause severe allergic reactions and anaphylactic shock.
- Often fail to neutralize toxins in limbs leading to disfigurement or the need for amputation.
- They cannot neutralize venoms from different geographical regions.

Naja kaouthia
Monocled cobra

lives in different parts of India. Antivenom DO NOT work!

A person could die from the snakebite in one region, if this person receives an antivenom for the same snake species from a different region.



Classical antivenom production

1 **METHOD**
Described by Césaire Auguste Phisalix & Albert Calmette in 1894

2 **STEP 1**
Milk the venom

3 **STEP 2**
Immunize an animal

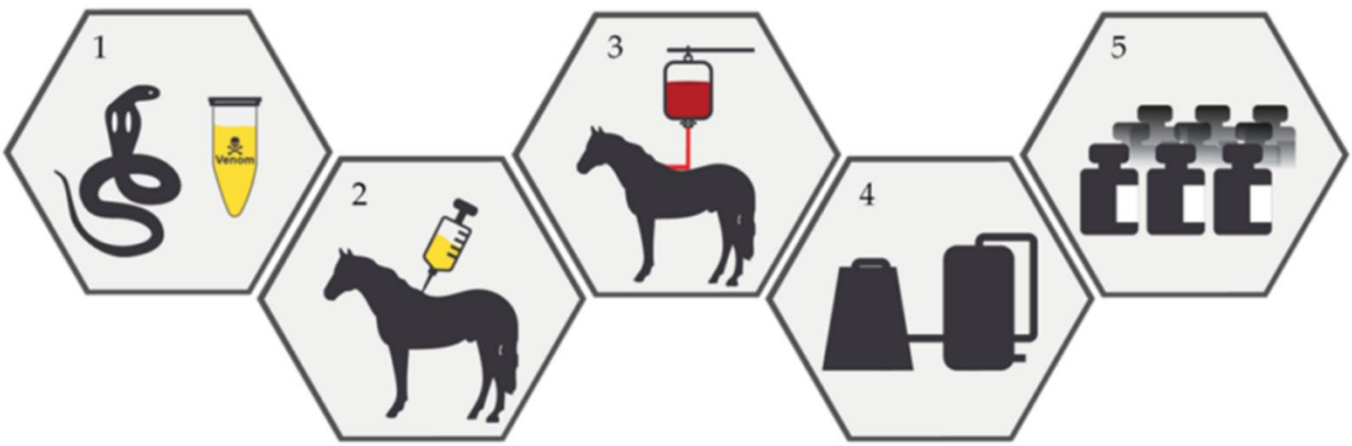
4 **STEP 3**
Draw blood & isolate antibodies

5 **STEP 4**
Concentration, isolation & bottling

1 Repeated immunization (for months to years) of large mammals (mostly horses and sheep),

2 purification of the immunoglobulin G (IgG) antibodies from the hyper-immunized plasma.

3 IgG purification is typically carried out by salting-out procedures using either caprylic acid or ammonium sulfate



Current antivenoms

1	COMPOSITION	• Plasma-derived immunoglobulins • Multiple antigenic peptides with a polylysine core • Immunoglobulin fragments from hyper-immunized animals.
2	AVAILABILITY	Limited and with affordability issues
3	PROBLEM	Laborious and costly

HELP

Can be around the corner

NEXT GENERATION ANTIVENOMS

Next Generation antivenoms

Information

1	COMPOSITION	• comprised of human antibody mixtures
2	MANUFACTURING	• produced biosynthetically

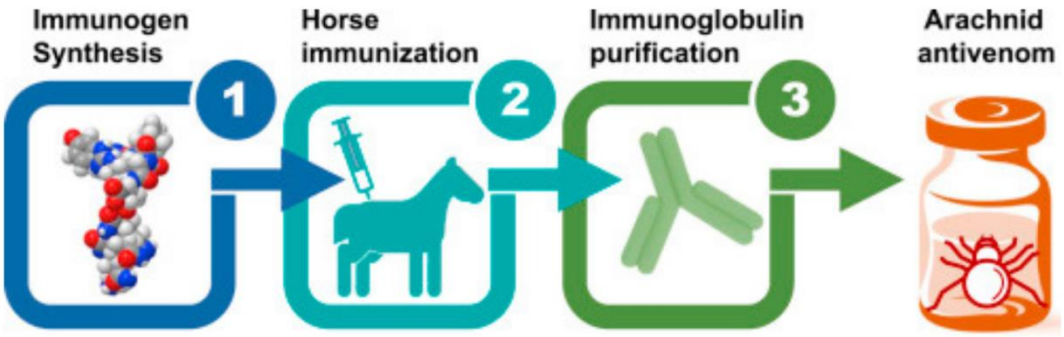
For next-generation antivenom, antibodies are mixed as a form of a cocktail.

FEXIBLE

- Each antibody targets a different toxin.
- These antibody mixtures can be used in many different ways.

