Overview and introduction:

Risk-benefit assessment process for WHO listing of antivenoms

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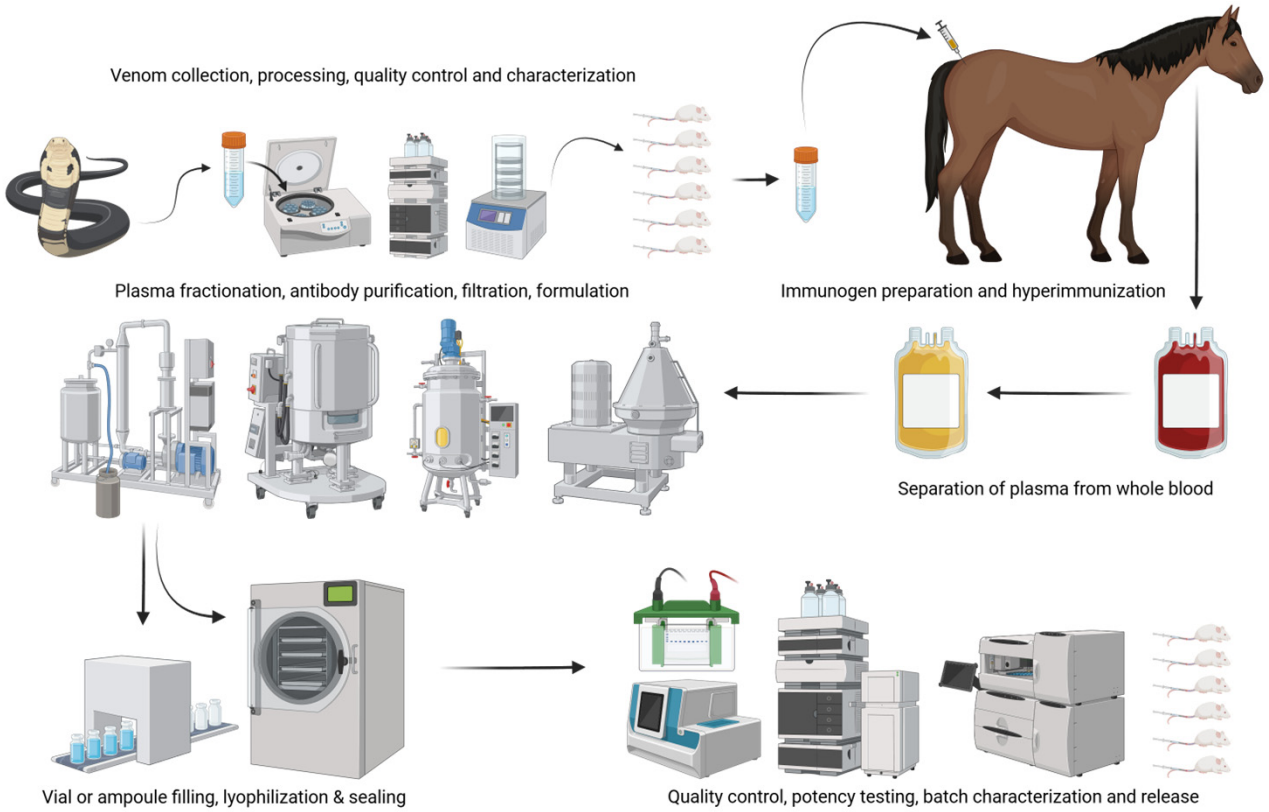
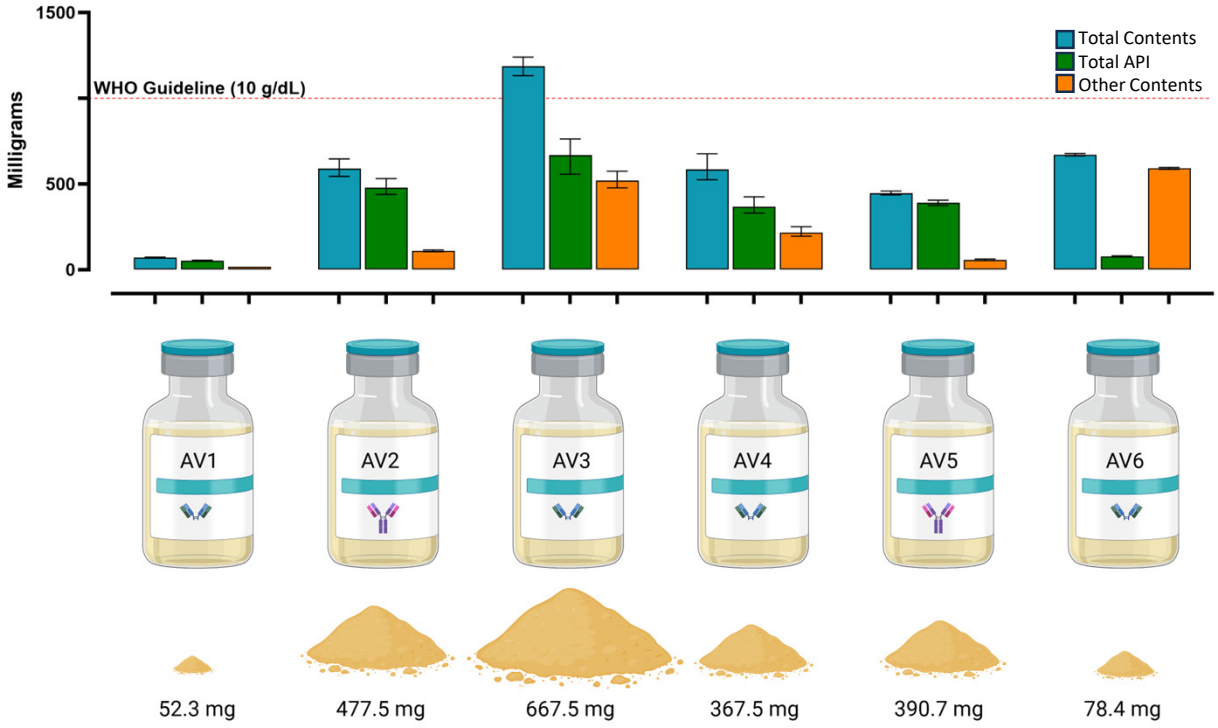
What is antivenom?

