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Global Challenges of Snake Antivenom Therapy

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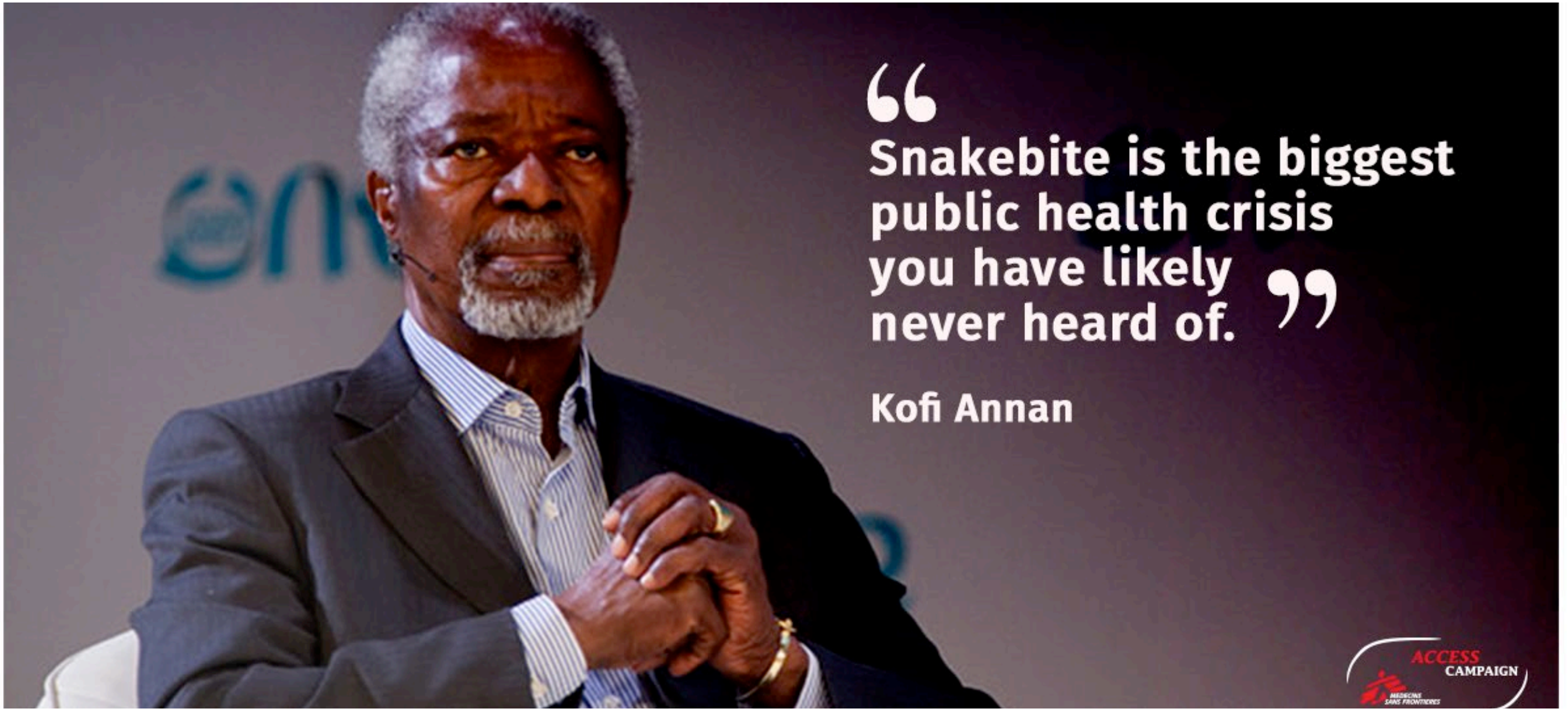
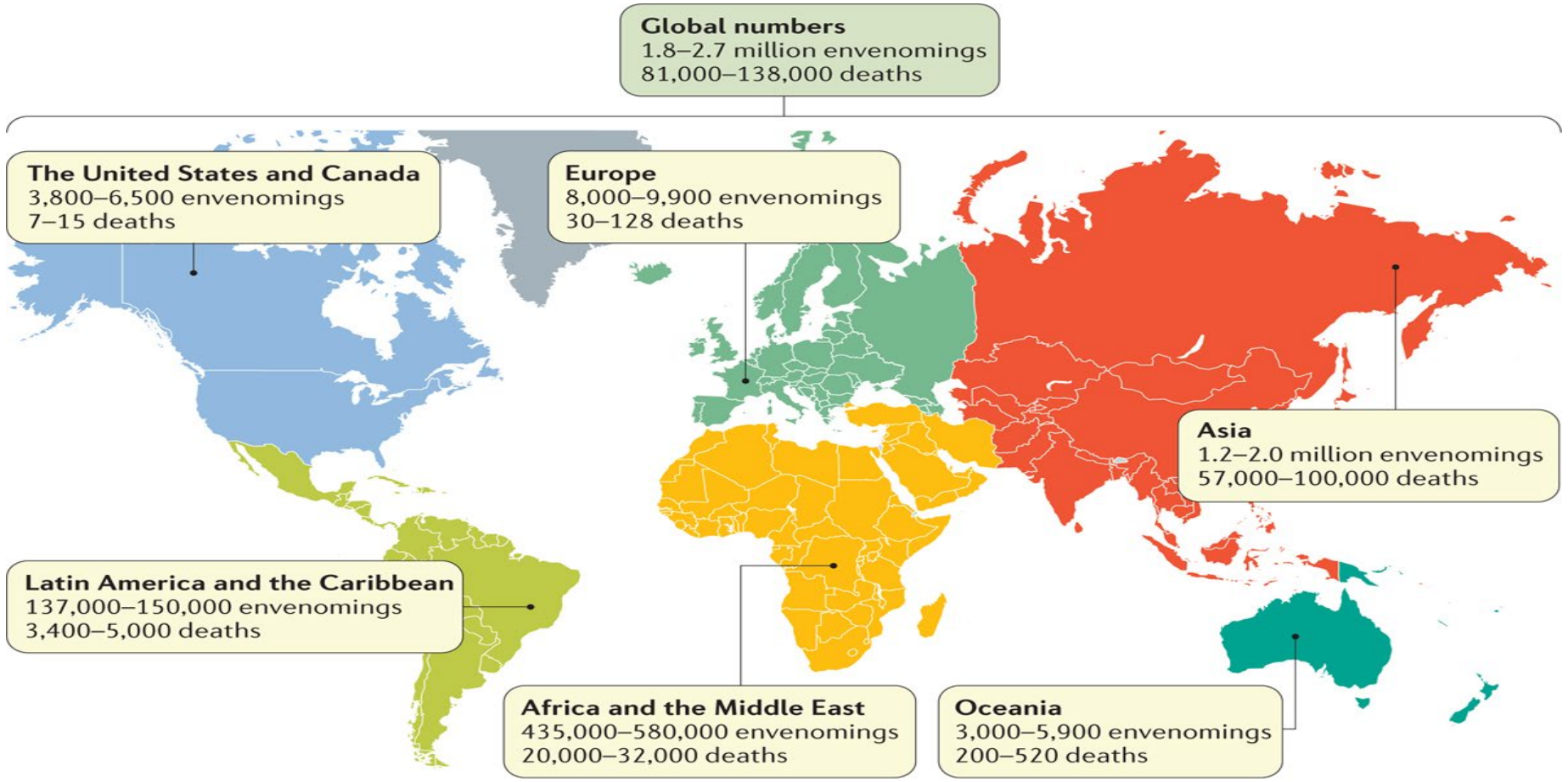
Outline - Challenges

- 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?



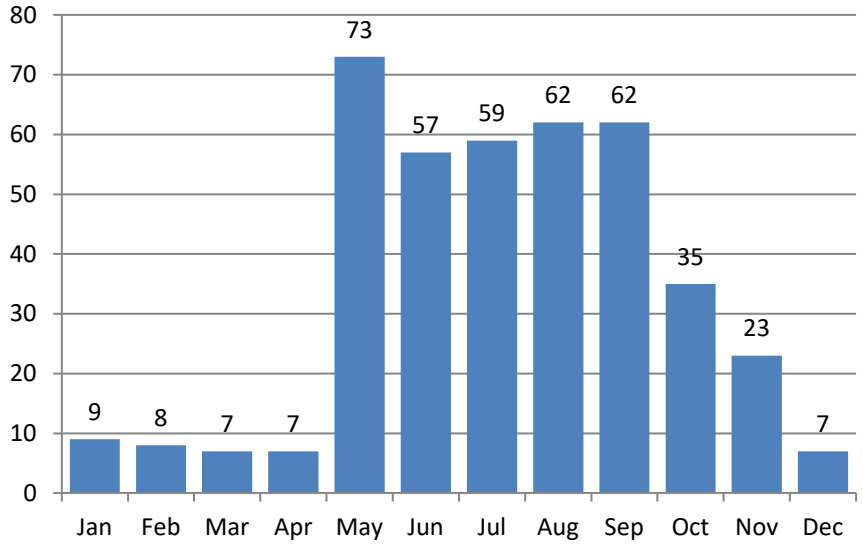
Geographical distribution of the estimated number of snakebite envenomings and deaths



Gutiérrez, J. M. *et al.* (2017) Snakebite envenoming
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2017.63