Next Generation antivenoms

Arachnids



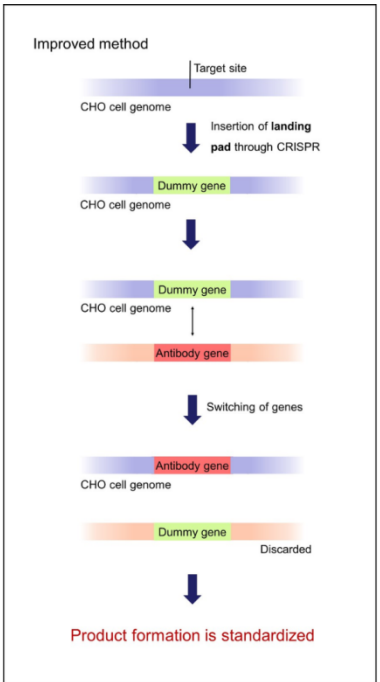
(Camperi *et al.*, 2020, Toxicon:X)

mimics a bacterial defense mechanism

faster and smarter way

Improved way of inserting an antibody gene into the CHO genome

generate numerous cell lines



Ways to produce antibody mixtures

potent recombinant antivenom against complex venoms.

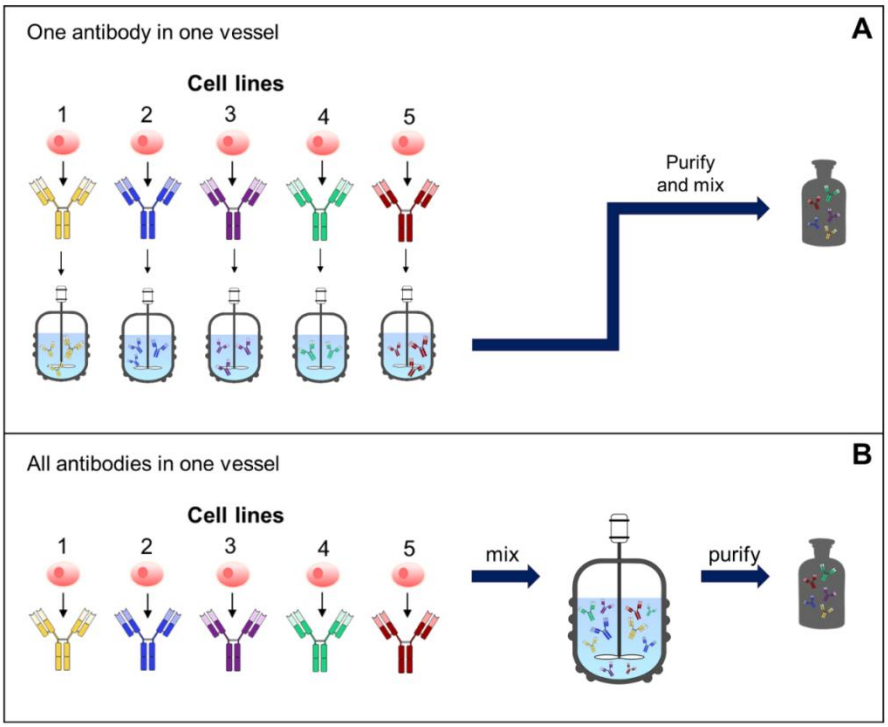
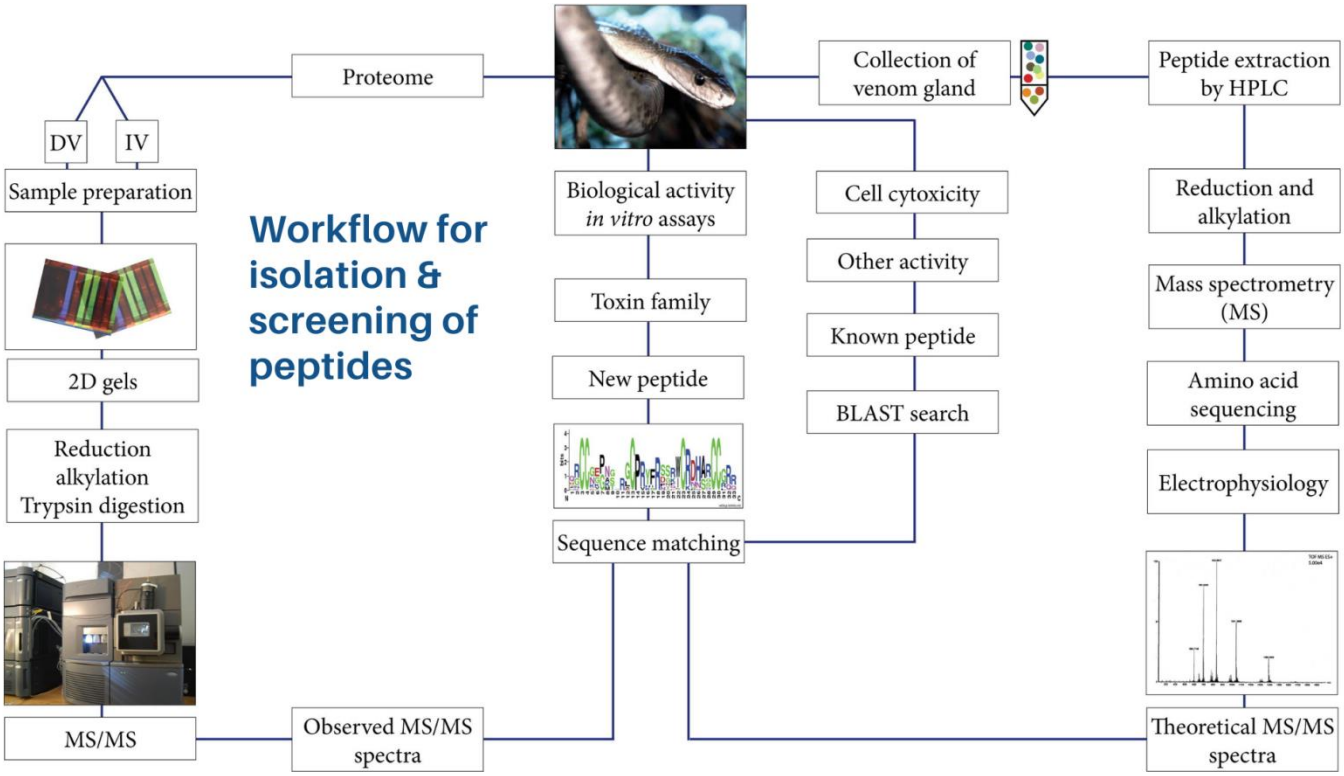