- Antivenoms are specialized biological medicines produced (typically) by immunizing an animal such as a horse with a mixture of snake venoms to produce antibodies which are then purified from plasma, processed and formulated for human use.
- The active pharmaceutical ingredient (API) are purified animal plasma-derived antibodies.
- Other substances may also be present in the product, including stabilizing agents, preservatives, sodium chloride and in some cases unintended contaminants.
- The regulation and control of antivenoms by drug regulatory authorities varies and this can have a direct impact on the quality, safety and efficacy of these products.
- WHO is working to improve regulation, control and surveillance of antivenom production and use.



Not all antivenoms are the same

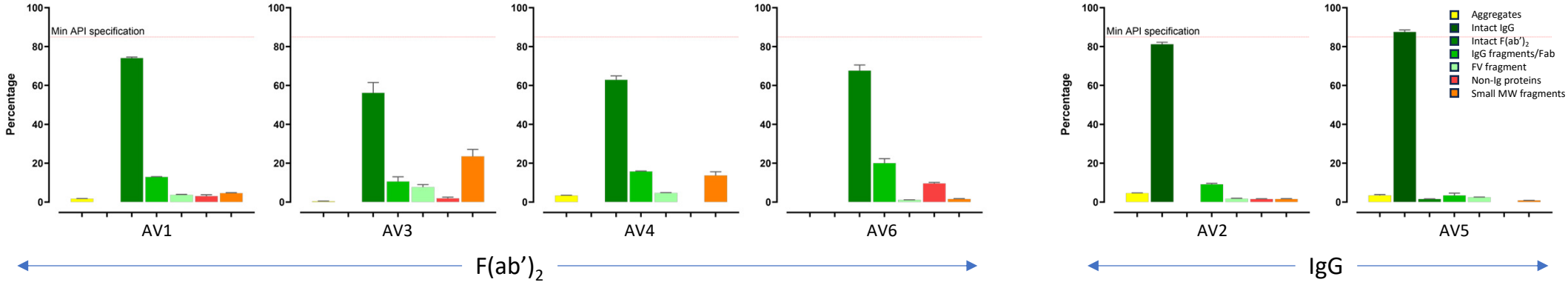
- There are substantial differences between different products, and even between different batch lots of the same product.
- Total protein, Active Pharmaceutical Ingredient (API), and other contents vary greatly between products, impacting efficacy and safety.
- The most important component is the API – the specific antibodies - either whole IgG or its $F(ab')_2$ fragment – since these are what neutralize venom.
- The potency of each antivenom against the venoms they cover also varies greatly.
- This has major implications for dosing as a product with high potency per mg may be less effective if the total API is low relative to less potent products with higher API content.
- Most manufacturers claim that API is at least 85% of total protein, but for most it is substantially lower.