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

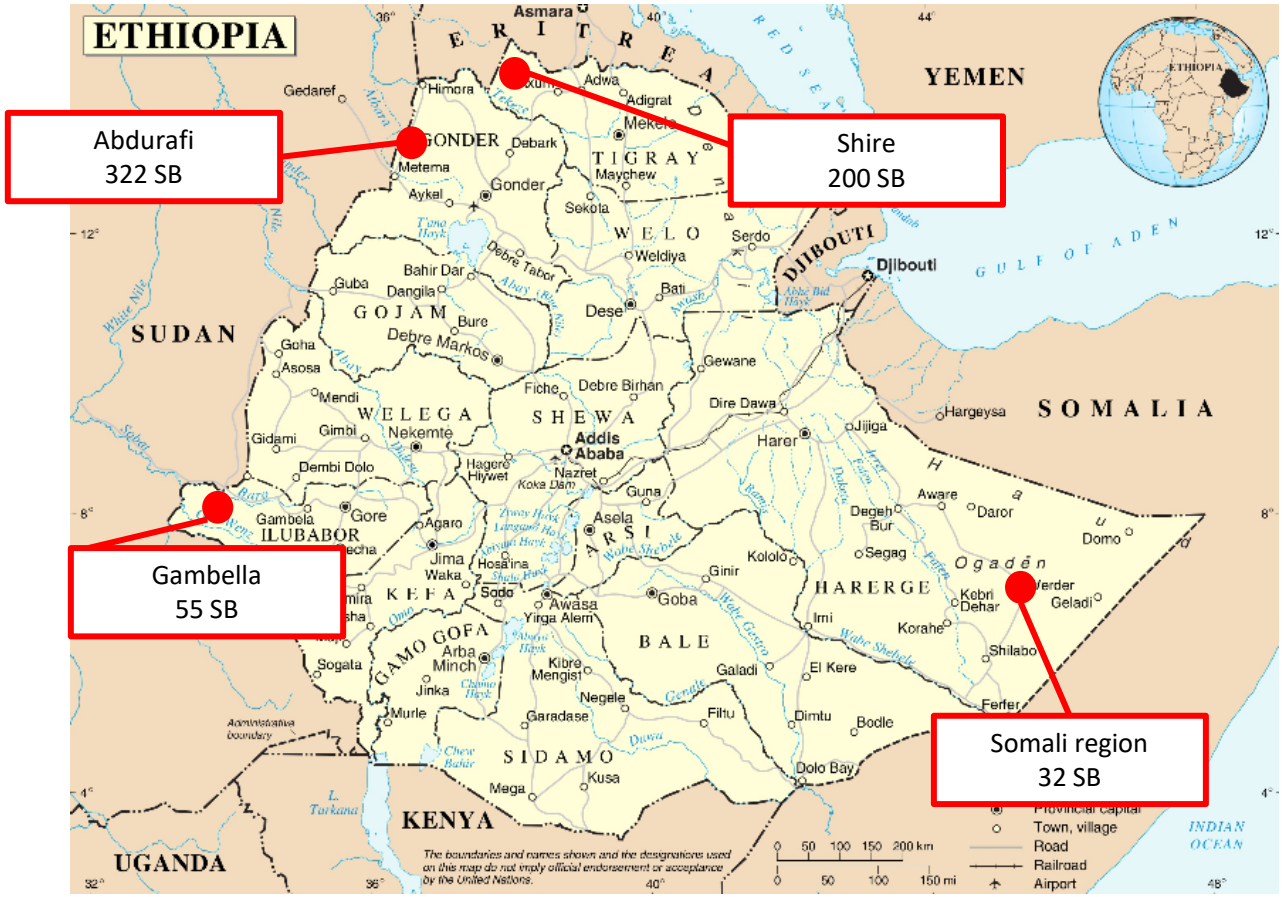
CAR (Paoua) ~750/y

South Sudan (Agok) ~ 350/y

Yemen ~ 450/y

About 50% needs an antivenom

Case Fatality rate = < 2%



Snakebite : Seasonality in Agok – S.Sudan

MEDECINS SANS FRONTIERES
ÄRZTE OHNE GRENZEN

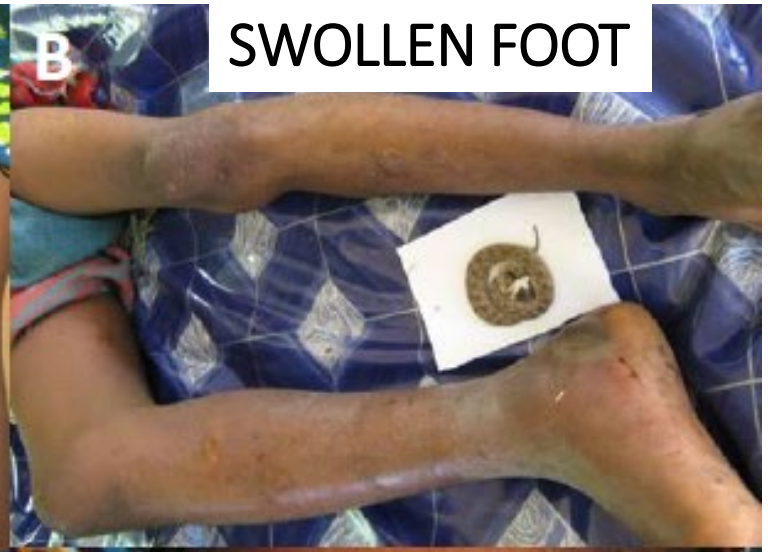
epicentre
ÉPIDÉMIOLOGIE • EPIDEMIOLOGY

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

BLOOD COLLECTION

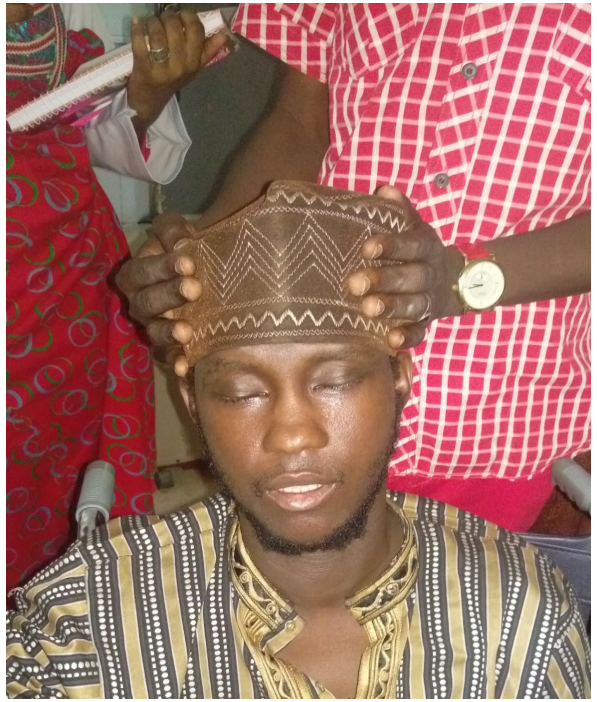


SWOLLEN FOOT

BLISTERING & GANGRENE

COMA & BLEEDING GUMS

NEUROTOXIC COBRA ENVENOMING IN NIGERIA



VENOM COMPLEXITY LEADS TO CHALLENGES IN POLYCLONAL ANTIBODIES

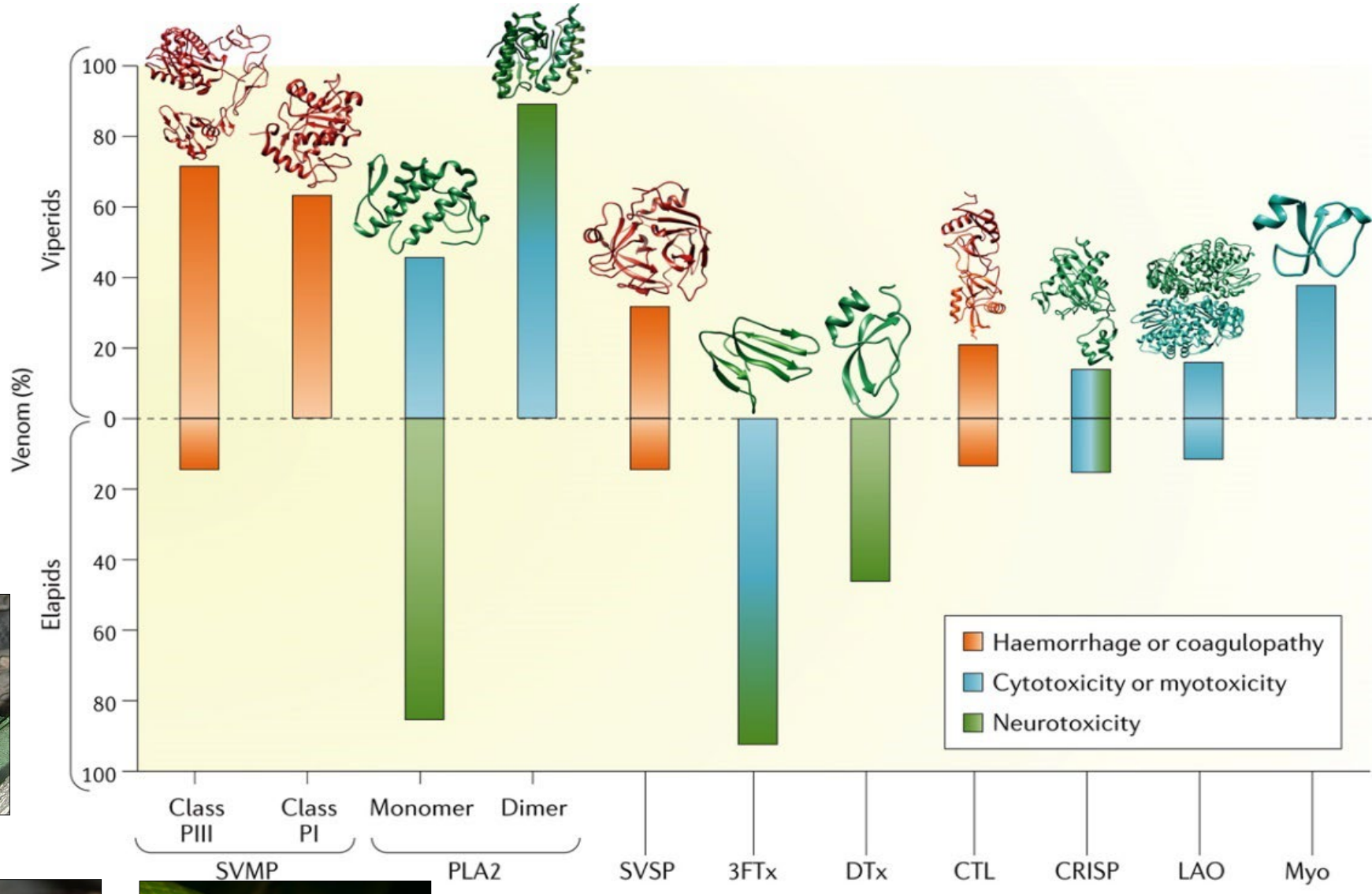
Elapids (mambas, cobras)

The spitting cobra

The Egyptian cobra

Vipers

The puff adder



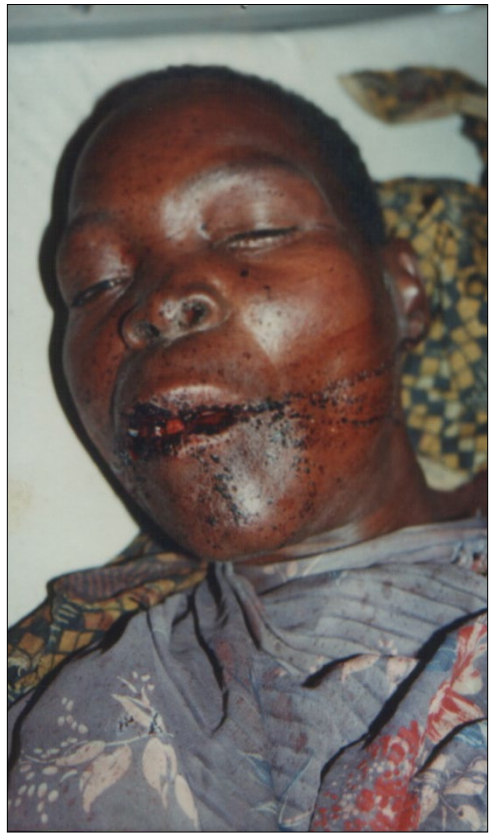
Nature Reviews | Disease Primers

Photographs:
Wuster

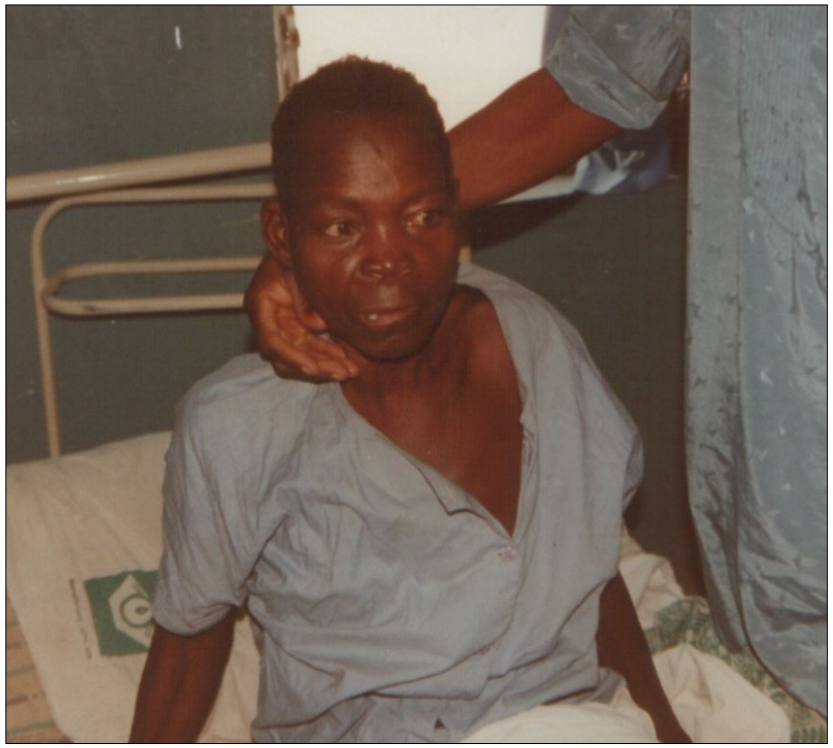
Snakebite can be cured!
Provision of effective reliable antivenom can reverse the poisonous effects of venom in 6 hrs (>80%) and preventing deaths in >75%!

EchiTAb Antivenom treatment

Before Treatment



After treatment



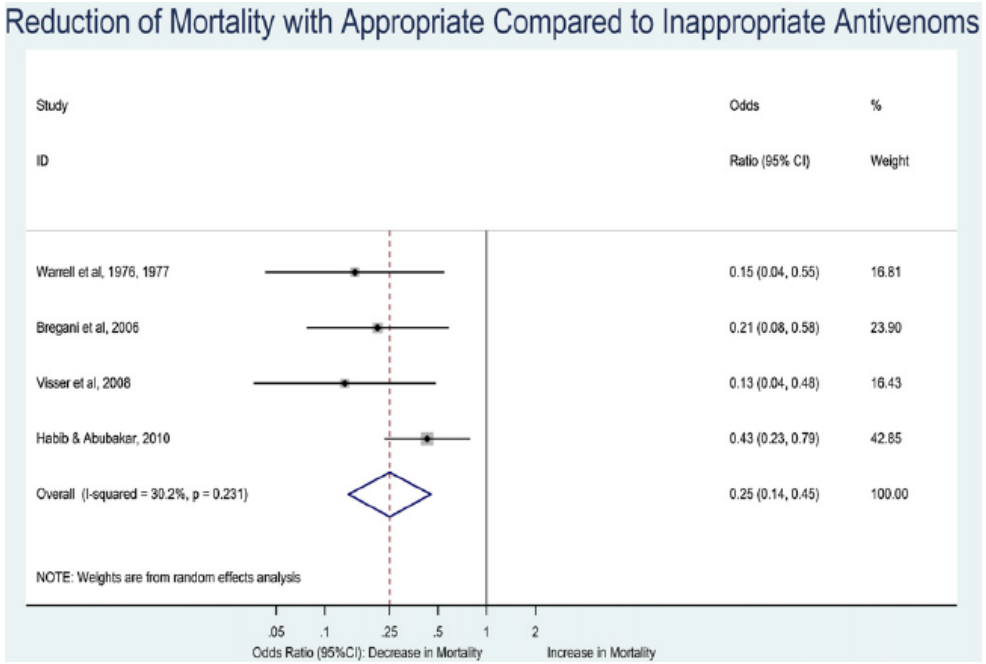


Table 1

Risk of mortality by period and availability of reliable antivenoms ($n = 94$[a])

Year/Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
2007													
Victims	39	95	110	181	160	158	190	177	173	232	190	98	1803
Mortalities	1	1	1	3	1	0	3	5	4	5	2	0	26
% Mortality	2.56	1.05	0.91	1.66	0.63	0	1.58	2.82	2.31	2.16	1.05	0	1.44
2008													
Victims	69	67	181	206	201	242	269	234	196	238	157	106	2216
Mortalities	0	1	1	3	1	4	3	0	0	4	0	0	17
% Mortality	0	1.49	0.55	1.46	0.5	1.65	1.12	0	0	1.39	0	0	0.77
2009													
Victims	105	104	173	254	245	264	271	288	262	345	255	102	2668
Mortalities	3	2	2	4	2	5	6	9[b]	7[b]	4	4	3	51
% Mortality	2.86	1.92	1.16	1.58	0.82	1.89	2.21	3.13	2.67	1.16	1.57	2.94	1.91

[a] Nine of the 94 fatal cases' folders were unavailable or had insufficient information for subsequent analysis.