Figure: by Christina Adams



Drugs, Vaccines and Biologicals Development

Prof. Ahmed Mudawi Musa

MBBS, DTM&H, DLSHTM, MSc TM& IH, MRCPI, Ph D
Clinical investigator and WHO/TDR Clinical Trials Monitor

The goal of conducting biomedical research
Improving Human Health

Drugs, Vaccines & Biologicals Development

Can be divided into two major steps:

Research- During which a molecule with specific and potentially useful characteristics is identified (basic research).

Development: When such a simple molecule undergoes numerous steps of stringent testing in order to develop it into a final product (Pre-clinical & Clinical).

Target Selection

- Exploratory disease-based basic research (Controlled studies)
- Informatics (Model).
- Human genetics (personalized medicine).
- Biomarkers for predictive medicine

Commit to Target

- Develop target knowledge (basic research)
- Create/identify chemical libraries (informatics)
- Create screen assays (based on target knowledge)
- Creation of pharmacological animal models (nature of the nature of the disease)
- Disease genetics
- Create physical form-biological or chemical extraction/synthesis of active substance at laboratory scale

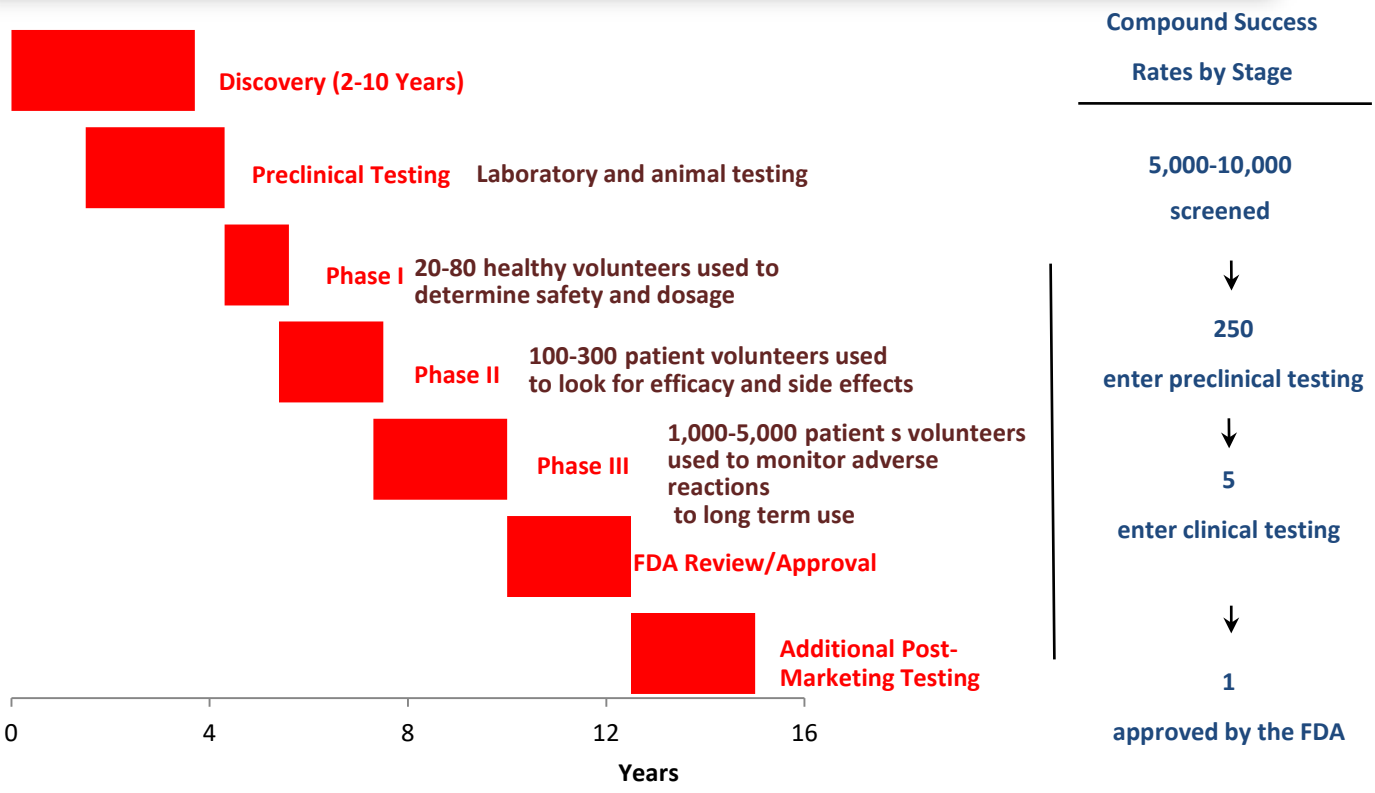
Lead to Candidate selection

- Validation by re-screening
- Basic enzyme/receptor potency and selectivity
- *In vitro/in vivo* metabolism, pharmacological and pharmacokinetic screening of potential active ingredients.
- Analytical characterisation of active ingredients.

