Global Challenges of Snake Antivenom Therapy

Abdulrazaq G. Habib
Bayero University Kano
NIGERIA

Antibody Engineering & Therapeutics Europe – Amsterdam, Netherlands, June 2022
Outline - Challenges

• Burden
  • Global burden
  • Benefit and effectiveness of antivenom (polyclonal) therapy

• Medical challenges
  • Immuno-biology
  • Early adverse reactions
  • Relative lack of efficacy and potency
    • Necrosis - amputation
    • Neurotoxicity

• Manufacturing and product development challenges
  • Quality, standards and benchmarks
  • Product development and clinical evidence
  • Disproportionate global production and utilization

• Security of supply, financing and funding

• Logistical and operational challenges
  • Delays in distribution, deployment and utilization

• Training

• Miscellaneous
Why the focus on snakebite today?

“Snakebite is the biggest public health crisis you have likely never heard of.”

Kofi Annan
Globally at least 1.8 million envenomings and 81,000 deaths pa. Reliable estimates (surveys) are needed.
MSF snakebite treatment sites, Ethiopia & S-Sudan 2017
(Source: Gabriel Alcoba)

MSF treats globally ~ 3000 SB’s yearly
Ethiopia ~ 600
CAR (Paoua) ~ 750/y
South Sudan (Agok) ~ 350/y
Yemen ~ 450/y

About 50% needs an antivenom
Case Fatality rate = < 2%

Snakebite: Seasonality in Agok – S. Sudan
Snakebite Admissions by Occupation at Kaltungo General Hospital, Gombe, Nigeria in 2013 (N=3797)

Burmese Paddy Rice Farmers
Snakebite is the 5th Commonest Cause of Deaths in Myanmar
ILLUSTRATIVE CASES FOLLOWING ECHIS OCELLATUS ENVENOMING

A. BLOOD COLLECTION

B. SWOLLEN FOOT

C. BLISTERING & GANGRENE

D. COMA & BLEEDING GUMS
NEUROTOXIC COBRA ENVENOMING IN NIGERIA
VENOM COMPLEXITY LEADS TO CHALLENGES IN POLYCLONAL ANTIBODIES

Elapids (mambas, cobras)

Vipers

Photographs: Wuster

Nature Reviews Disease Primers
Snakebite can be cured!
Provision of effective reliable antivenom can reverse
the poisonous effects of venom in 6 hrs (>80%) and
preventing deaths in >75%!

EchiTAb Antivenom treatment

Before Treatment

After treatment

Reduction of Mortality with Appropriate Compared to Inappropriate Antivenoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wormald et al., 1977</td>
<td>0.11 (0.04, 0.35)</td>
<td>16.81</td>
</tr>
<tr>
<td>Stogdale et al., 2010</td>
<td>0.27 (0.08, 0.88)</td>
<td>23.90</td>
</tr>
<tr>
<td>Uwazuruike et al., 2000</td>
<td>0.11 (0.04, 0.30)</td>
<td>15.15</td>
</tr>
<tr>
<td>Harb et al., 2010</td>
<td>0.41 (0.23, 0.73)</td>
<td>42.63</td>
</tr>
<tr>
<td>Overall (I-squared = 36.2%, p = 0.22)</td>
<td>0.25 (0.14, 0.44)</td>
<td>120.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
RR of mortality rose to 2.29 (95%CI: 1.35-3.89) over 2mths period (Aug-Sept 2009) without reliable antivenom

It was not due to seasonality as RR for mortality still rose for Aug-Sept 2009 cf Aug-Sept of 2007/8 to 2.52 (95%CI: 1.12-5.66)
ETSG (UK) - production of snake antivenom

- **EchiTAbG** *(MICROPHARM, U.K)*
- *E. ocellatus* monospecific antivenom
- Ovine IgG

- **EchiTAb** *(PAN AFRICAN ANTIVENOM - ICP COSTA RICA)*
- *E. ocellatus/B. arietans/N. nigricollis* polyspecific AV
- Equine IgG
EchiTAb Antivenoms