[b] Stock-out of Government supplied antivenom occurred during this period.

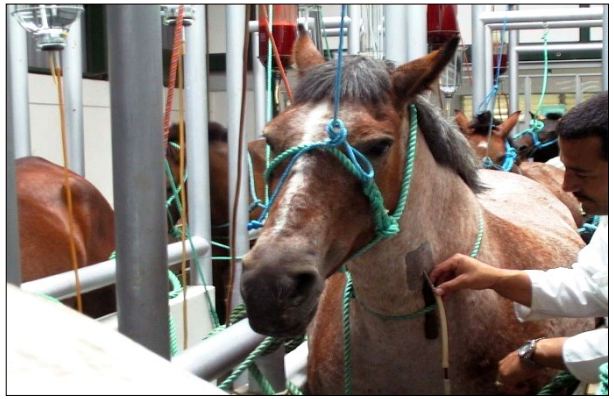
RR of mortality rose to 2.29 (95%CI: 1.35-3.89) over 2mths period (Aug-Sept 2009) without reliable antivenom

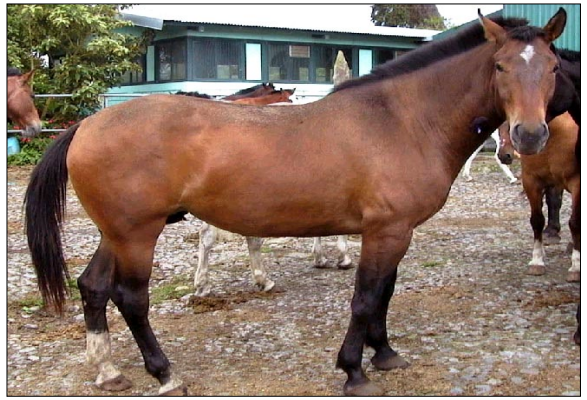
It was not due to seasonality as RR for mortality still rose for Aug-Sept 2009 cf Aug-Sept of 2007/8 to 2.52 (95%CI: 1.12-5.66)

ETSG (UK) - production of snake antivenom

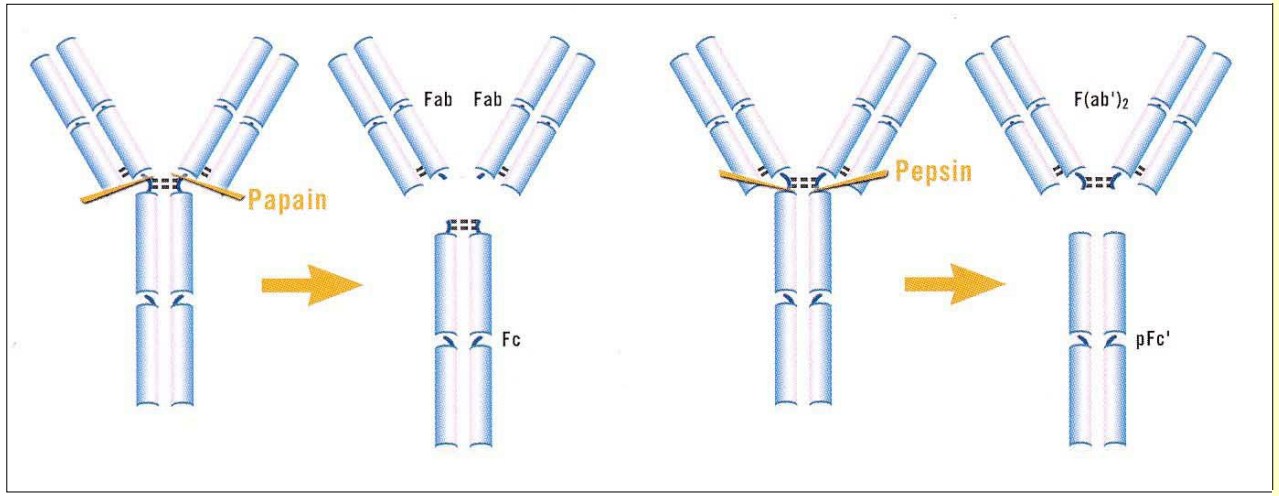
- EchiTAbG **(MICROPHARM, U.K)**
- *E. ocellatus* monospecific antivenom
- Ovine IgG

- **EchiTAb^{+} (PAN AFRICAN ANTIVENOM – ICP COSTA RICA).**
- *E. ocellatus/B. arietans/N. nigricollis* polyspecific AV
- Equine IgG





EchiTAb Antivenoms

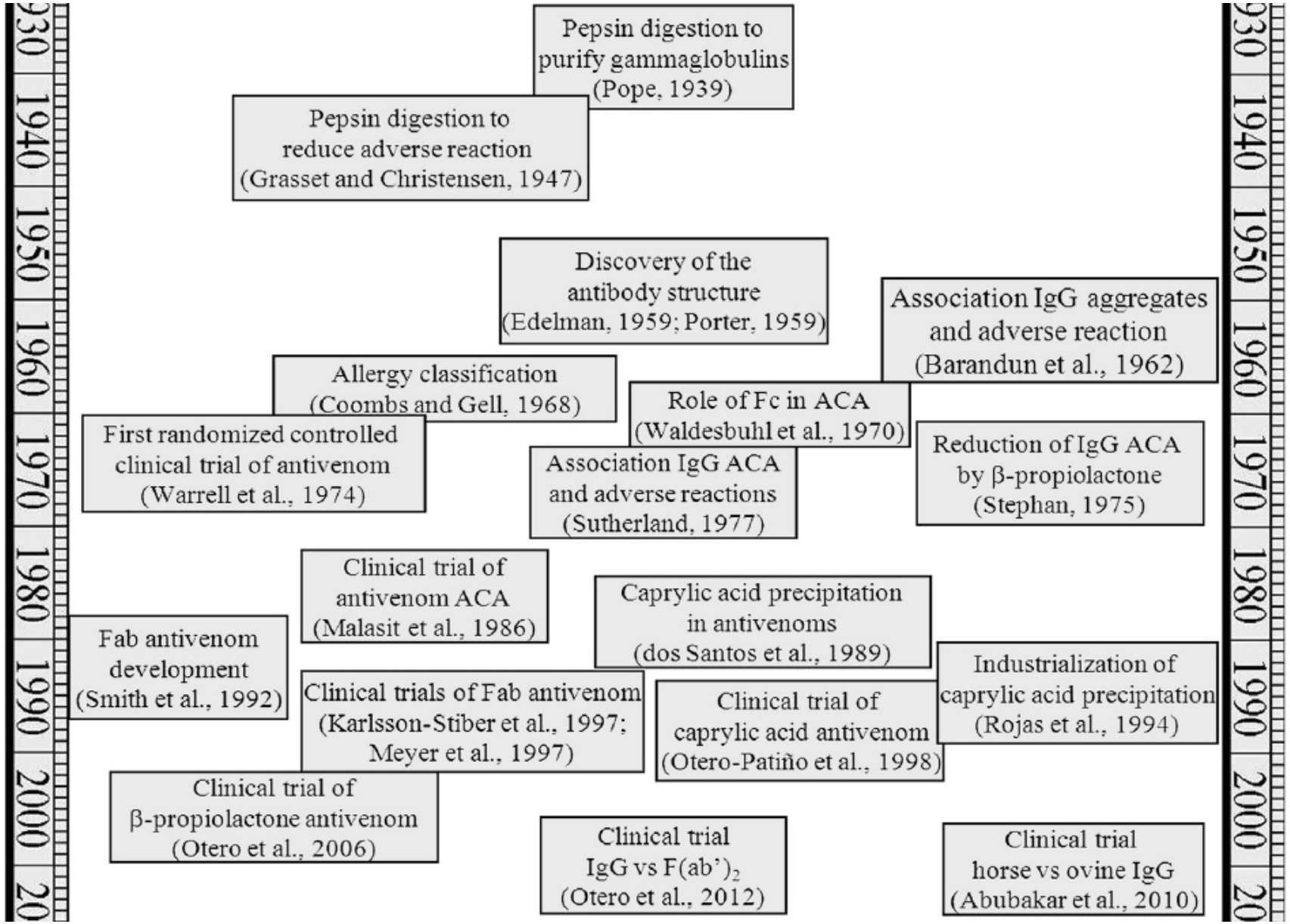


- Fab - EchiTAb
- $F(ab')_2$ - EchiTAb2

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



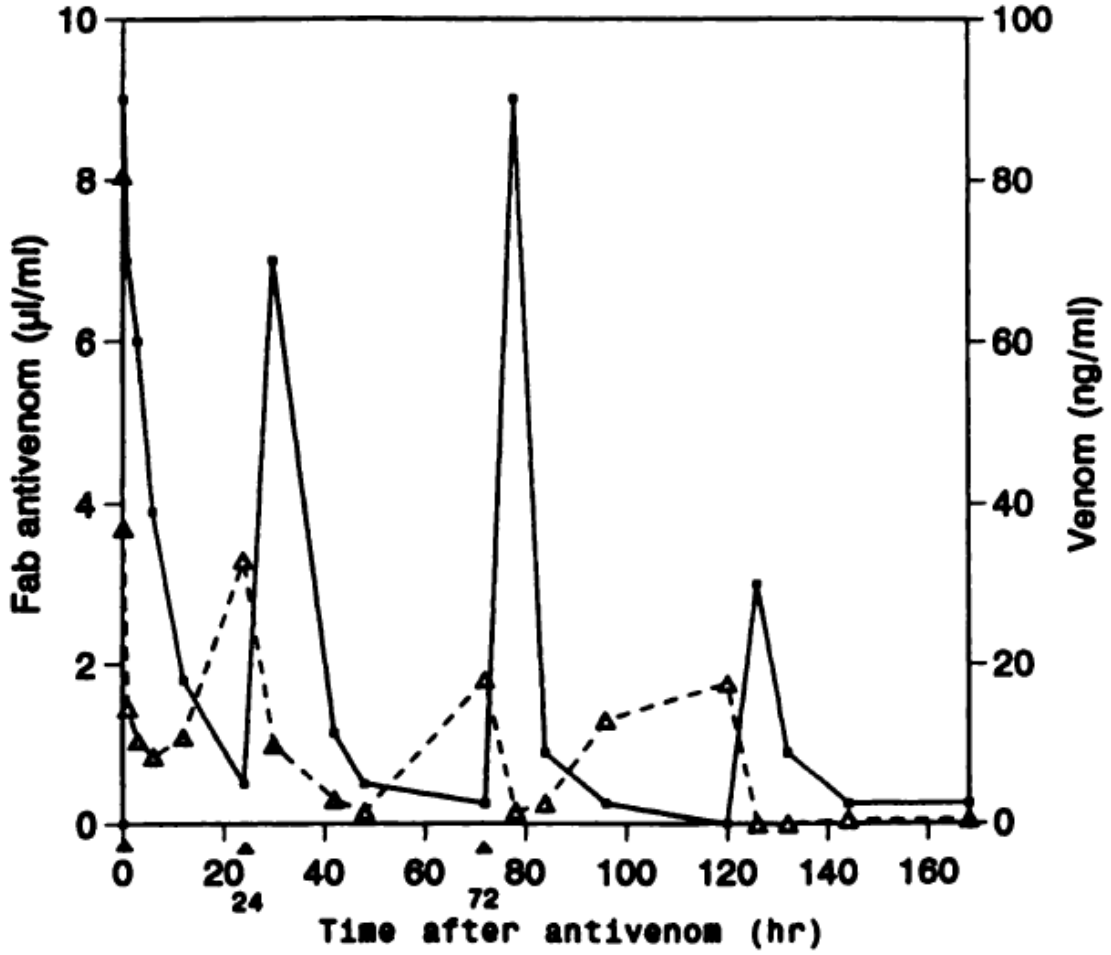


FIGURE 6. Venom **(dashed line)** and EchiTab antivenom **(solid line)** levels in two patients treated with four doses of 0.5 g (10 ml). Note the recurrence of venom antigenemia and incoagulable blood indicating inadequate antivenom therapy. The **dark triangles** are points at which antivenom was administered. Each point is the mean level in each patient.