Lead to Candidate selection

- Assess developability of active ingredients.
- Make range of lead compounds screen against targets.
- evaluate options and select chemical or biosynthetic routes.
- Formulation studies to determine formulation possibilities and constraints.

The Drugs, vaccines and biologicals Development Process (GLP, GMP, GCP)



Source: PhRMA, based on data from Center for the Study of Drug Development, Tufts University, 1995.

Preclinical Development

- Preliminary metabolism (Animal models)
- Assay development (active ingredients)
- Screening toxicity (laboratory: cell lines)
- Preliminary genotoxicity (laboratory: (Xenometrix)
- *in vivo* toxicology selection (Animals Models)
- Acute toxicity: single administration to two animal species.
- Dose range finding toxicity
- Detailed safety and pharmacology studies (CVS, CNS and other major systems)
- Pharmacokinetics: absorption, distribution, metabolism and elimination

Clinical Development

Phase I

- 20+ Volunteers
- Safety and tolerability in health volunteers
  - highest tolerable dose
  - smallest effective dose
  - mode of action
  - dose/effect relationship
  - duration of effect & side effects
- Pharmacokinetics in human

Phase II

- 50+ patients
- First controlled trials in patients to establish proof of concept
- Indication of efficacy
- Confirmation of safety
- Bioavailability and bioequivalence of different formulations
- Development of clinical genetics databases
- Evaluation of biomakers of disease outcomes.
- Evaluation of surrogates for early Phase IIb clinical trials

Phase III

- 1000+patients
- large scale multicentre trials with different patient populations to demonstrate proof of efficacy and safety.
- Expand diseases and product knowledge
  - use of predictive medicine agents in prognosis and diagnosis
  - Validation of surrogate markers and pharmacogenetic tests.

- **Establishment of the therapeutic profile:**
  - indications
  - dosage and routes of administration
  - contra-indications
  - side effects
  - precautionary measures
- **Demonstration of therapeutic advantage e.g. Vs competitors**

- **Healthcare Outcomes**
  - Quality of Life
  - Pharmacoeconomics

Phase IIIB & IV

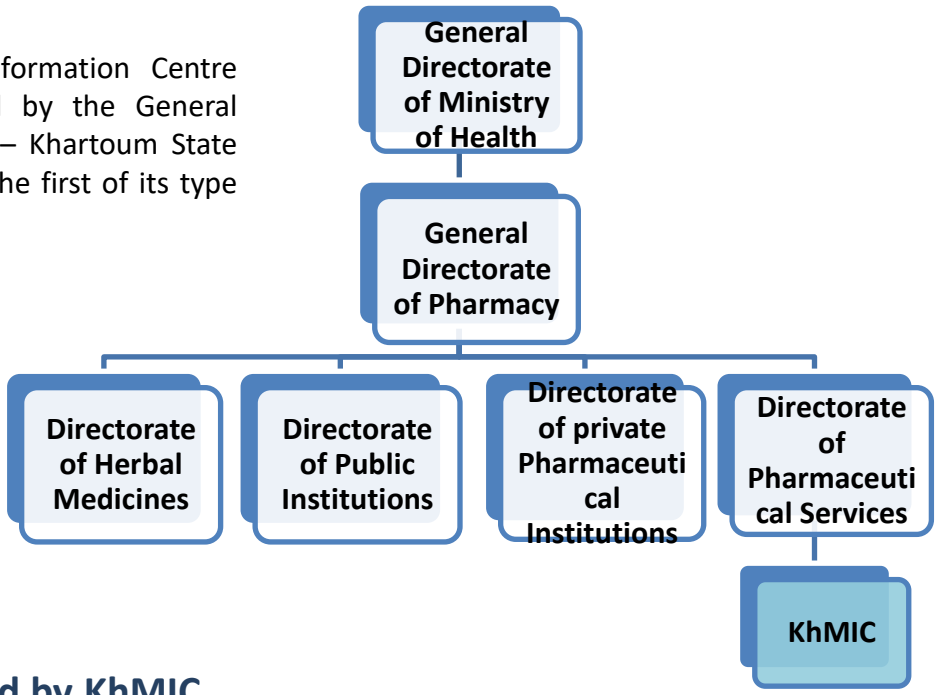
- Trials to support marketing
- Further comparative trials with competitor products
- Post-marketing surveillance
- Answering questions on Submissions

Khartoum Medicines Information Centre (KhMIC) An overview

Dr. Hisham Elhag A Abdelrahim

Consultant Clinical Pharmacist
Senior MI Pharmacist
Khartoum Medicines Information Centre

•Khartoum Medicines Information Centre (KhMIC) was established by the General Directorate of Pharmacy – Khartoum State in the year 2000, it was the first of its type to be established in Sudan



Services provided by KhMIC

Enquiry Answering:

1. Responding to all questions and queries related to medicines and received from the customers, using the latest methods and taking advantage of the scientific references used globally
2. The services of the center have been provided even to Non-Khartoum State publics
3. The center also provides initial care information and guidance for poisoning cases at home and hospitals
4. The center receives and responds to questions daily from 8 am to 10 pm including Fridays and Saturdays

➢ **Resources**

1. World's leading drug and healthcare references via online library
2. Databases
3. Textbooks
4. Local standard treatment guidelines and protocols