Active Pharmaceutical Ingredient (API) content in 6 different antivenoms that are marketed in sub-Saharan Africa

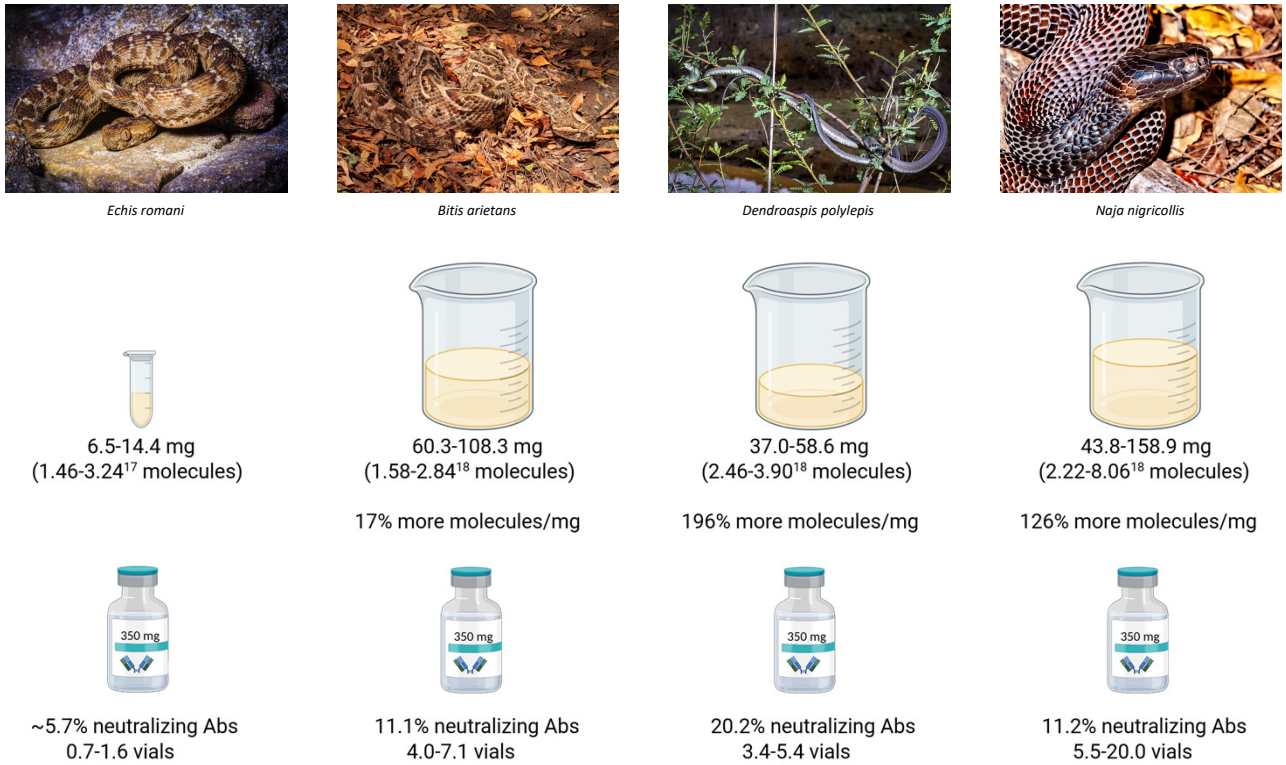
Not all antivenoms are the same

- In addition to differences in the total contents there are wide differences in the actual composition of different antivenom products.
- Most manufacturers claim that API is at least 85% of total protein, but particularly for F(ab')$_2$ antivenoms it is generally substantially lower.
- Antibody digestion processes designed to cleave the Fc region of IgG often result in a mixture of fragments some of which have no antigen-binding capability.
- Whole IgG antivenoms are typically higher purity with fewer non-API and non-Ig contents. Antivenoms made with intact IgG also have higher antibody yields and cost less to produce.
- High MW aggregates, and non-Ig animal proteins such as antithrombin III, alpha-2-macroglobulin, fibrinogen side chains, and alpha-1B-glycoprotein are likely to be implicated in early adverse reactions to antivenom.
- Strengthening regulation and control will improve quality and safety of antivenoms.



Not all snake venoms are the same either

- Snake venoms are complex mixtures of proteins and peptides with a wide range of biological activities.
- Different species of snakes produce very different venom mixtures, with different combinations of toxins and other contents.
- The volume of liquid venom they express, and the concentration of the biologically active components in that liquid can also vary substantially.
- This has important implications for antivenom dosing. The potential mass of injected venom and the number of toxin molecules in that mass of venom directly affect the dose of antivenom needed to effectively neutralize the venom.
- One antivenom molecule may be able to bind two molecules of toxin. Taking different factors into account an excess of antivenom molecules is necessary for effective treatment.