Fab and recurrence of envenoming and bleeding

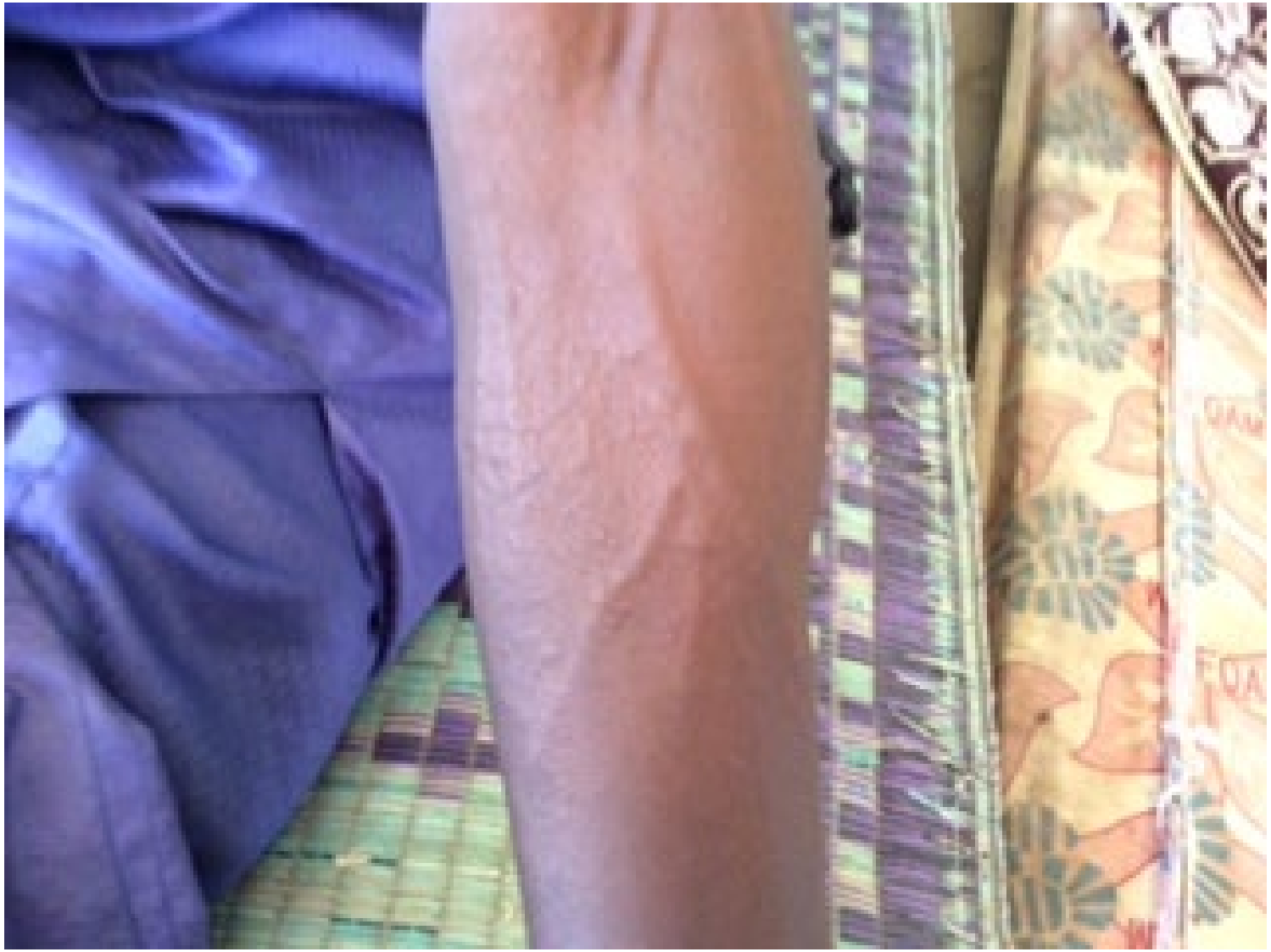
Meyer, Habib, Yakubu et al 1997

Incidence of early (anaphylactic) adverse reactions induced by antivenoms, as reported in several clinical trials.

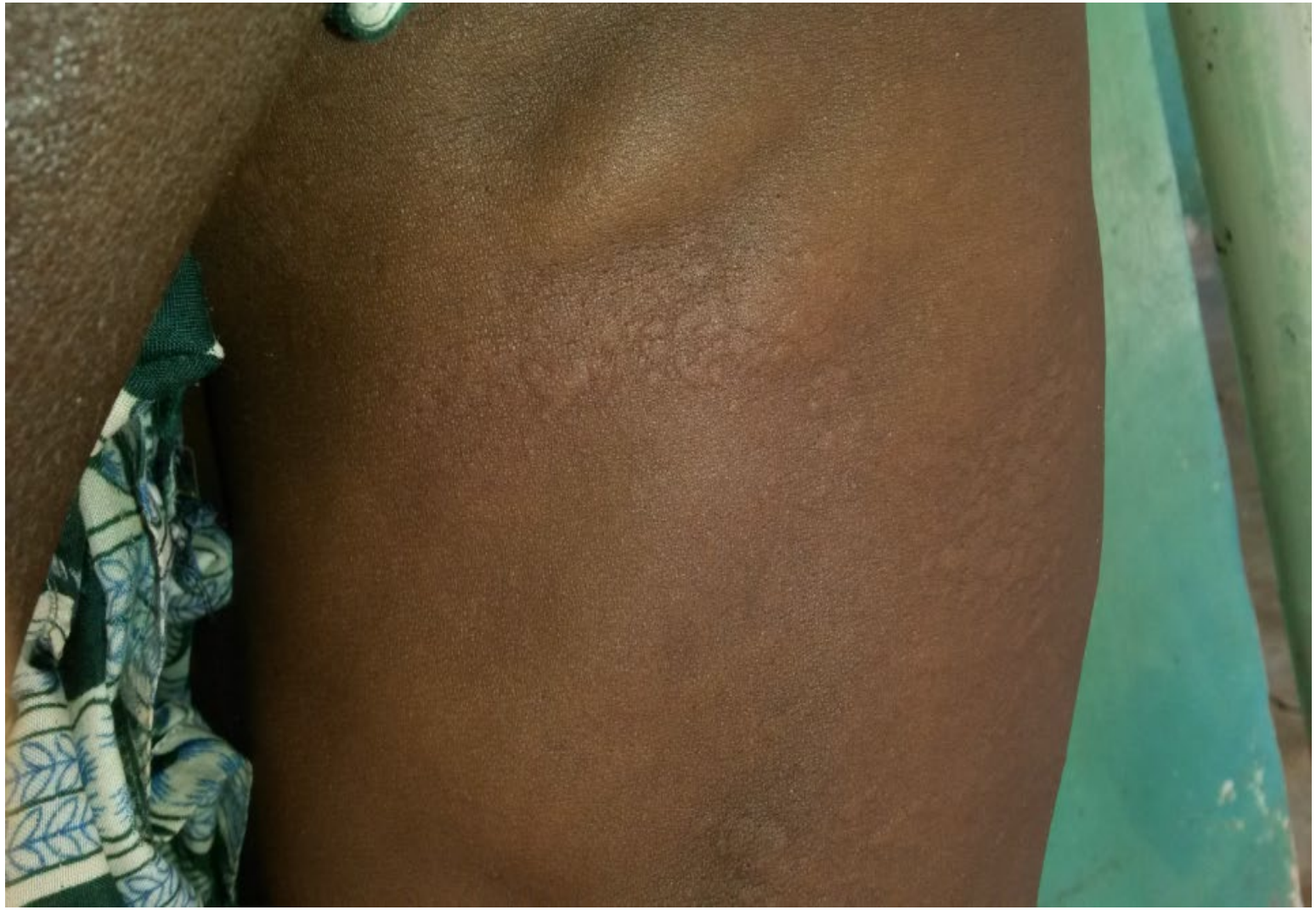
Manufacturer	Source	Active substance	Incidence of ears	Country of study	Reference
Polonga TAb™	Sheep	Fab	48%	Sri Lanka	Ariaratnam et al., 2001
Protherics UK Ltd	Sheep	Fab	5%	United States	Cannon et al., 2008
	Sheep	Fab	7%	United States	Farrar et al., 2012
Pasteur Merieux	Horse	$F(ab')_2$	6%	Martinica	Thomas et al., 1996
Ipser Africa	Horse	$F(ab')_2$	6%	Cameroon	Chippaux et al., 1998
Aventis Pasteur	Horse	$F(ab')_2$	4%	Cameroon	Chippaux et al., 1999
Bioclon	Horse	$F(ab')_2$	11%	Benin	Chippaux et al., 2007
SAIMR	Horse	$F(ab')_2$	76%	South Africa	Moran et al., 1998
ViperFab	Horse	$F(ab')_2$	13%	France	Haro et al., 1998
Instituto Butantan	Horse	$F(ab')_2$	25%	Brasil	Hui et al., 1999
Haffkine	Horse	$F(ab')_2$	43%	Sri Lanka	Premawardhena et al., 1999
Haffkine	Horse	$F(ab')_2$	81%	Sri Lanka	Ariaratnam et al., 2001
Inst. Butantan	Horse	$F(ab')_2$	18%	Brasil	Pardal et al., 2004
Fundaçao Ezequiel Dias	Horse	$F(ab')_2$	19%	Brasil	Pardal et al., 2004
Vins Bioproduct	Horse	$F(ab')_2$	81%	Sri Lanka	Gawarammana et al., 2004
Bioclon	Horse	$F(ab')_2$	19%	Colombia	Otero-Patiño et al., 2007
Commonwealth Serum Laboratories	Horse	$F(ab')_2$	18%	Papua New Guinea	Williams et al., 2007
Saovabha Memorial Institute	Horse	$F(ab')_2$	3%	Thailand	Thiansookon and Rojnuckarin, 2008
Haffkine Bio-Pharmaceuticals	Horse	$F(ab')_2$	88%	Bangladesh	Amin et al., 2008
Bharat Serums and Vaccines Ltd	Horse	$F(ab')_2$	61%	Sri Lanka	Isbister et al., 2012
Instituto Clodomiro Picado	Horse	$F(ab')_2$ (caprylic)	29%	Colombia	Otero-Patiño et al., 2012
Instituto Clodomiro Picado	Horse	IgG (sulphate)	52%	Colombia	Otero et al., 1999
Instituto Clodomiro Picado	Horse	IgG (caprylic)	25%	Colombia	Otero et al., 1999
Instituto Clodomiro Picado	Horse	IgG (caprylic)	26%	Nigeria	Abubakar et al., 2010
MicroPharm	Sheep	IgG (caprylic)	19%	Nigeria	Abubakar et al., 2010

Mortality from AV EAR 0.9% - *Leon et al 2013; Williams D et al 2007*

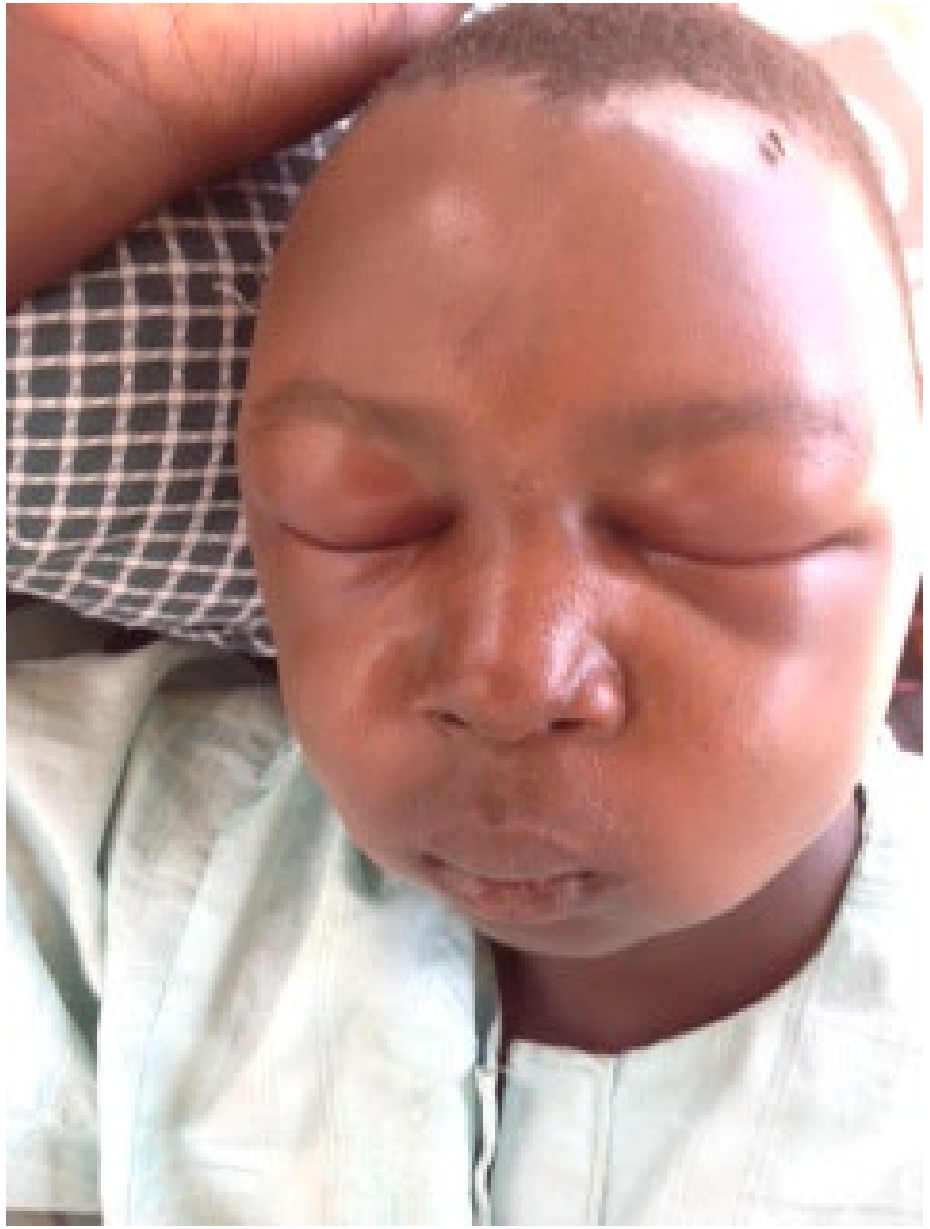
Maculopapula and urticarial skin reaction 30mins following antivenom administration