- Fab - EchiTAb
- F(ab')_2 - EchiTAb2
- Whole IgG
  - EchiTAbG, (MICROPHARM, U.K)
  - EchiTAb+ (PAN AFRICAN ANTIVENOM, ICP Costa Rica)
Time table in study of AR and technological interventions to reduce AR

- 1890: Pepsin digestion to reduce adverse reaction (Grasset and Christensen, 1947)
- 1939: Pepsin digestion to purify gammaglobulins (Pope, 1939)
- 1959: Association IgG aggregates and adverse reaction (Barandun et al., 1962)
- 1968: Allergy classification (Coombs and Gell, 1968)
- 1970: Role of Fc in ACA (Waldesbuhl et al., 1970)
- 1977: Association IgG ACA and adverse reactions (Sutherland, 1977)
- 1975: Reduction of IgG ACA by β-propiolactone (Stephan, 1975)
- 1974: First randomized controlled clinical trial of antivenom (Warrell et al., 1974)
- 1986: Clinical trial of antivenom ACA (Malasit et al., 1986)
- 1989: Caprylic acid precipitation in antivenoms (dos Santos et al., 1989)
- 1992: Fab antivenom development (Smith et al., 1992)
- 1994: Industrialization of caprylic acid precipitation (Rojas et al., 1994)
- 1997: Clinical trials of Fab antivenom (Karlsson-Stiber et al., 1997; Meyer et al., 1997)
- 1998: Clinical trial of caprylic acid antivenom (Otero-Patiño et al., 1998)
- 2006: Clinical trial of β-propiolactone antivenom (Otero et al., 2006)
- 2012: Clinical trial IgG vs F(ab')2 (Otero et al., 2012)
- 2010: Clinical trial horse vs ovine IgG (Abubakar et al., 2010)
Fab and recurrence of envenoming and bleeding