25-75 percentile interquartile range of venom yields following defensive strikes by *Echis romani*, *Bitis arietans*, *Dendroaspis polylepis*, and *Naja nigricollis* with approximate number of toxin molecules per yield. Compared to *Echis romani*, the number of molecules per milligram venom for *Bitis arietans*, *Dendroaspis polylepis*, and *Naja nigricollis* are 17%, 195%, and 126% higher respectively. This has implications for antivenom dose estimation, something that is also dependent upon the amount of total antibodies/vial and the proportion of venom-specific neutralizing antibodies.

Example 1: A hypothetical antivenom with 350 mg of total $F(ab')_2$ antibodies with varying percentages of toxin neutralizing antibodies has the potential to be highly effective at various dose ranges per species, against the 25-75 percentile interquartile range of venom yields shown above.

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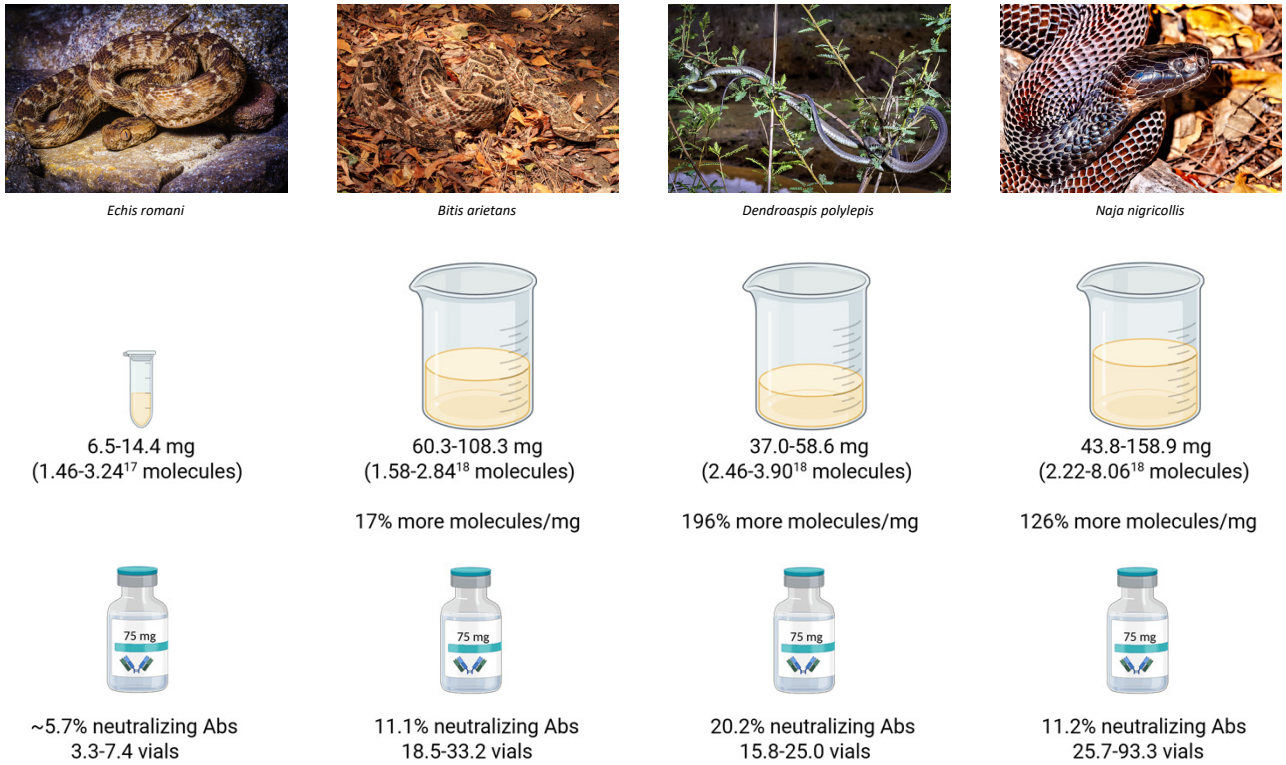