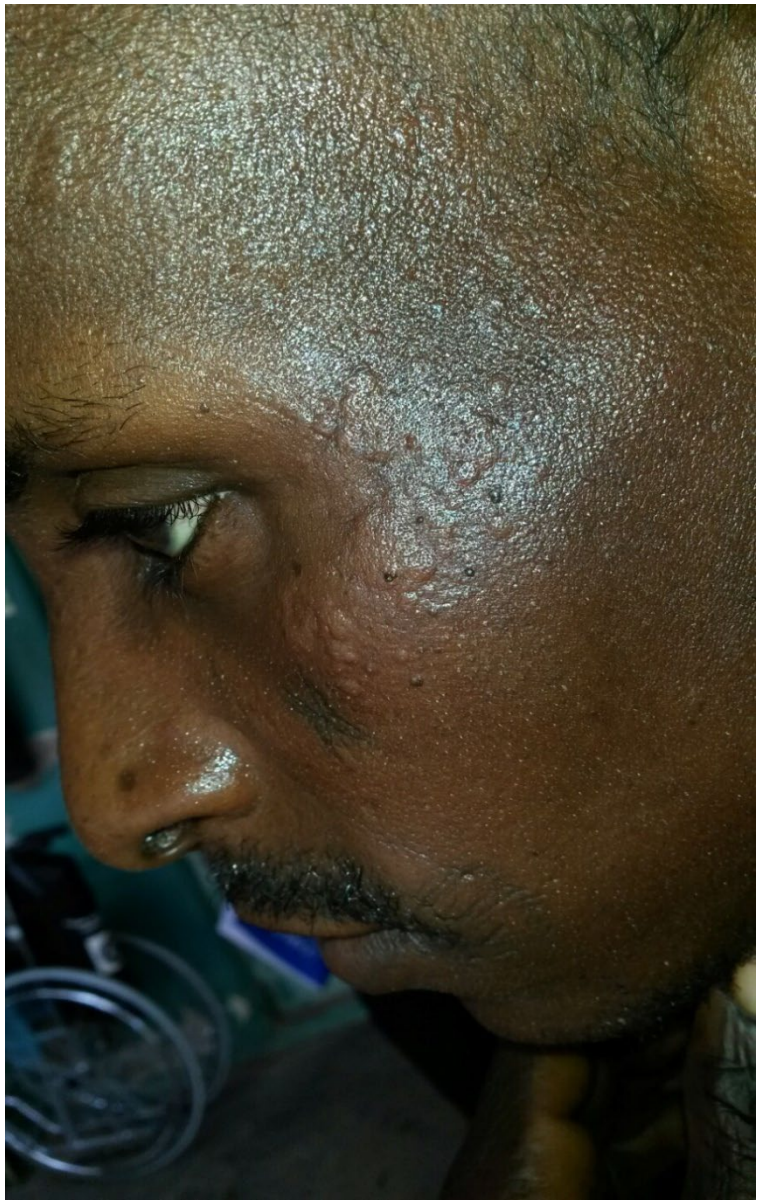
Urticaria on the Trunk

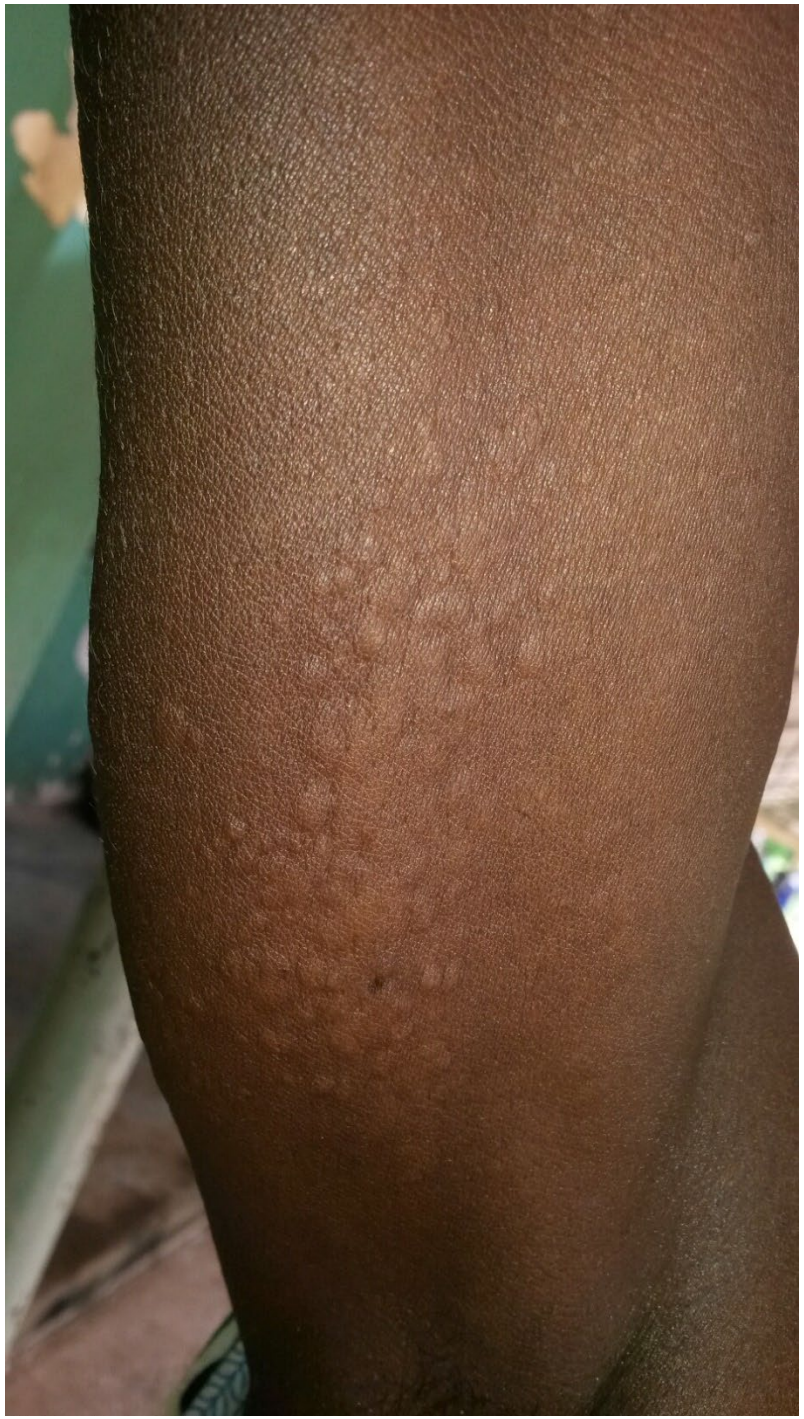


Peri-orbital oedema



URTICARIA





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*]

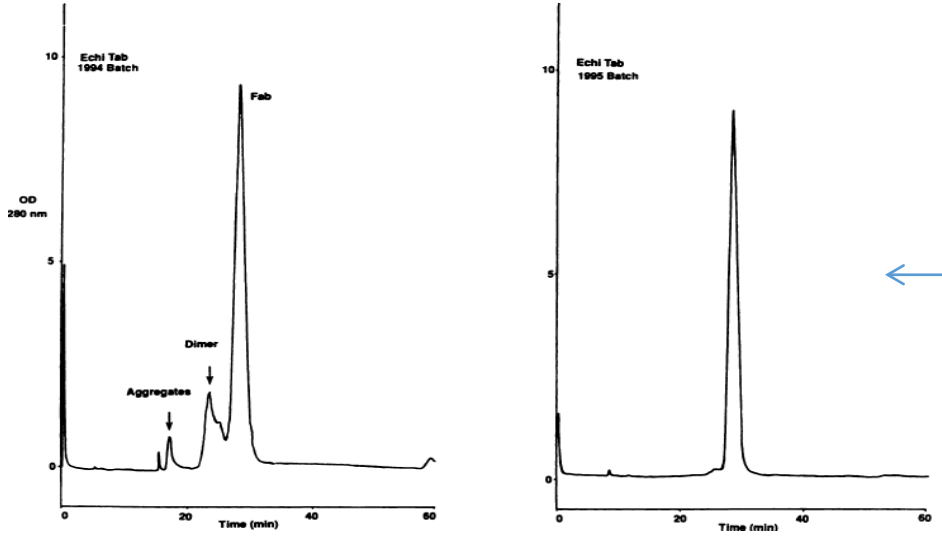
Pathogenesis of EAR

- 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

	Dose-finding 2 vials 20 ml (1.0 g) EchiTab	Comparative trial		Total in trial
		1 vial 10 ml (0.5 g) EchiTab	4 ampules 40 ml (2.12 g) Ipser Africa	
n	7	22	17	
No. of patients developing early reactions	4 (57%)	5 (23%)	2 (12%)	
Occasions on which antivenom was given				
EchiTab	7	46	10	56
Ipser Africa			37	37
Total no. of reactions				
EchiTab	4	7	1	8
Ipser Africa			2	2
% reactions/antivenom dose				
EchiTab	57.1	15.2	10.0	14.3
Ipser Africa			5.4	5.4

	1994	1995
Fc (%)*	23.4	2.8
Albumin (%)†	<1.0	<1.0
Dimer (%)	21.7	1.2
Aggregate (%)	4.1	0
Monomeric Fab (%)	50.4	95.2
Sterility	Sterile	Sterile
Endotoxin (Eu/ml)‡	<0.125	<0.125

* As measured by specific ovine Fc radioimmunoassay.
† As measured by specific fluoroimmunoassay.
‡ As measured by the *Limulus* amebocyte assay gel clot method.[21]



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

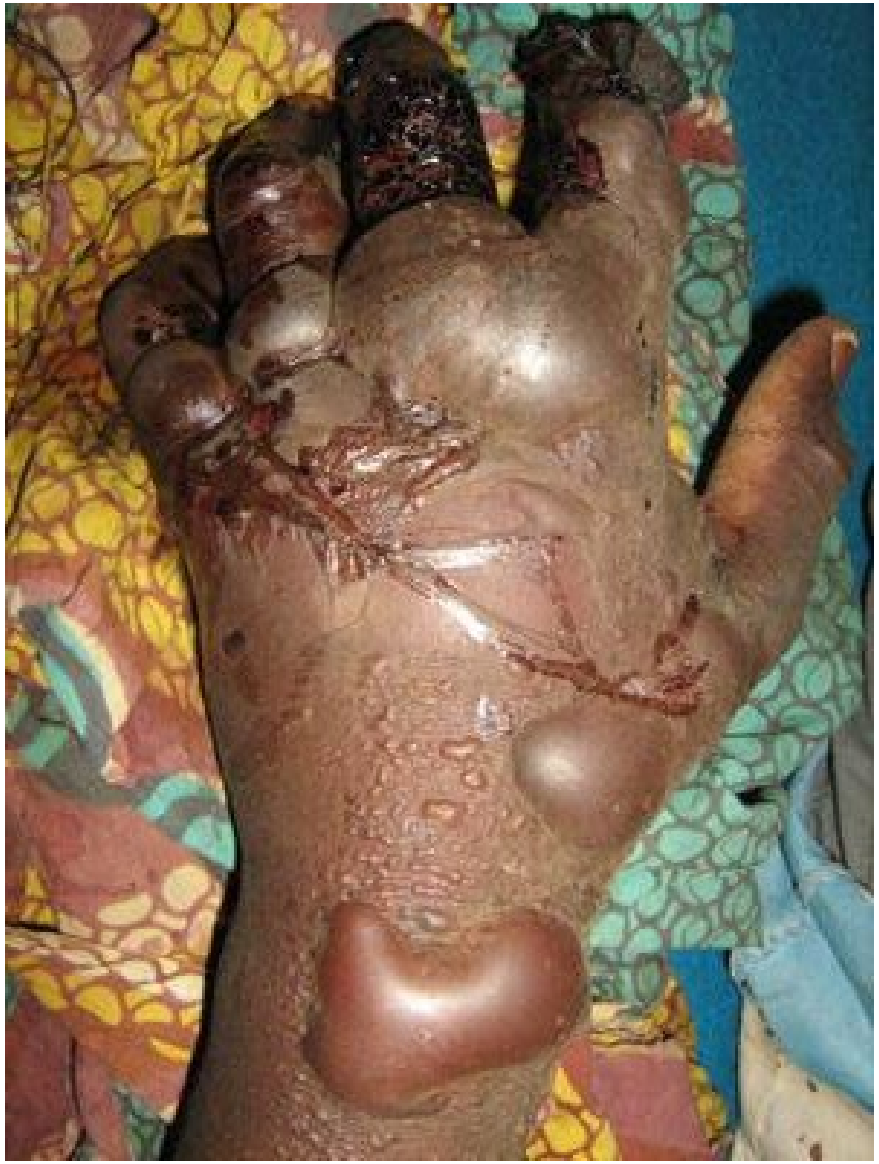
Gel filtration liquid chromatography

Meyer WP, Habib AG, Onayade AA, et al (1997)