Meyer, Habib, Yakubu et al 1997

**Figure 6.** Venom (dashed line) and EchiTab antivenom (solid line) levels in two patients treated with four doses of 0.5 g (10 ml). Note the recurrence of venom antigenemia and incoagulable blood indicating inadequate antivenom therapy. The dark triangles are points at which antivenom was administered. Each point is the mean level in each patient.
Incidence of early (anaphylactic) adverse reactions induced by antivenoms, as reported in several clinical trials.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Source</th>
<th>Active substance</th>
<th>Incidence of ears</th>
<th>Country of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polonga TAB™</td>
<td>Sheep</td>
<td>Fab</td>
<td>48%</td>
<td>Sri Lanka</td>
<td>Ariaratnam et al., 2001</td>
</tr>
<tr>
<td>Protherics UK Ltd</td>
<td>Sheep</td>
<td>Fab</td>
<td>5%</td>
<td>United States</td>
<td>Cannon et al., 2008</td>
</tr>
<tr>
<td></td>
<td>Sheep</td>
<td>Fab</td>
<td>7%</td>
<td>United States</td>
<td>Farrar et al., 2012</td>
</tr>
<tr>
<td>Pasteur Merieux</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>6%</td>
<td>Martinica</td>
<td>Thomas et al., 1996</td>
</tr>
<tr>
<td>Ipser Africa</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>6%</td>
<td>Cameroon</td>
<td>Chippaux et al., 1998</td>
</tr>
<tr>
<td>Aventis Pasteur</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>4%</td>
<td>Cameroon</td>
<td>Chippaux et al., 1999</td>
</tr>
<tr>
<td>Bioclon</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>11%</td>
<td>Benin</td>
<td>Chippaux et al., 2007</td>
</tr>
<tr>
<td>SAIMR</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>76%</td>
<td>South Africa</td>
<td>Moran et al., 1998</td>
</tr>
<tr>
<td>ViperFab</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>13%</td>
<td>France</td>
<td>Haro et al., 1998</td>
</tr>
<tr>
<td>Instituto Butantan</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>25%</td>
<td>Brasil</td>
<td>Hui et al., 1999</td>
</tr>
<tr>
<td>Haffkine</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>43%</td>
<td>Sri Lanka</td>
<td>Premawardhena et al., 1999</td>
</tr>
<tr>
<td>Haffkine</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>81%</td>
<td>Sri Lanka</td>
<td>Ariaratnam et al., 2001</td>
</tr>
<tr>
<td>Inst. Butantan</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>18%</td>
<td>Brasil</td>
<td>Pardal et al., 2004</td>
</tr>
<tr>
<td>Fundação Ezequiel Dias</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>19%</td>
<td>Brasil</td>
<td>Pardal et al., 2004</td>
</tr>
<tr>
<td>Vins Bioprodut</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>81%</td>
<td>Sri Lanka</td>
<td>Gawarammanna et al., 2004</td>
</tr>
<tr>
<td>Bioclon</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>19%</td>
<td>Colombia</td>
<td>Otero-Patiño et al., 2007</td>
</tr>
<tr>
<td>Commonwealth Serum Laboratories</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>18%</td>
<td>Papua New Guinea</td>
<td>Williams et al., 2007</td>
</tr>
<tr>
<td>Saovabha Memorial Institute</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>3%</td>
<td>Thailand</td>
<td>Thiansookon and Rojnuckarin, 2008</td>
</tr>
<tr>
<td>Haffkine Bio-Pharmaceuticals</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>88%</td>
<td>Bangladesh</td>
<td>Amin et al., 2008</td>
</tr>
<tr>
<td>Bharat Serums and Vaccines Ltd</td>
<td>Horse</td>
<td>F(ab′)₂</td>
<td>61%</td>
<td>Sri Lanka</td>
<td>Isbister et al., 2012</td>
</tr>
<tr>
<td>Instituto Clodomiro Picado</td>
<td>Horse</td>
<td>F(ab′)₂ (caprylic)</td>
<td>29%</td>
<td>Colombia</td>
<td>Otero-Patiño et al., 2012</td>
</tr>
<tr>
<td>Instituto Clodomiro Picado</td>
<td>Horse</td>
<td>IgG (sulphate)</td>
<td>52%</td>
<td>Colombia</td>
<td>Otero et al., 1999</td>
</tr>
<tr>
<td>Instituto Clodomiro Picado</td>
<td>Horse</td>
<td>IgG (caprylic)</td>
<td>25%</td>
<td>Colombia</td>
<td>Otero et al., 1999</td>
</tr>
<tr>
<td>Instituto Clodomiro Picado</td>
<td>Horse</td>
<td>IgG (caprylic)</td>
<td>26%</td>
<td>Nigeria</td>
<td>Abubakar et al, 2010</td>
</tr>
<tr>
<td>MicroPharm</td>
<td>Sheep</td>
<td>IgG (caprylic)</td>
<td>19%</td>
<td>Nigeria</td>
<td>Abubakar et al, 2010</td>
</tr>
</tbody>
</table>

Mortality from AV EAR 0.9% - Leon et al 2013; Williams D et al 2007
Maculopapula and urticarial skin reaction 30mins following antivenom administration
Urticaria on the Trunk

Peri-orbital oedema
Total of 2410 received antivenom therapy (Nigeria); Jan-Dec 2021 (unpublished)

Of these, 98 (or 4.07%) developed EAR.