Proactive work

KhMIC promotes the pharmaceutical services and the dissemination of the concept of rational use of medicines through:

Issuing selected articles and topics on various pharmaceutical subjects in the mass-circulation newspapers

Issuing Medicines Information Bulletins (monthly)

Publishing Khartoum Pharmacy Journal (quarterly)

Issuing Educational posters, pamphlets and brochures to provide simple and concise information for publics

- Issuing guidebooks and booklets for medical care professionals
  Example: Enquiry Answering Guidelines,
- Pediatric Doses
- Offering regular lectures for medical staff and publics

Participation in many audio visual media programs

Participation in various seminars, workshops and exhibitions

Training programs

KhMIC provides several training programs for its staff and other colleagues inside and outside Khartoum State

Collaborations

In addition, there are some sort of collaboration and partnerships with other MI centers outside Sudan to share experiences

Quality Assurance

- These are the steps taken to help ensure services are of a sufficiently high standard.
- Standards cover:
  - ❑ Resources
  - ❑ Enquiry Answering
  - ❑ Publications and proactive work
  - ❑ Training

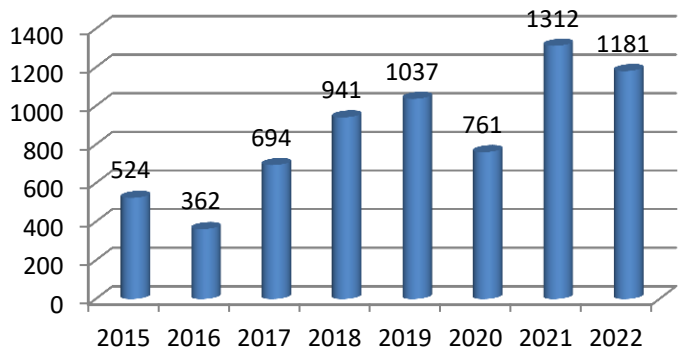
Publications, researches and participations in conferences

- An evaluation study of the service provided by the center has been done and the research findings have been published in an international peer-reviewed journal (Pharmacy World & Science, 2008)
- The 8th Asian Conference on Clinical Pharmacy 2008 (8th ACCP) in Surabaya, Indonesia
- The 1st UAE Toxicology and Drug Information Conference 2008 in Abu Dhabi, UAE
- The 6th Annual International Conference of Pharmaceutical Care 2010 in Khartoum, Sudan

Future planning

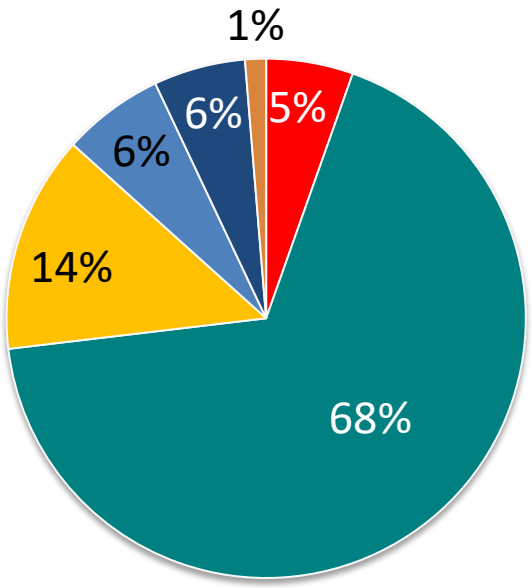
- 24-hrs service
- MI unit in each hospital
- Conduct researches
- Reach the target standards
- Build more partnerships with international MI centers