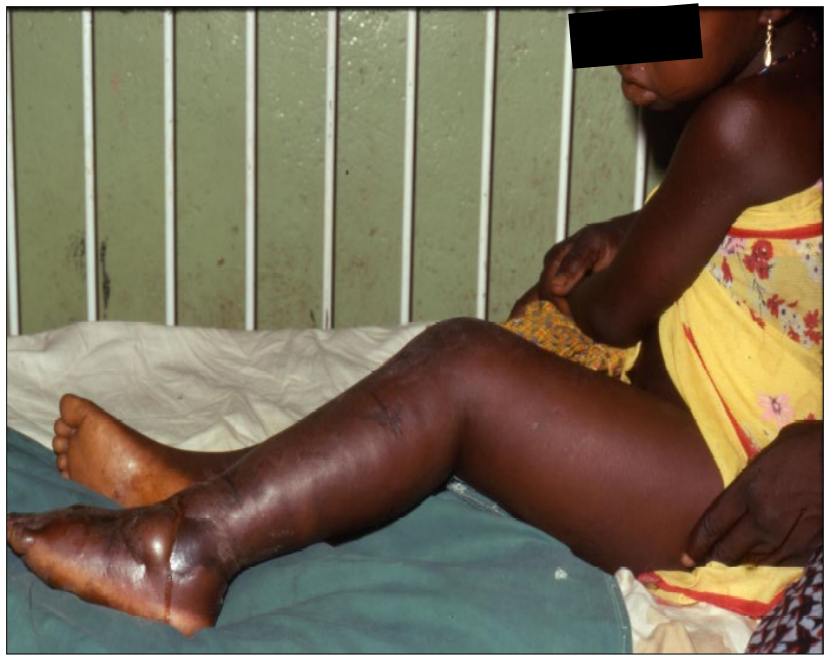
Challenges with Definitions and Nomenclature of Antivenom Reactions

- Gell and Coombs (1963)
  - Types I and III
- WHO (1981)
  - Early rxns (<24h): anaphylactic/anaphylactoid
  - Late rxns (5-24d)
- World Allergy Organization (2004)
  - 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

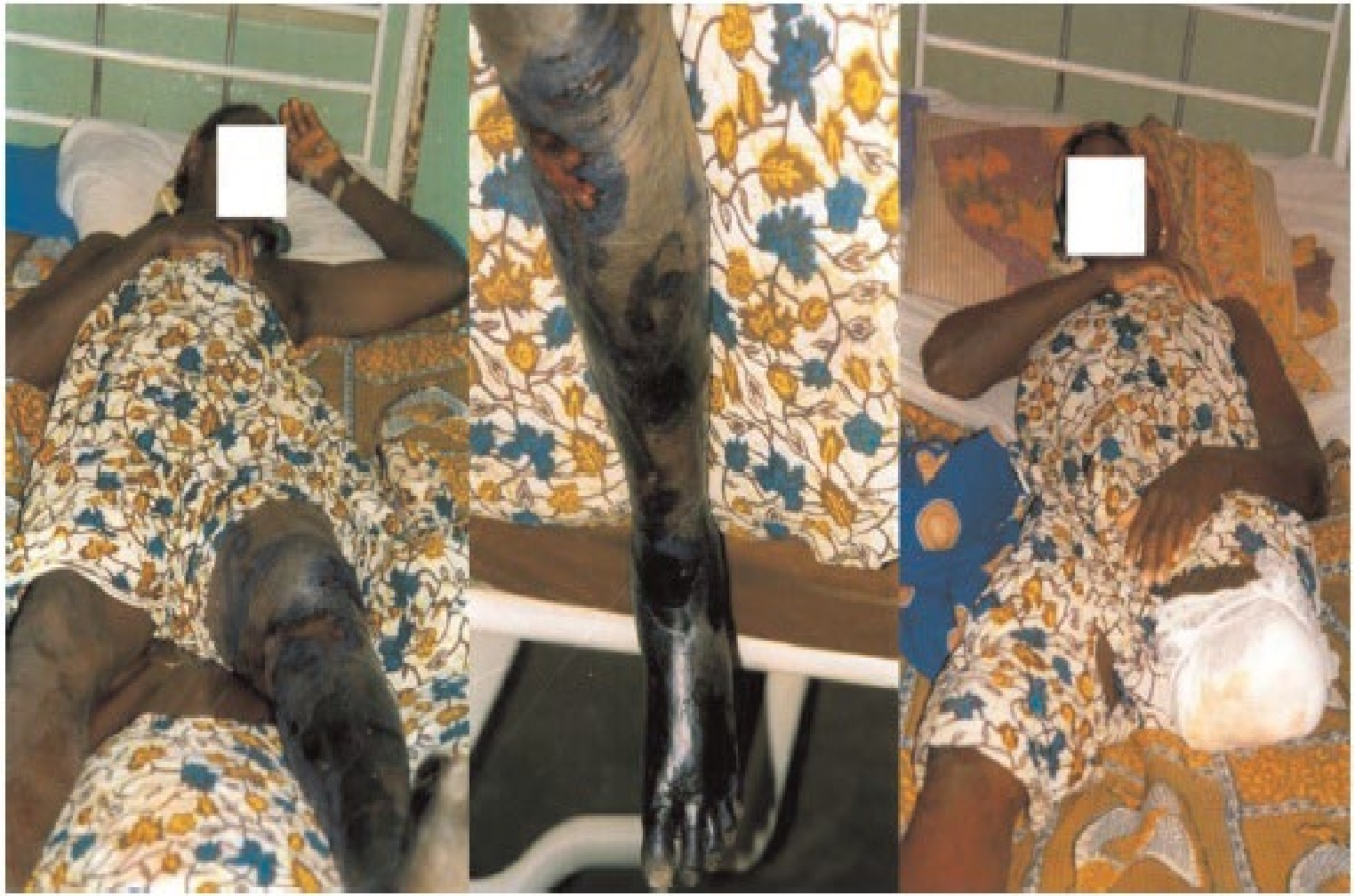


Figure 1 A nomadic Fulani woman who had a left above-knee amputation following a carpet viper bite

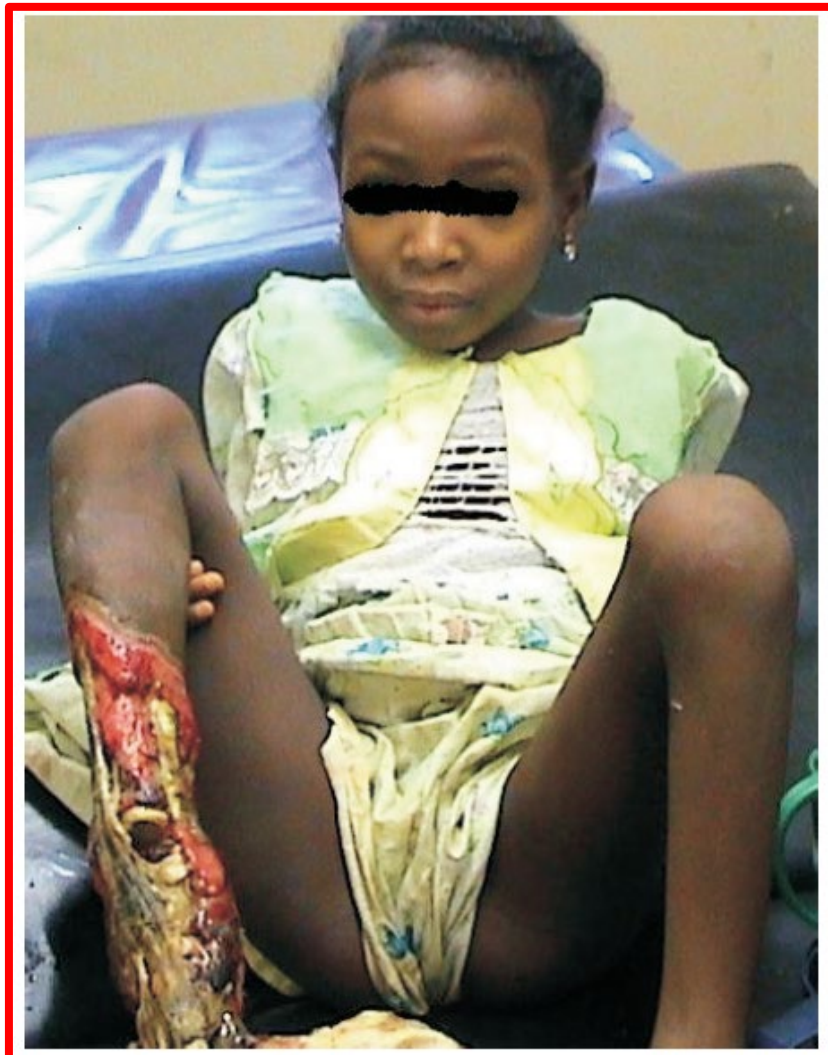


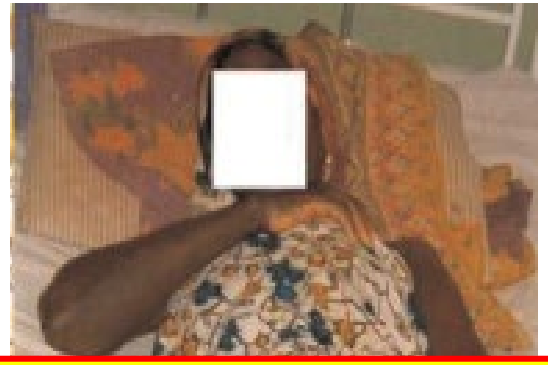
Figure 1. case 2: showing gangrene of the right foot and distal two-third of the leg.

Limb Loss following SB

Amputation (2015)

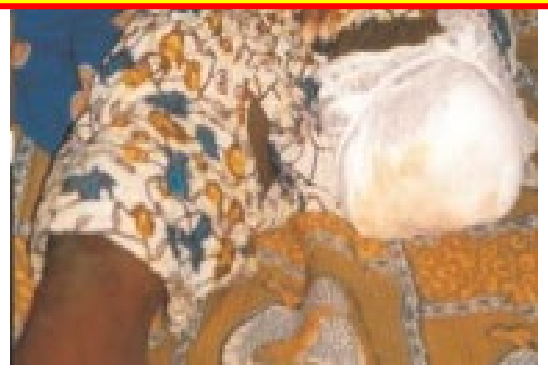
frequency – 3%

disability weight – 0.102



Surgical Amputation

(16/33 – *Abubakar, Habib, Mathew 2010*)



Declined Surgery – Digits Fall Off

Non-Viable Foot

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

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

Isa S. Abubakar[1], Saidu B. Abubakar[2], Abdulrazaq G. Habib[3]*, Abdulsalam Nasidi[4], Nandul Durfa[4], Peter O. Yusuf[5], Solomon Larnyang[†], John Garnvwa[6], Elijah Sokomba[7], Lateef Salako[8], R. David G. Theakston[6], Ed Juszczak[9], Nicola Alder[9], David A. Warrell[10], for the Nigeria-UK EchiTab Study Group

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** Alistair Reid 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

48 hr after treatment. Secondary (safety) outcomes were the incidences of anaphylactic, pyrogenic and late serum sickness-type antivenom reactions.

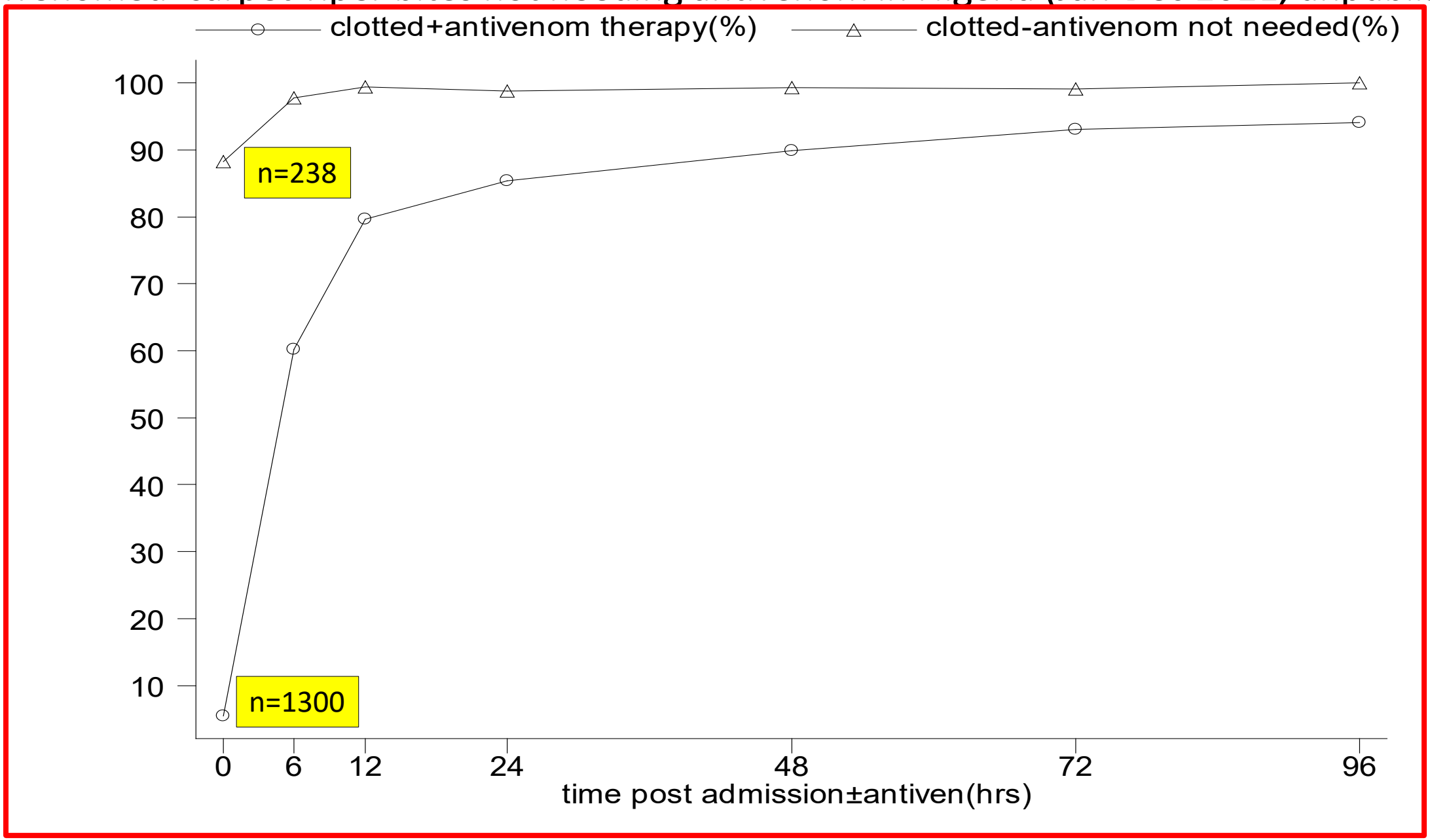
Findings: Initial doses permanently restored blood coagulability at 6 hours in 161/194 (83.0%) of ET-Plus and 156/206 (75.7%) of ET-G treated patients (Relative Risk [RR] 1.10 one-sided 95% CI lower limit 1.01; P = 0.05). ET-Plus caused early reactions on more occasions than did ET-G [50/194 (25.8%) and 39/206 (18.9%) respectively RR (1.36 one-sided 95% CI 1.86 upper limit; P = 0.06). These reactions were classified as severe in 21 (10.8%) and 11 (5.3%) of patients, respectively.