The type of EAR were:
* pruritis (80, 83.3%)
* pyrexia (7, 7.3%)
* anaphylaxis (2, 2.1%)
* other (7, 7.3%)

[rigors 3, difficulty in breathing 1, vomiting 1, sneezing 1 and all of above 1]
Pathogenesis of EAR

• Factors relating to manufacturing
  • Contamination with LPS, pathogens, lack of GMP

• Factors relating to physicochemical characteristics
  • Purity and content of aggregates

• Factors relating to immunochemical characteristics
  • Heterologous Igs
    • Anticomplementary activity etc

• Others
RCT of EchiTab (Fab) vs Ipser Afrique (Fab') antivenoms among 46 Carpet viper envenomed patients

EAR were higher in EchiTab 1g doses

Impurities and purification using ion-exchange chromatography and iodoacetamide inactivation

Gel filtration liquid chromatography

Challenges with Definitions and Nomenclature of Antivenom Reactions

- Gell and Coombs (1963)
  - Types I and III
- WHO (1981)
  - Early rxns (<24h): anaphylactic/anaphylactoid
  - Late rxns (5-24d)
  - Anaphylactic = IgE mediated
  - Anaphylactoid = Immediate hypersensitivity
  - Late serum rxns = IgG mediated
- WHO (2010)
  - Early rxn (pyrogen/anaphylactic) and both IgE/non-IgE
  - Late rxns (serum sickness)

Leon et al 2013
Blister following snakebite
Disability from Bites: amputation, blindness (venom ophthalmia), contractures, scarring, psychological upset, etc

Warrell & Ormerod 1976, Abubakar et al 2010; Abbas AD et al 2009

Figure 1. A nomadic Fulani woman who had a left above-knee amputation following a carpet viper bite.

Figure 1. Case 2: showing gangrene of the right foot and distal two-third of the leg.
Amputation (2015)
frequency – 3%
disability weight – 0.102

Surgical Amputation
(16/33 – Abubakar, Habib, Mathew 2010)

Declined Surgery – Digits Fall Off

Non-Viable Foot
Randomised Controlled Double-Blind Non-Inferiority Trial of Two Antivenoms for Saw-Scaled or Carpet Viper (Echis ocellatus) Envenoming in Nigeria


1 Department of Community Medicine, Bayero University of Kano, Kano, Nigeria; 2 General Hospital Kaltungo, Kaltungo, Gombe State, Nigeria; 3 Department of Medicine, Bayero University Kano, Kano, Nigeria; 4 Special Projects Unit, Federal Ministry of Health, Abuja, Nigeria; 5 Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria; 6 Alli Aseki Reptile Venom Research Unit, Liverpool School of Tropical Medicine, Liverpool, United Kingdom; 7 Department of Pharmacology, University of Jos, Jos, Nigeria; 8 Department of Pharmacology and Therapeutics, University of Ibadan, Ibadan, Nigeria; 9 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom; 10 Nuffield Department of Clinical Medicine, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom.

Given the risks, placebo-controlled trial may not be (ethically) possible making it a challenge to derive efficacy of polyclonal antibody antivenoms. This allows controversy that antivenoms may be ineffective.
Restoration of clotting following antivenom in carpet viper envenoming compared to ‘non-envenomed’ carpet viper bites not needing antivenom in Nigeria (Jan-Dec 2021, unpublished)

<table>
<thead>
<tr>
<th>time post admission±antiven(hrs)</th>
<th>clotted+antivenom therapy(%)</th>
<th>clotted-antivenom not needed(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=1300
n=238
Dose-finding by Continual Re-assessment Method (CRM) with “3+3” dose escalation design

<table>
<thead>
<tr>
<th>Number cured with dose $d$</th>
<th>Treat 3 further patients with following dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or 3 (of 3)</td>
<td>$d$</td>
</tr>
</tbody>
</table>

Given risks of EAR traditional Phase I and II studies in developing new polyclonal antibody antivenoms may be challenging

*Abubakar SB et al 2009; Habib AG et al 2010*
>36 antivenom manufacturers (N. Casewell)

Sub-Saharan Africa
Manufacturer in: South Africa

N America
Manufacturers in: USA Mexico

C America
Manufacturers in: Costa Rica

S America
Manufacturers in: Brazil Colombia Argentina Peru Venezuela Uruguay Ecuador

Europe
Manufacturers in: Poland UK Russia Serbia Spain

Middle East/N Africa
Manufacturers in: Iran Saudi Arabia Israel Egypt Tunisia Algeria