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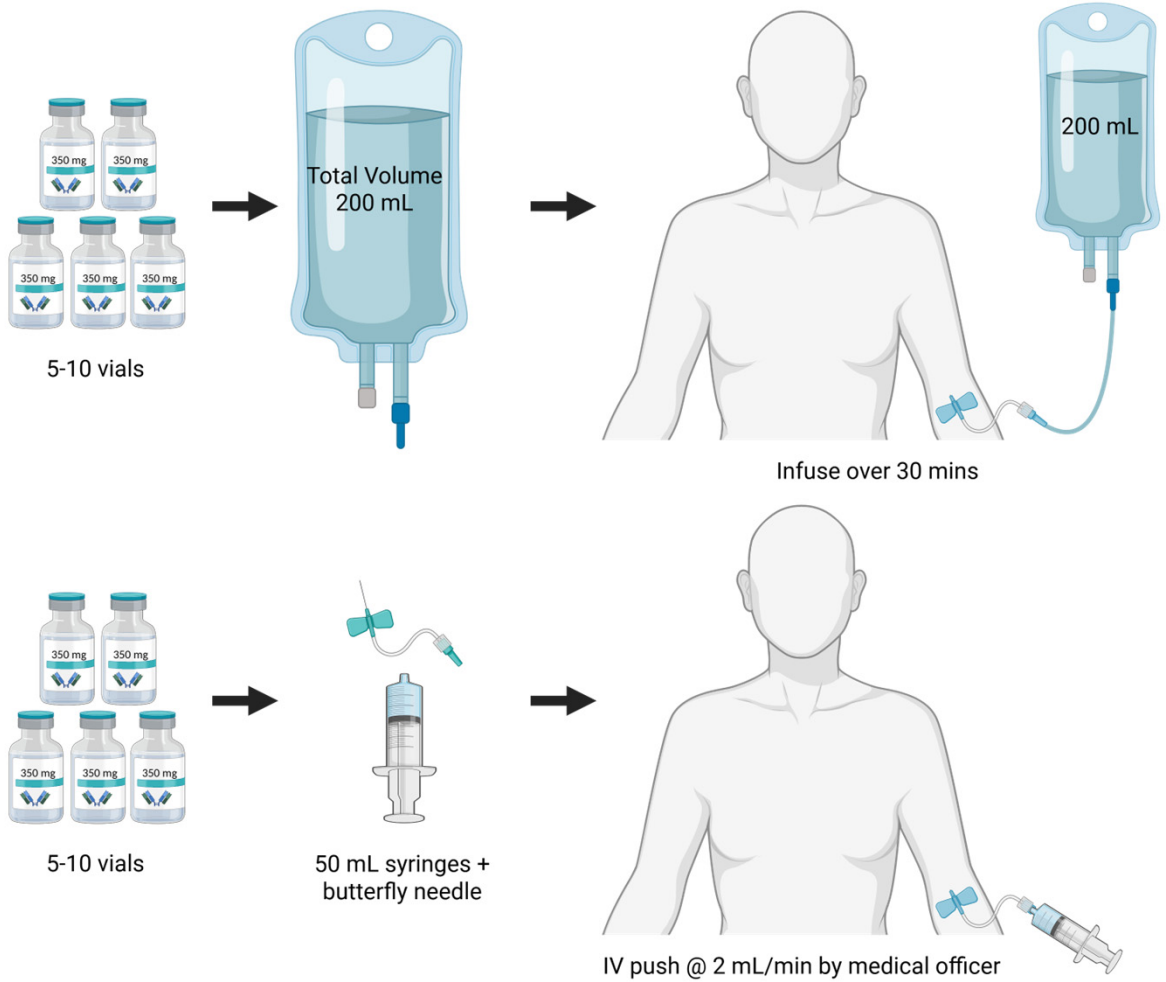
Example 2: A hypothetical antivenom with just 75 mg of total $F(ab')_2$ antibodies with varying percentages of toxin neutralizing antibodies would be ineffective, except in exceptionally large dose ranges for 3 of 4 species, against the 25-75 percentile interquartile range of venom yields shown above.

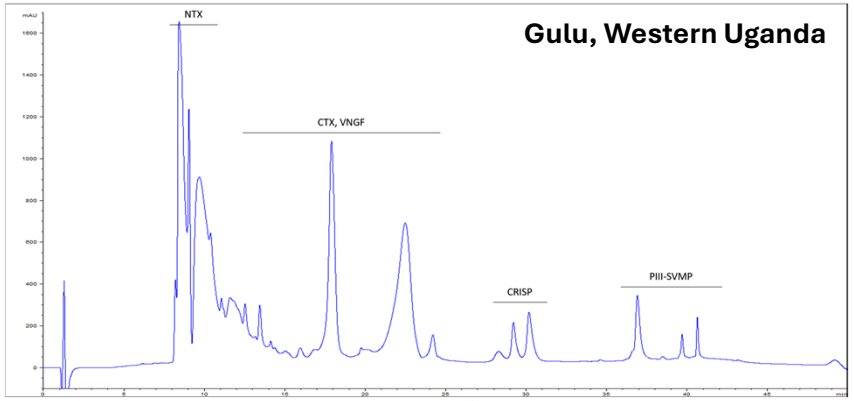
Administering antivenoms safely and effectively

- Antivenoms need to be administered as soon as possible once signs of envenoming have been observed.
- They should be administered either as an intravenous infusion, or by intravenous push using a suitable needle and syringe.
- Guidelines on the use of premedication with subcutaneous adrenaline (0.25 mg SC) vary from one place to another. My personal experience is that it does reduce the rate of early adverse reactions and is safe for all patients.
- If premedication is used it should be given subcutaneously 5-10 minutes before the start of antivenom administration.
- Additional adrenaline doses should be prepared for intramuscular use in the event of an adverse reaction.
- Hydrocortisone has no role. Antihistamines can be titrated to ease cutaneous reactions.