اسئلة التسمم التي تم استقبالها عبر مركز المعلومات الدوائية من العام 2015 -2022



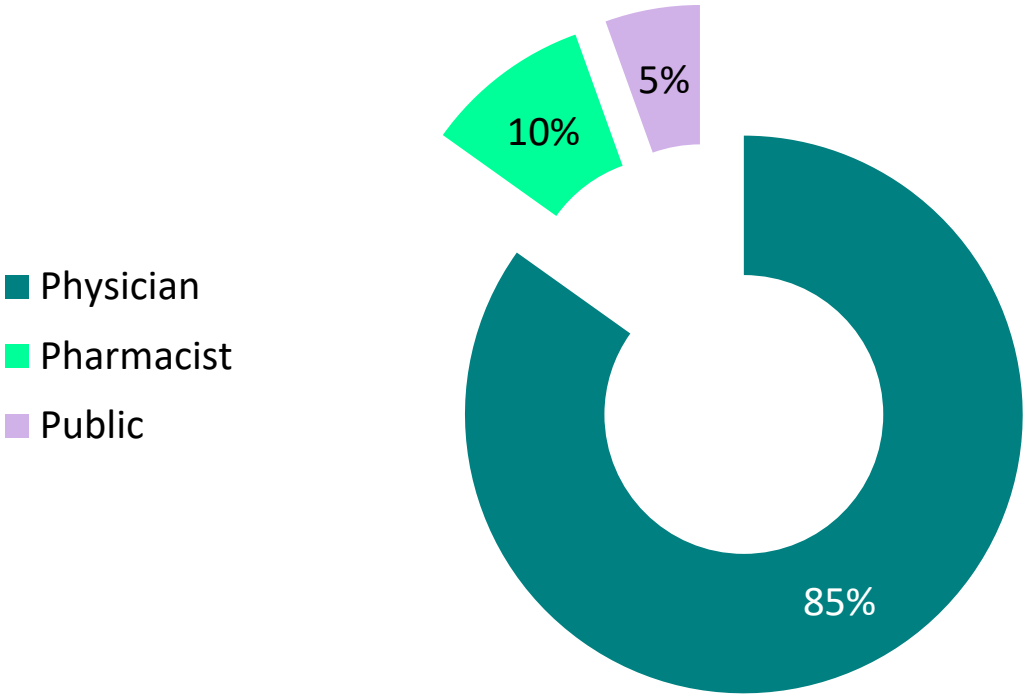
الفئات العمرية التي تتعرض لحالات التسمم

Children < 5 years	**68%**
Children > 5 years (5-11)years	14%
Adult > 19 years	6%
Teens(12-19) years	6%
Infants <1yrs	5%
Elderly > 65 years	1%

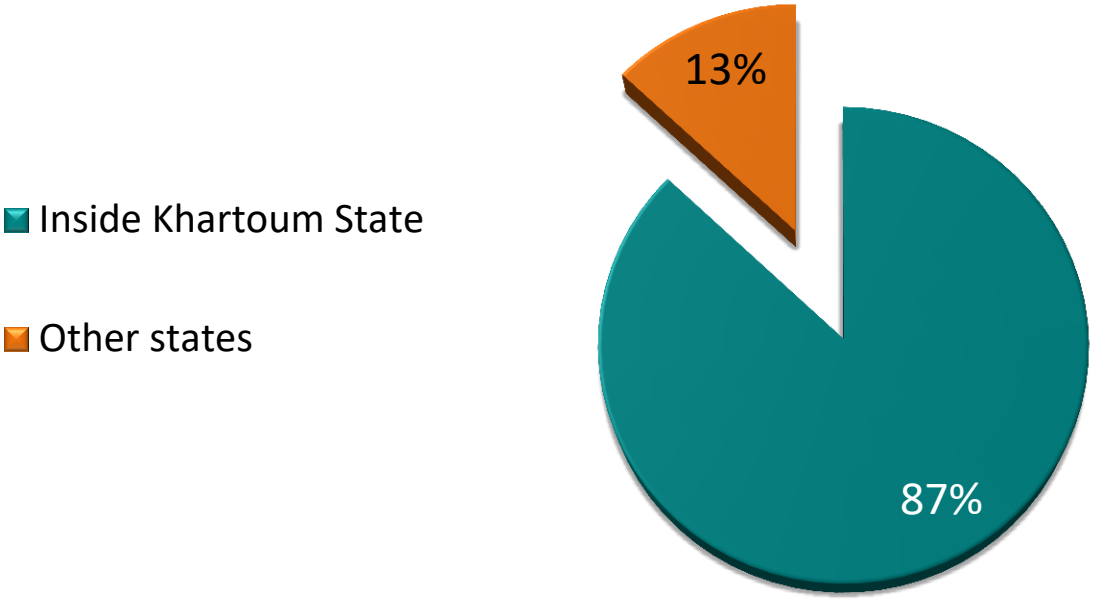


KhMIC Enquirer

تصنيف الاسئلة حسب المتصلين



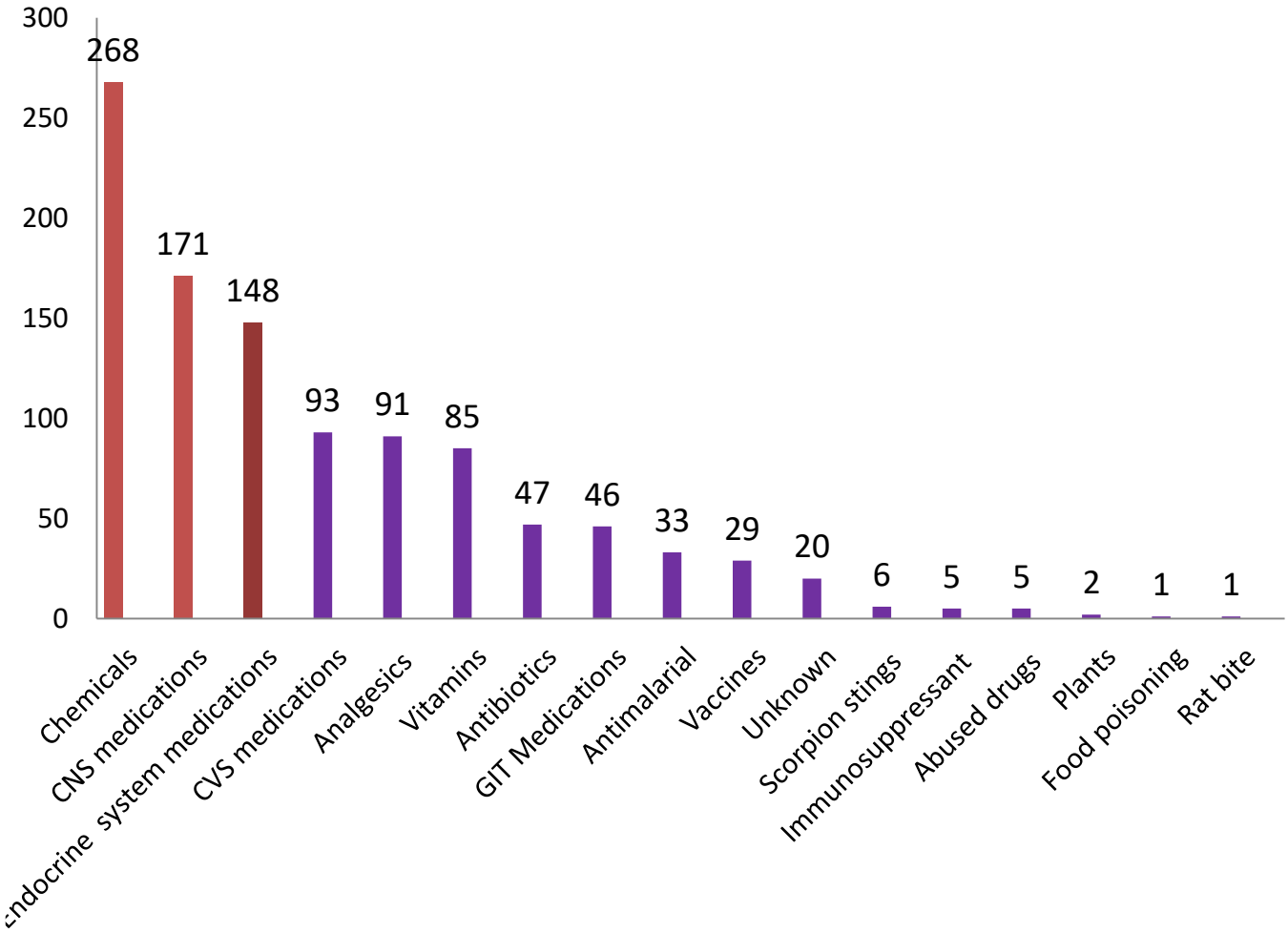
Distribution of enquirer according to location