India
5 manufacturers

Other Asia
Manufacturers in: Thailand Japan China Indonesia Philippines Korea Myanmar Pakistan

Australasia
Manufacturers in: Australia

Global Poverty

http://apps.who.int/bloodproducts/snakeantivenoms/database/
Commitment of existing laboratories to produce antivenoms for other regions and countries (JM Gutierrez)
I – Security of Supply: Antivenoms for SBE in SSA

(Habib et al 2020)

• **Diversity of Supply** – Few numbered companies were making AV in the 1970s and 80s then ceased production e.g, Behringwerke, Ipser Pasteur Afrique and recently FAV Afrique, etc. The market picked up with new comers detailed earlier from other parts, mostly from Asia, UK, Latin America and SA. Initially few but steadily increasing producers.
  
  • Currently all are imported. While a similar pattern obtains for most vaccines, AV dependence on imports in these SSA countries places security of supply at a low to moderate risk

• **Expenditure on AV:** The high cost of AV affects health budgets and out-of-pocket expenditure for individuals especially rural dwellers in SSA

• **Infrastructure:** Infrastructure/Mechanisms in many countries for procurement, supply chain management and distribution network is weak
  
  • Two years ago funds for AV was wrongly routed to the immunization agency that has no experience with AV procurement which led to adverse consequence before rectification
  
  • Rural facilities in hotspots are usually not provided sufficiently
II – Security of Supply: Antivenoms for SBE in SSA  
(Habib et al 2020)

- **Stability of exporting countries**: Main countries exporting AV for SSA (India, Latin America, Mexico, UK) are reasonably stable.
  - By contrast importing SSA countries may not be stable – S-Sudan, CAR, DR-Congo.

- **Stability of prices**: Prices of AV vary between countries and are generally high. A variety of factors affect the price to the health system and the individual.

- **Affordability**: Affordability is a challenge for patients and health systems. AV is purchased by MoH using domestic revenues not funds from donors in contrast to some public health programmes where substantial subsidy is often provided e.g., HIV-AIDS, some NTDs
  - With increased production cost price may reduce through economies of scale

- **Access and Equity**: Generally access is grossly sub-optimal and often related to affordability. Coverage is equally sub-optimal.
  - In some ‘stable’ countries certain areas may not be accessible (e.g., NE Nigeria) further compromising access
  - Deployment is through a ‘pull’ rather than a ‘push’ model
  - Deployment is mostly through a ‘central-urban-tertiary’ rather than a ‘rural-lower facilities’
III – Security of Supply: Antivenoms for SBE in SSA
   (Habib et al 2020)

• **Who owns production:** India-7, South Africa- 1 (but 3 products), Mexico-2, Costa Rica- 1, Egypt- 1, United Kingdom- 1, France- 1, ?Spain- 1

• **Safety and reliability of supply:** Many AVs are liquid formulations requiring cold chain though some are freeze-dried. Some earlier AV formulations had unacceptable efficacy, safety and should be removed from the market by manufacturers or improved. This WHO pre-qualification programme hopefully will usher in better QA/QC and quality products

• **Vulnerability to disruption:** This exists in several forms.
  - Disruptions of supply leads to serious consequences – e.g., cessation of FAV Afrique was followed by adverse effects in Ghana, Chad, CAR, Nigeria
  - The fewer the producers the more vulnerable the supply chain

• **Capacity to adapt to market changes:** Countries have very little capacity to adapt given limited suppliers and there is little alternative for SBE patients.

• **Intellectual property:** This may be an issue with some of the newer products in the pipeline.
Table 3. Results from model outputs by country and scenarios.