Conclusion: At these doses, ET-Plus was slightly more effective but ET-G was slightly safer. Both are recommended for treating *E. ocellatus* envenoming in Nigeria.

Trial Registration: Current Controlled Trials ISRCTN01257358

Citation: Abubakar IS, Abubakar SB, Habib AG, Nasidi A, Durfa N, et al. (2010) Randomised Controlled Double-Blind Non-Inferiority Trial of Two Antivenoms for Saw-Scaled or Carpet Viper (*Echis ocellatus*) Envenoming in Nigeria. PLoS Negl Trop Dis 4(7): e767. doi:10.1371/journal.pntd.0000767

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)



Dose-finding by Continual Re-assesment Method (CRM) with “3+3” dose escalation design

Number cured with dose d	Treat 3 further patients with following dose
2 or 3 (of 3)	d

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

FUNDED BY
NIHR | National Institute for Health Research
UKaid from the British people
Department for International Development
AFRICAN SNAKEBITE RESEARCH GROUP

>36 antivenom manufacturers (N. Casewell)

Sub-Saharan Africa
Manufacturer in:
- South Africa

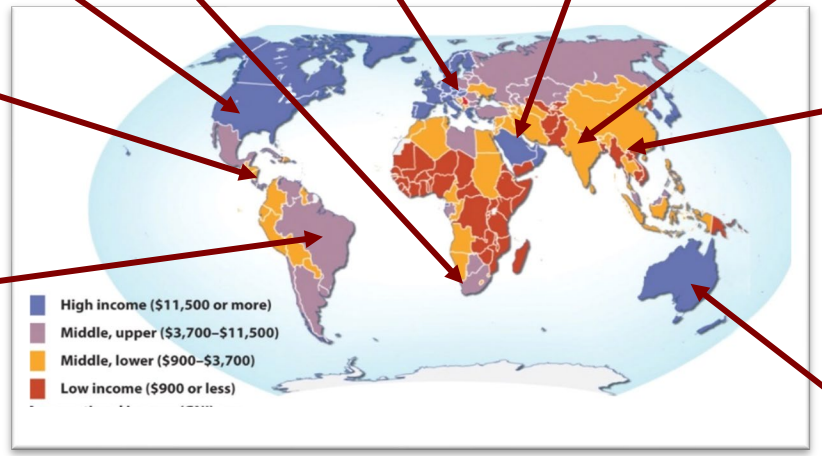
N America
Manufacturers in:
- USA
- Mexico

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



Global Poverty

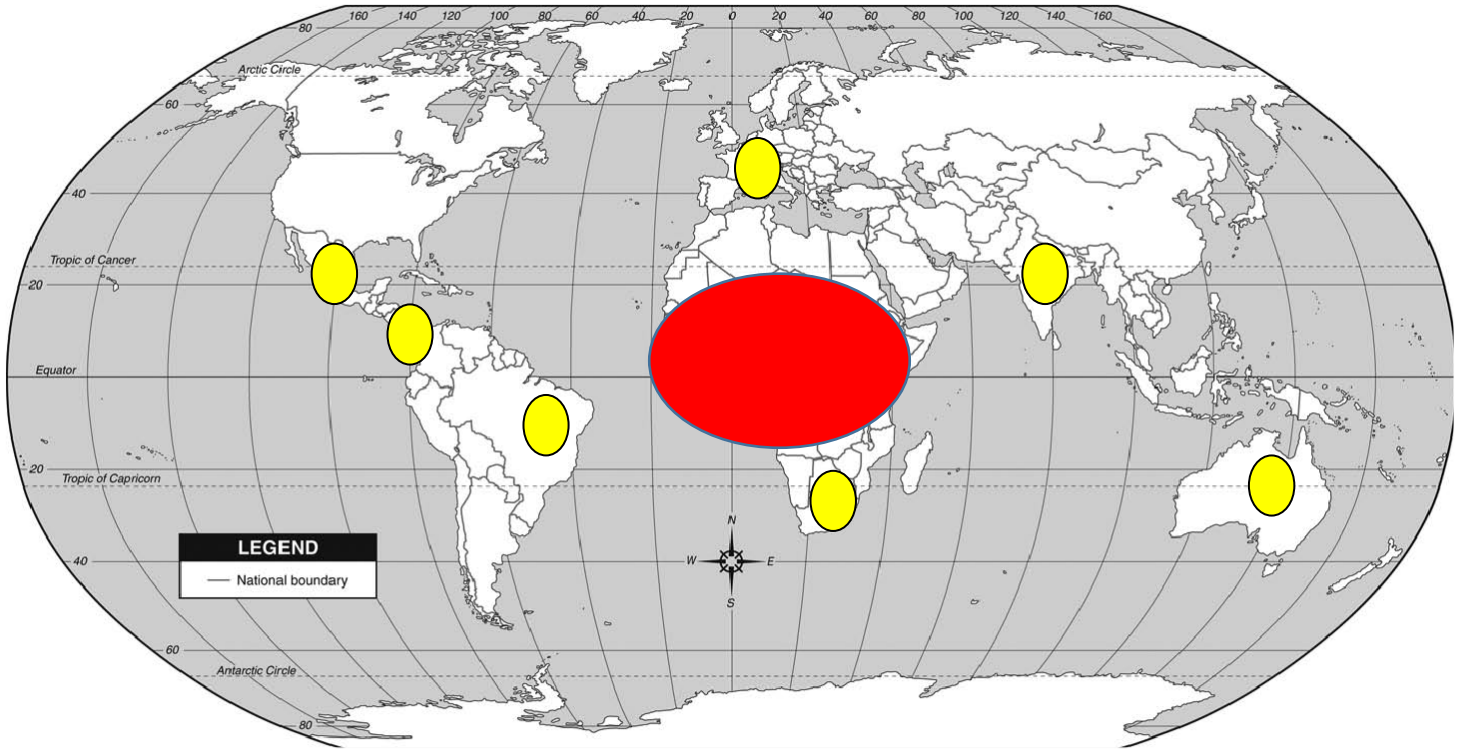
India
5 manufacturers

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

Australasia
Manufacturers in:
- Australia

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.

ICERS @ $82-280/DALY averted are Highly Cost-Effective

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

Country and GDP/Capita ($) [49]	Increm Cost Effect Ratio [ICER]/DALY ($) (95% Conf. Interval)	Cost/ Death Averted ($)	Probability Antivenom is cost-effective (%)	ICER if Antivenom Cost = $125	ICER if Antivenom Cost = $306	ICER if proportion of Carpet Viper = 0% ($)	ICER if Av Effect for Non Carpet Viper = 0% ($)	ICER if the 'No Antivenom' arm paid for Basic costs of $65.63*
Benin (751)	82.63 (36.41–240.09)	1997.91	99.99	72.87	135.96	81.75	97.26	59.75
B/Faso (652)	99.44 (40.39–377.40)	2384.81	99.61	87.98	164.05	226.53	107.18	71.94
Cameroun (1220)	86.97 (38.47–240.43)	2030.05	100.00	76.70	143.11	238.39	92.01	62.89
Chad (1035)	136.94 (51.33–704.75)	3070.80	99.13	120.77	225.34	376.61	144.89	99.03
Cote d'Ivoire (1366)	128.24 (51.20–461.64)	2916.02	99.97	113.09	211.04	278.37	139.16	92.73
Gambia (509)	150.08 (72.18–305.49)	3628.88	99.99	132.25	247.47	261.77	229.59	108.30
Ghana (1646)	103.61 (42.04–372.87)	2532.73	99.99	91.38	170.50	227.63	111.21	74.93
Guinea Bissau (576)	87.09 (44.96–171.55)	2032.72	100.00	76.75	143.60	84.76	226.64	62.85
Guinea Conakry (493)	83.54 (36.59–236.35)	1997.41	99.98	73.67	137.49	82.68	100.72	60.40
Liberia (414)	256.61 (147.67–417.68)	6204.95	97.28	226.00	423.92	261.77	13,964.26	184.85
Mali (696)	160.48 (82.21–306.83)	3836.74	100.00	141.52	264.06	243.47	178.09	116.04
Niger (385)	97.23 (39.84–328.02)	2351.06	98.64	85.75	159.99	261.77	102.98	70.31
Nigeria (2742)	92.56 (40.27–242.63)	2160.33	100.00	81.61	152.35	232.04	107.96	66.91
Senegal (1023)	143.81 (67.34–317.76)	3515.25	100.00	126.73	237.14	258.95	216.41	103.78
Sierra Leone (590)	280.77 (158.51–456.68)	6204.95	99.86	247.27	463.83	286.42	15,278.99	202.25
Togo (589)	120.42 (47.62–455.04)	2878.98	98.86	106.19	198.14	264.75	129.25	87.08

*Scenario of Basic costs in the No antivenom arm = Cost of supportive care ($18.75) + Cost of feeding and transportation ($43.75) + Cost of 20min Whole Blood Clotting Test ($3.125) = $65.63

AV—antivenom; ICER—Incremental Cost Effectiveness Ratio;

Hamza M, Idris MA, Maiyaki MB, Lamorde M, Chippaux JP, et al. (2016) Cost-Effectiveness of Antivenoms for Snakebite Envenoming in 16 Countries in West Africa. PLOS Neglected Tropical Diseases 10(3): e0004568. https://doi.org/10.1371/journal.pntd.0004568
https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004568

PLOS | NEGLECTED TROPICAL DISEASES

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

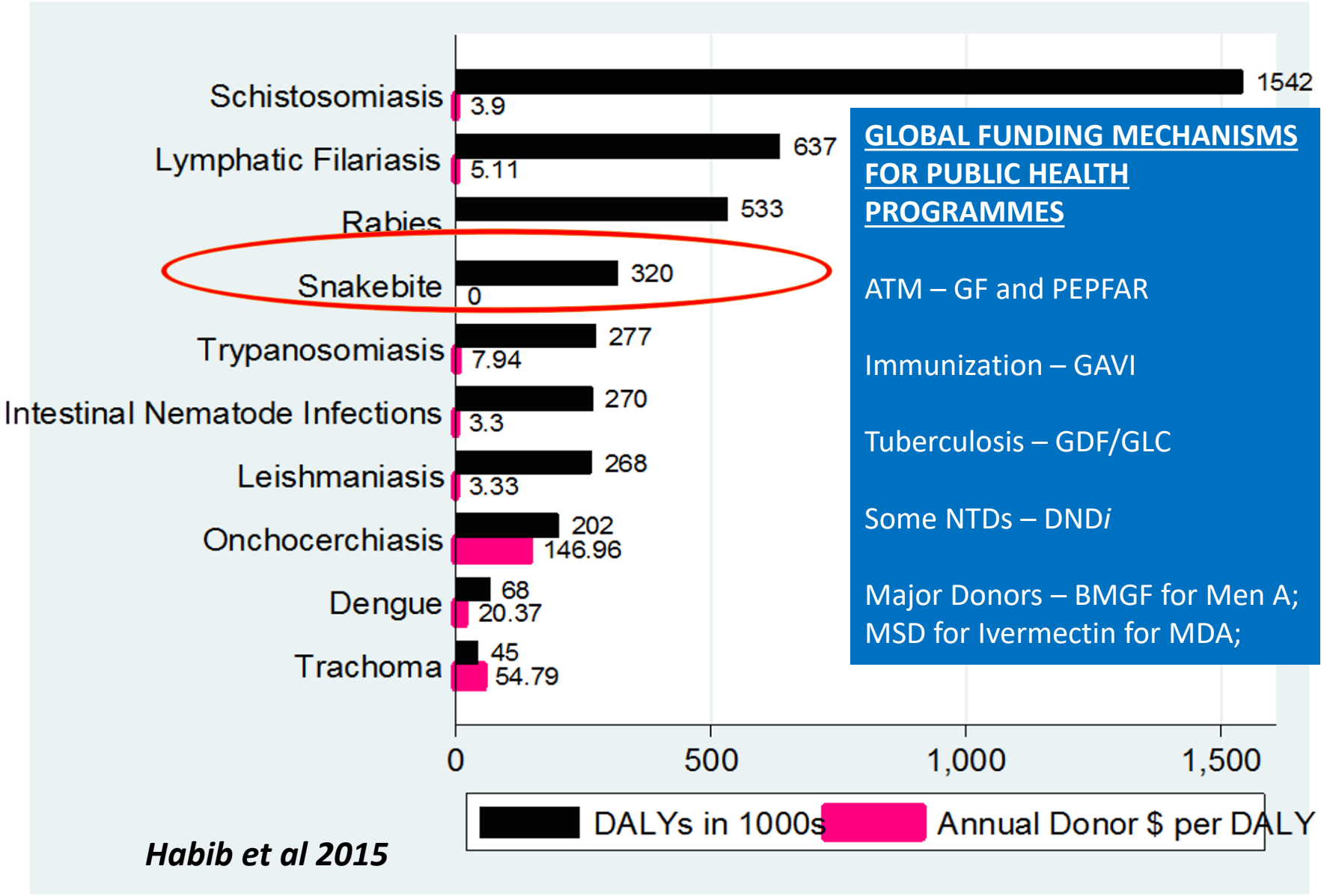
- AV availability: public sector (~25-33%) and private sector (~67-75%)
- In the 1990s to early 2000s, the Nigeria Government invested about GBP 2million to develop antivenoms against Nigerian snakes as a prelude to local production platform through technology transfer or a N-S and or S-S partnership
  - 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

YEAR	AMOUNT BUDGETED [$] (VIALS)	RELEASED AMOUNT [$] (VIALS)
2017	N100 million (4000)	N69 million (2760)
2018	N51 million (2040)	N19 million (760)
2019	N131 million (5240)	Yet to be released

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



GLOBAL FUNDING MECHANISMS FOR PUBLIC HEALTH PROGRAMMES

ATM – GF and PEPFAR

Immunization – GAVI

Tuberculosis – GDF/GLC

Some NTDs – DND*i*

Major Donors – BMGF for Men A; MSD for Ivermectin for MDA;

Habib et al 2015

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journal homepage: http://www.elsevier.com/locate/inhe

Factors affecting snakebite mortality in north-eastern Nigeria

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[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*

sn	Type of delay
1	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.
2	Delay in reaching an appropriate facility for reasons of distance, infrastructure and transport.
3	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.