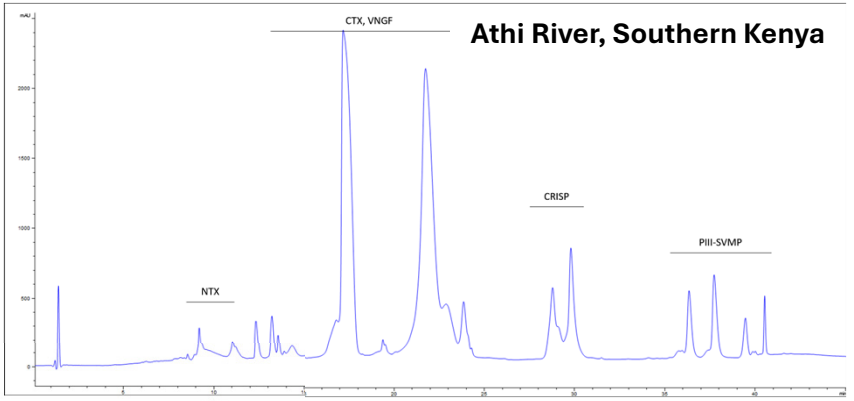
Methods for antivenom administration: (Top) intravenous infusion with 5-10 vials (50-100 mL) antivenom diluted to a total volume of 200 mL in a burette or small iv fluid bag and infused over 30 minutes, [Bottom] intravenous push injection of 50 mL antivenom at a time with a 50 mL syringe and butterfly needle @ 2 mL per minute by the medical officer. The MO should always be present with drugs/equipment prepared to treat any early reaction.

Venom variation is a major issue for production of antivenoms

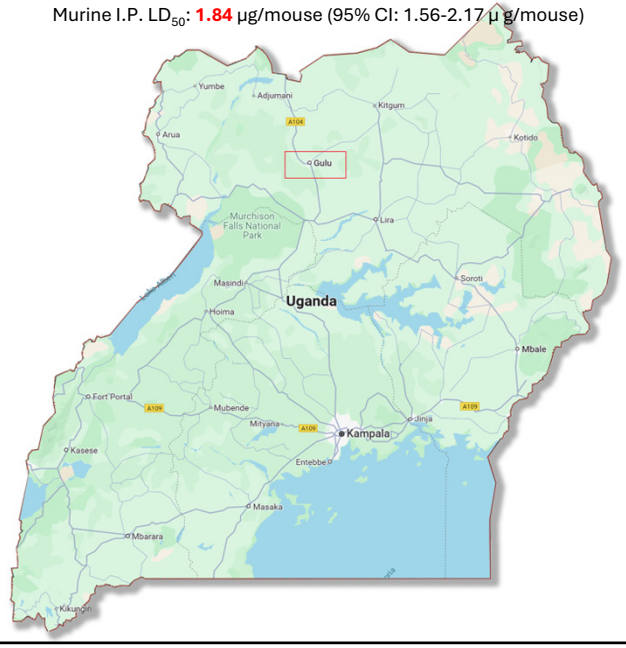


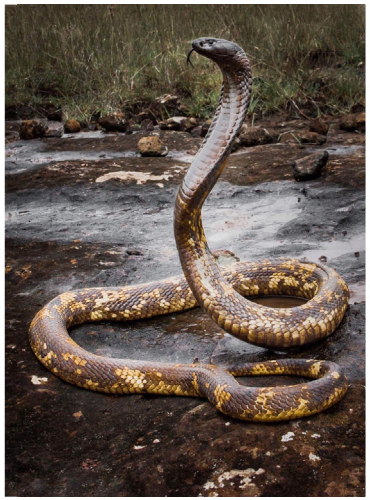
Murine I.P. LD_{50}: **1.84** µg/mouse (95% CI: 1.56-2.17 µ g/mouse)

Egyptian cobra
(Naja haje)



Murine I.P. LD_{50}: **65.7** µg/mouse (95% CI: 44.8-117.6 µ g/mouse)