<table>
<thead>
<tr>
<th>Antivenom</th>
<th>US $/vial</th>
<th>Antibody content (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS&amp;V - PAN AFRICA poly</td>
<td>$ 84</td>
<td>63.3</td>
</tr>
<tr>
<td>VINS - African</td>
<td>$ 48</td>
<td>21.7</td>
</tr>
<tr>
<td>Inosan – PANAFRICAIN</td>
<td>$ 105</td>
<td>31.7</td>
</tr>
<tr>
<td>Sanofi – FavAfrique</td>
<td>$ 79-99</td>
<td>96.7</td>
</tr>
<tr>
<td>SAVP - SAIMR polyvalent</td>
<td>$ 315</td>
<td>111.7</td>
</tr>
<tr>
<td>SAVP - SAIMR Echis</td>
<td>$ 315</td>
<td>71.7</td>
</tr>
</tbody>
</table>

Antivenom Supply Challenges: Burkina Faso, 2010-14 (Gampini et al 2016)

- SB is among the 5 leading causes of consultation in health districts

- A total of 114,126 cases were recorded over 5 year period with 54.6% hospitalized cases and 2% deaths recorded

- A total of 5738 AV doses were utilized during the period equating to an average of 1148 doses at $107,811 annually

- Cost of AV ranged from $42-170 per dose which was prohibitive to victims

- This led to only 4% of patients receiving AV
  - Ipser Africa and FAV Afrique availability cf Earlier Production or Demand/Need fell to 5000/200000=2.5% (Chippaux & Habib, 2015)
Challenges and Limitations of AV Access and Funding: Nigeria

- AV availability: public sector (~25-33%) and private sector (~67-75%)

- In the 1990s to early 2000s, the Nigeria Government invested about GBP 2million to develop antivenoms against Nigerian snakes as a prelude to local production platform through technology transfer or a N-S and or S-S partnership
  - Two very effective and reasonably safe AVs were developed (ET and ET-ICP)

- Current main AV funding sources: FGN, States, LGA, PCNI, private, others

Current FGN Funding – SB and AV Programme in Nigeria

<table>
<thead>
<tr>
<th>YEAR</th>
<th>AMOUNT BUDGETED [+] (VIALS)</th>
<th>RELEASED AMOUNT [+] (VIALS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>N100 million (4000)</td>
<td>N69 million (2760)</td>
</tr>
<tr>
<td>2018</td>
<td>N51 million (2040)</td>
<td>N19 million (760)</td>
</tr>
<tr>
<td>2019</td>
<td>N131 million (5240)</td>
<td>Yet to be released</td>
</tr>
</tbody>
</table>

Note: $1=N360; Each AV vial priced at N25,000
Reaching out to the “Bottom Billion”: There is urgent need for increased funding and for more balanced allocation of resources.
Factors affecting snakebite mortality in north-eastern Nigeria

A.G. Habib a,*, S.B. Abubakar b

a Infectious & Tropical Diseases Unit, Department of Medicine, Bayero University Kano/Aminu Kano Teaching Hospital, PMB 3452, Kano, Kano State, Nigeria
b Snakebite Ward, Kaltungo General Hospital, Kaltungo, Gombe State, Nigeria

• A stringent retrospective review in northeastern Nigeria
• 6687 snakebite patients (94 deaths or 1.41%) in 36 months
• Predictors of mortality compared to survivors:
  • New CNS features OR(95%CI) = 24.61 (6.93-87.41)
  • Use of an antivenom was 83% protective against dying
  • Presence of anaemia and or shock did not predict mortality after adjusting for above factors in a logistic regression
• 1 hour delay = 1.01(1.00-1.02) or 1% increased odds of dying/1hr delay
Model of ‘3’ Delays of *Maternal Mortality* Applied to *Snakebite*

<table>
<thead>
<tr>
<th>sn</th>
<th>Type of delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Delay in seeking appropriate medical help for a [snakebite] emergency for reasons of cost, lack of recognition of an emergency, poor education, lack of access to information and gender inequality.</td>
</tr>
<tr>
<td>2</td>
<td>Delay in reaching an appropriate facility for reasons of distance, infrastructure and transport.</td>
</tr>
<tr>
<td>3</td>
<td>Delay in receiving adequate care when a facility is reached because there are shortages in qualified staff or medical supplies [e.g., reliable antivenoms] are not available.</td>
</tr>
</tbody>
</table>
Rapid Transport and Community Education