Classification of questions according to the type of questions

Category	Number	Percentage
Availability	5432	73.30%
Poisoning	1037	13.99%
Public Consultation	190	2.56%
Dose & Administration	168	2.26%
Therapy	138	1.86%
Pharmaceutical	108	1.45%
Interactions	79	1%
Pregnancy	72	0.97%
Adverse drug reactions	66	0.87%
lactation	49	0.66%
Registration	34	0.45%
Contraindications	16	0.21%
Identifications	10	0.13%
Others	11	0.14%

Substances types



Centers' achievements

- **Best scientific paper award at the Middle East Toxicology Conference MENATOX 2017 in Muscat**
- **Best scientific paper award at the Abu Dhabi Pharmaceutical Safety Conference 2018**
- **Participation with a poster in the International Society of Pharmacoviglance conference**
- **Scientific paper on user satisfaction**

Best scientific paper award at the Middle East Conference on Toxicology Dr. Azza Fadl MENATOX 2017

Best scientific paper award at the Abu Dhabi Pharmaceutical Safety Conference 2018 Dr. Tasneem Taj Elsir

DUPHAT conference in Dubai (Poster) 2017

Training of medical staff

Dr. Sarah Youssef: Training workshop on envenomation

Challenges

- A severe shortage in the number of trained cadres to work in the various units.
- Frequent breakdowns of the call center
- Frequent internet outages
- There is a need to train cadres to improve work quality of provided services
- Financial problems (subscription fees in specific sites to provide sources of information on which the center relies).

Contact us at KhMIC

- **Tel:**
- **4141**
- **0183793201**
- **0155100044**
- **0155100044**

Budget & Instrumentation

Hassan Hussein Musa, PhD

Professor of Molecular Genetics & Immunology
Department of Medical Microbiology, Faculty of Medical Laboratory Sciences, University of Khartoum, Sudan
Biomedical Research Institute, Darfur College, Nyala, Sudan
Institute of Microbiology, Chinese Academy of Science, Beijing, China

Toxic Organisms Research Centre (TORC)

- TORC was established by the University of Khartoum on April 14th 2021
- The aim was to

1. Provide evidence based strategies to control poisonous and venomous organisms including, but not limited to, scorpions and snakes.
2. Produce local efficient monovalent and polyvalent antivenoms.
3. Train appropriate cadre in the affected areas to work with poisonous and venomous organisms.
4. To raise the locals' awareness about the importance of biodiversity as well as to train them to avoid being bitten or stung.

Scientific units

The centre is composed of four scientific units and 2 service units:

1. Unit of Taxonomy and Environmental Studies.
2. Unit of Biotoxicology.
3. Unit of Toxicogenomics and Bioinformatics.
4. Unit of Nanotoxicology & Natural Antidotes.

The service units are:

1. Experimental animals' house and plant nursery
2. Outreach Unit

Urgent equipment's needs for antivenom production

1.Venom milking apparatus
2. Lyophilizer
3. Nanodrop®
4. Gel Electrophoresis and documentation system
5. PCR machine
6. RT-PCR machine
7. Protein Analyzer
8. -20°C fridge
9. Centrifuge
10. Reagents
11. Disposables

Fridge

Incubators

Safety cabinet

Microwave

Centrifuges

Sensitive Balance

DNA extraction & PCR

Gel Electrophoresis & Documentation System

RT-PCR

Enzyme-linked immunoassay (EIA) Microplate reader

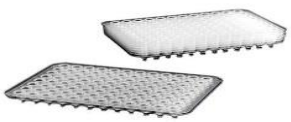
ELISA reader

HPLC

Protein Analyzer

Reagents & Kits

Disposables



Equipment Budget

- General equipment's = 45,772.28
- Molecular Biology apparatus = 798,490.94
- Protein Analysis & Antivenom production =750,760
- Personal Protective Equipment = 4,362.87
- Others = 610,286.06
- Administrative cost (15%) = 370,496.83
- **Total = 2,580,168.98 $**