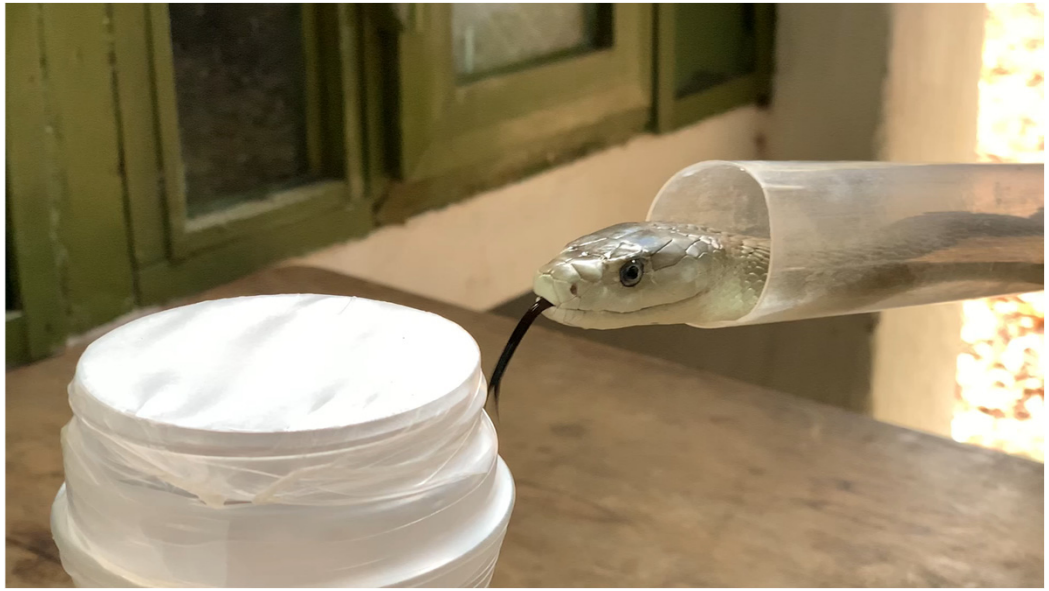
Venom yield, like potency, is critical to the design of effective antivenoms

Species	Conventional Manual Venom Extractions		Simulated Defensive Snakebites (single strikes)	
	Median [mg]	*IQR (Maximum) [mg]*	*Median [mg]*	*IQR [mg]*
Bitis arietans	89.9	64.5-149.9 (310.0)	84.4	60.3-108.3
Echis ocellatus	10.1	6.5-13.7 (14.4)	8.14	6.5-14.4
Dendroaspis polylepis	74.4	57.5-94.6 (338.2)	41.5	37.0-58.6
Naja nigricollis	366.2	255.7-489.1 (882.0)	99.4	43.8-158.9

NB: These are data from an ongoing study of multiple species from multiple locations. Data shown is for specimens of *B. arietans* from Kenya, Morocco, Togo, Ghana, and South Africa; for *E. ocellatus* from Togo; *Dendroaspis polylepis* from Kenya, Tanzania, and South Africa; and for *N. nigricollis* from Kenya, Tanzania, Togo, and Ghana. We plan to publish this study next year.

- For antivenom to be effective it must be administered in a dose that provides sufficient neutralizing antibodies to counter the clinical effects of the mass of injected venom.
- Different species produce different quantities of venom, and each snake has control over how much venom it injected under different conditions.
- Some manufacturers use the average venom yield that is obtained during manual extraction as a proxy estimate of venom yield and formulate products to neutralize at least this amount per dose.
- Most do not consider venom yield in the formulation of products, and this is a large part of the reason why treatment outcomes are often poor, especially in the absence of clinical trial data.
- More accurate data, based on yields obtained during both manual extractions and simulated defensive bites by various species is being collated by WHO to provide better data to manufacturers.
- Antivenomics enables calculations of estimated minimum binding capacity of antivenoms to be made and compared to venom yield data for each species.