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

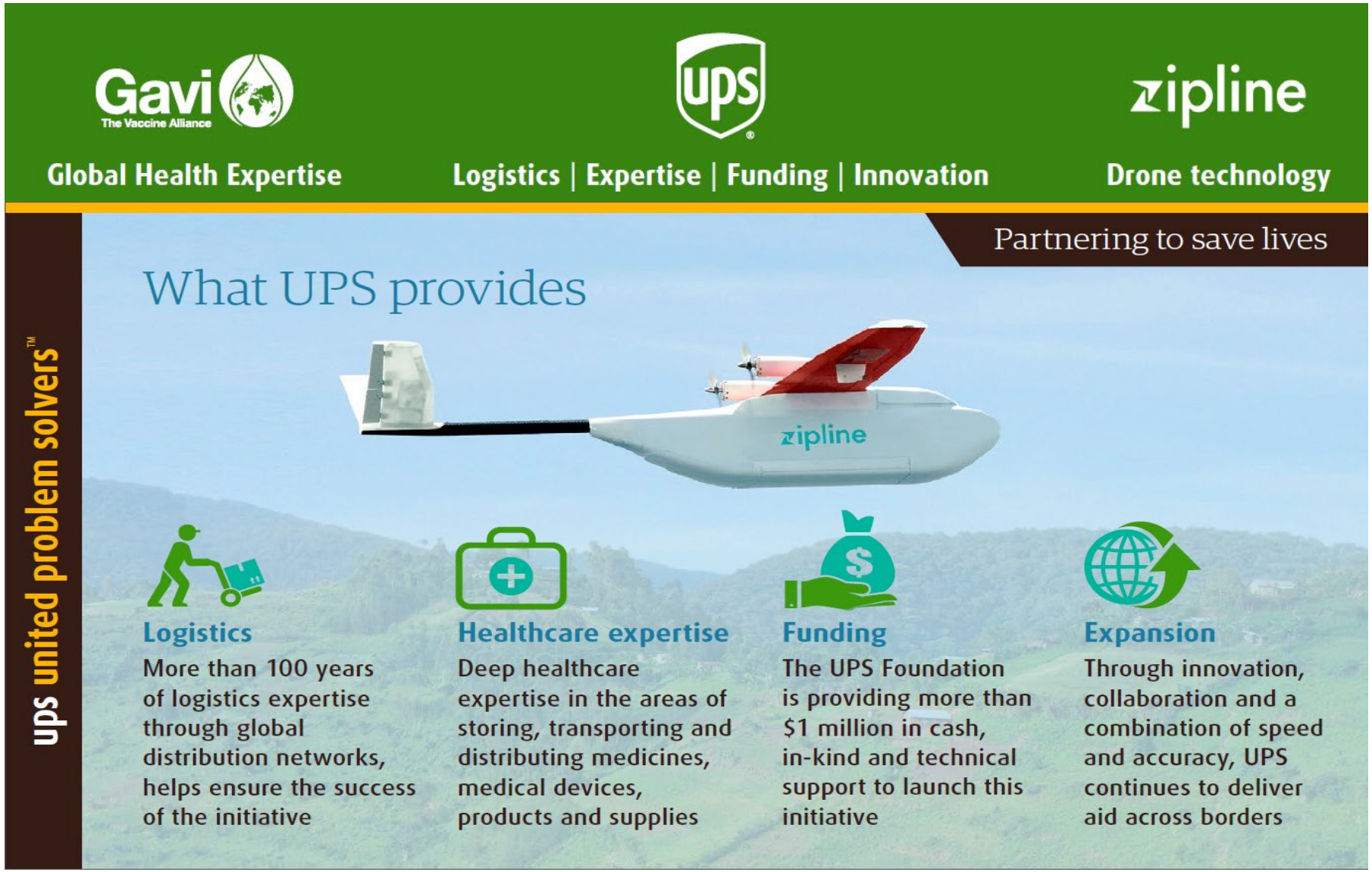
Improving access to effective healthcare - the Snakebite Emergency Response System (SERS)

Funded by the NIHR, UK

- Motorcycle ambulance – paramedic attending victim

Motorcycle ambulances can get to remote communities
Are cheap to purchase, run and maintain

Humanitarian Drone Project



"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

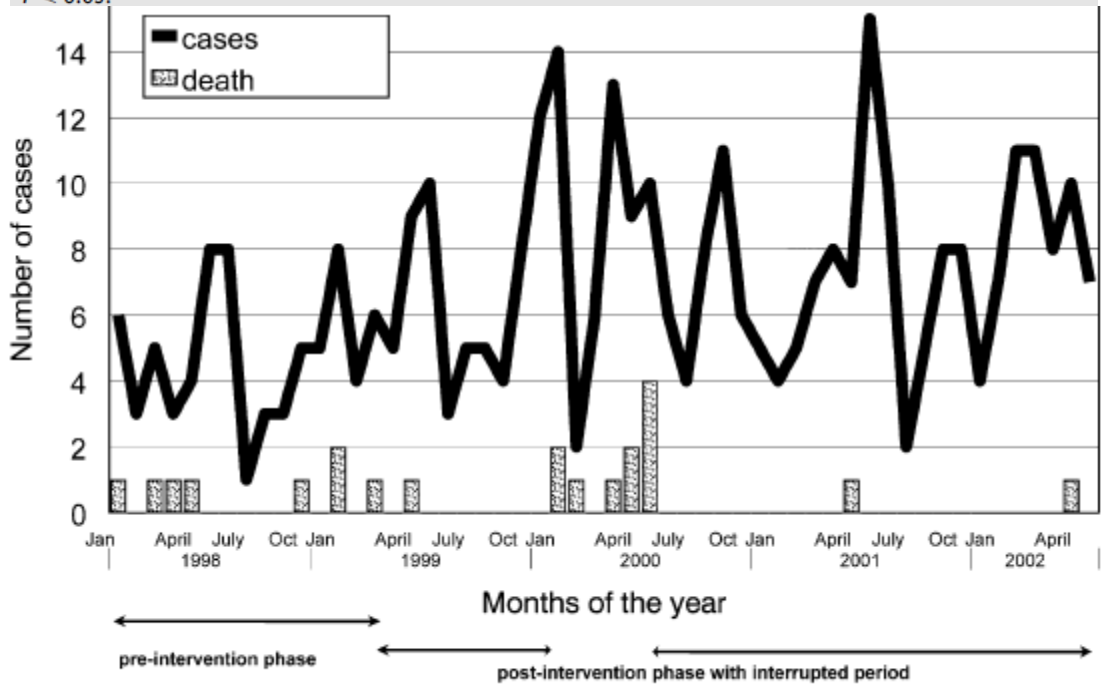
Director General,

World Health Organization

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

Variable	Pre-intervention ($n = 72$)	Post-intervention ($n = 238$)
Age (mean in years)	27	25
Males	72%	65%
Bite site is leg	81%	88%
Admitted within 24 h	60%	76%*
Average time to admission (d)	2.7	1.6*
Clinical envenoming	78%	73%
Debridement required (no. of patients)	5 (6.9%)	5 (2.2%)
Anaemia at arrival		
<11 gm/dl	22%	35%
<7 gm/dl	12%	4%
Give blood transfusion	18%	9%
Antivenom[a]		
Initial (average ampoules)	2.5	4.3*
Repeat (average ampoules)	1.9	1.5
Totals (average ampoules)	4.3	5.6*
Deaths	8	3
Mortality rate	11.1%	1.3%*

[a] 10 ml per ampoule.
* $P < 0.05$.



Frequency distribution of 364 cases of snake bite and deaths in Yeji, an area of Ghana, 1998-2002.

Education of staff and patients, use of standardized protocol and ensuring adherence to it led to better outcomes and increased uptake of care

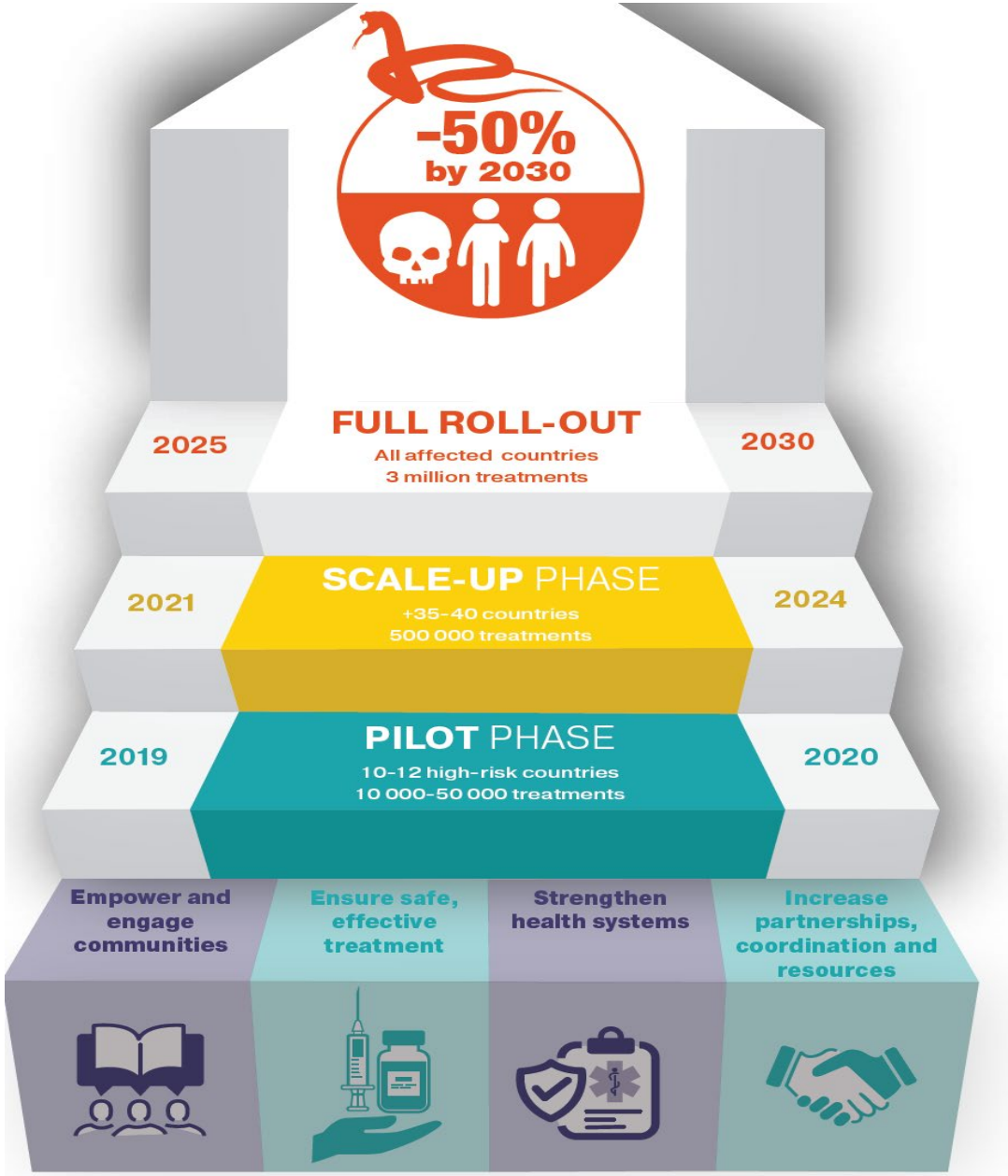
Global Challenges to Snakebite Antivenom Therapy

- Medical
  - Immuno-biology
  - Early adverse reactions
  - Relative lack of efficacy and potency
    - Necrosis - amputation
    - Neurotoxicity
- Manufacturing
  - Quality, standards and benchmarks
  - Product development and clinica 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



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