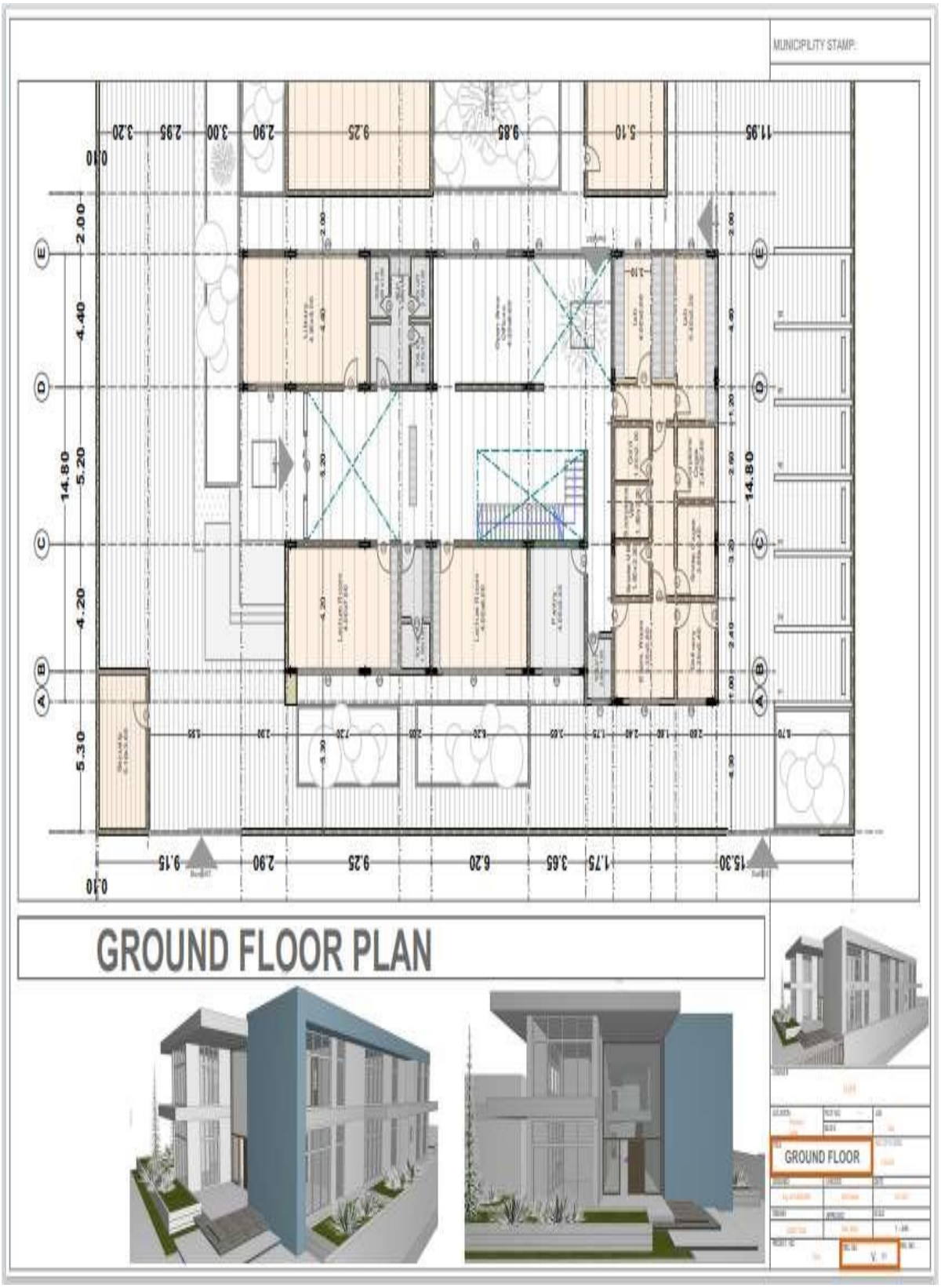
Building, furniture & vehicles Budget

- Building; 2 floors laboratory and office spaces building: plan, construction, taxes, etc = 1,300,000
- Furniture = 21,524
- Vehicles (truck mounted Laboratory & Toyota Tundra 4-wheel drive) = 83,825
- **Total =1,405,349**

Total budget

- **Equipment Budget = 2,580,168.98 $**
- **Building, furniture & vehicles Budget =1,405,349**
- **Total budget = 3,985,517.98**

The new building must include



MUNICIPALITY STAMP

FIRST FLOOR PLAN

FIRST FLOOR

Final recommendations

Fund raising committee establishement to acquire funding for TORC building and antivenoms production.

Members include:

- TORC Director
- Dean, Faculty of Pharmacy, U. of K.
- Dr. Osama SidAhmed AlCardinal

Approach:

- Ministry of Defense
- Oil companies
- Zakat Office, Gedarif State

A presentation should be prepared for the purpose of fund raising

- Building refurbishment contest for graduation project
- Research graduate projects affiliated with TORC

- Add budget for training at international and regional institutes
- TORC can train Horn of Africa member countries affiliates

Establishment of mass media committee

Dr. Osama SidAhmed AlCardinal donnated $50K to TORC

University of Khartoum

www.uofk.edu

Faculty of Science
Toxic Organisms Research Centre