• In a before/after rapid community transportation and education CFR reduced from 10.5% to 0.5% (RR reduction, 0.95 (95%CI: 0.70-0.99)

• Incidence decreased from 502 bites/100,000 population to 315 bites/100,000 population in the 4 intervention villages (relative risk reduction = 0.373, 95% confidence interval = 0.245-0.48) as against non-intervention

• Conclusions: Simple educational messages and promotion of immediate and rapid transport of victims to a treatment center decreased the mortality rate and incidence of snake bite in southeastern Nepal

Sharma SK et al 2013
Improving access to effective healthcare - the Snakebite Emergency Response System (SERS)

Funded by the NIHR, UK
- Motorcycle ambulance - paramedic attending victim

Motorcycle ambulances can get to remote communities
Are cheap to purchase, run and maintain
“Drones can deliver many other health interventions. Since post-partum hemorrhage is the leading cause of maternal mortality, the life-saving potential is vast. Post-exposure treatments for rabies and snakebites are especially important, as most deaths from these conditions occur in rural areas.”

-Dr. Margaret Chan

Director General,
World Health Organization
Education of staff and patients, use of standardized protocol and ensuring adherence to it led to better outcomes and increased uptake of care.

Table 2: Comparison of variables and mortality rates before and after intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-intervention (n = 72)</th>
<th>Post-intervention (n = 236)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years)</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Males</td>
<td>72%</td>
<td>65%</td>
</tr>
<tr>
<td>Bite site is leg</td>
<td>81%</td>
<td>88%</td>
</tr>
<tr>
<td>Admitted within 24 h</td>
<td>60%</td>
<td>76%</td>
</tr>
<tr>
<td>Average time to admission (d)</td>
<td>2.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Clinical envenoming</td>
<td>78%</td>
<td>73%</td>
</tr>
<tr>
<td>Debridement required (no. of patients)</td>
<td>5 (6.9%)</td>
<td>5 (2.2%)</td>
</tr>
<tr>
<td>Anaemia at arrival</td>
<td>22%</td>
<td>35%</td>
</tr>
<tr>
<td>&lt;7 gm/dl</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Antivenom²</td>
<td>18%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Mortality rate

<table>
<thead>
<tr>
<th></th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XX%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Note: 10 ml per ampoule.

Frequency distribution of 364 cases of snake bite and deaths in Yeji, an area of Ghana, 1998-2002
Global Challenges to Snakebite Antivenom Therapy

• Medical
  • Immuno-biology
  • Early adverse reactions
  • Relative lack of efficacy and potency
    • Necrosis - amputation
    • Neurotoxicity

• Manufacturing
  • Quality, standards and benchmarks
  • Product development and clinical evidence of efficacy
  • Disproportionate global production and utilization

• Sub-optimal supply security, financing, funding, affordability, etc

• Logistical and operational issues
  • Delays in distribution, deployment and utilization

• Training

• Others
WHO Roadmap: a multifaceted response

Reduce burden by half by 2030

- Education, prevention, awareness
- Training, capacity building
- Mapping, epidemiology
- Stockpiling of quality antivenom
- Guidance on new antivenoms and innovative therapies
- Partnerships and collaborations
Acknowledgements

**VASP-NSRIC-ASRG Colleagues**
MY Gwarzo, Garba Iliyasu, H Lawal, Muhammad Hamza, BA Chedi, Z Tukur, Isa S. Abubakar, B Kurfi, BUK, Saidu B. Abubakar, KGH, Nigeria

**African Snakebite Research Group ASRG) - LSTM**
Rob A Harrison, David Lalloo, Nick Casewell, others

**Funders - National Institute for Health Research (UK), UK-AID DfID & BUK-Nigeria**
Funding support for VASP, ASRG and NSRIC

THANK YOU FOR LISTENING