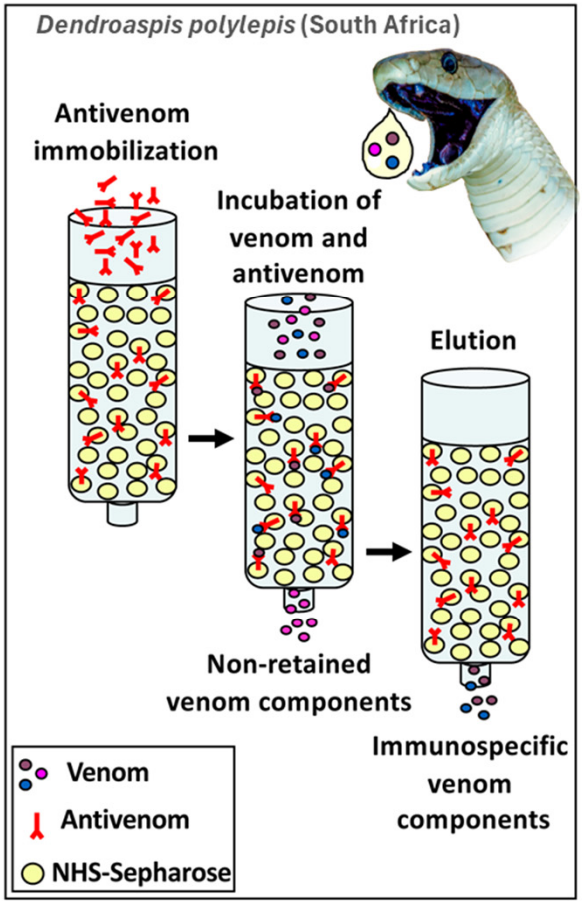
Simulated defensive bites

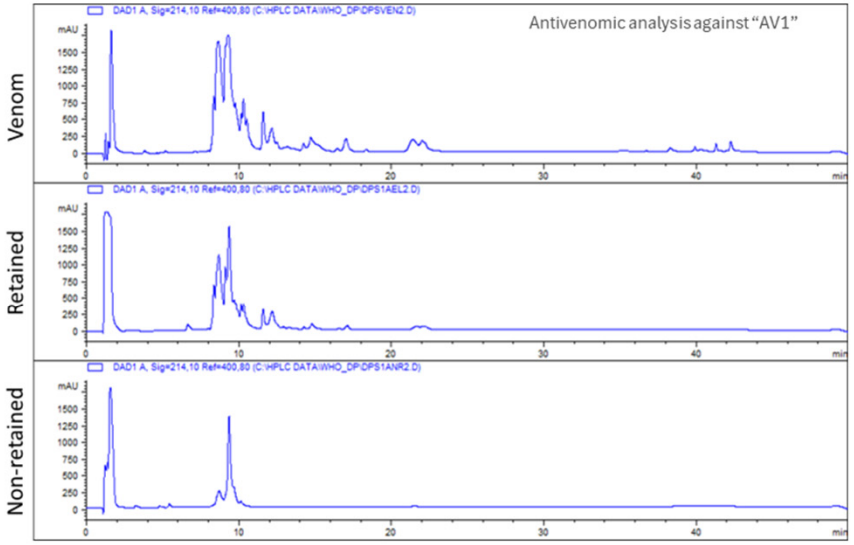


Dendroaspis polylepis

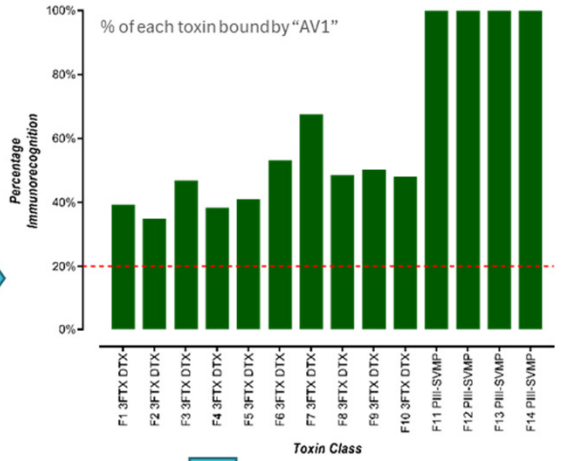
Naja haje

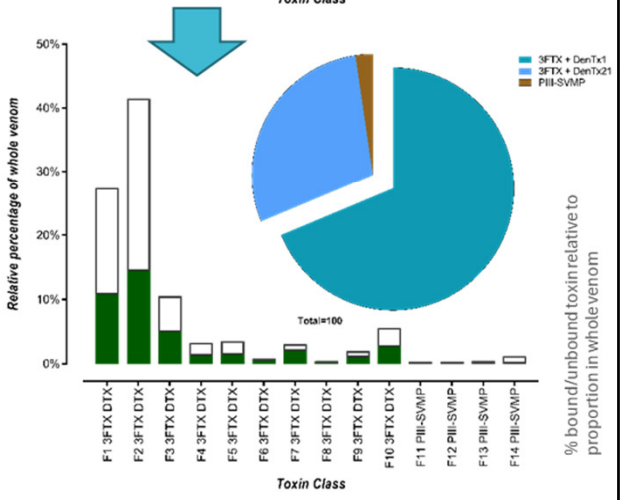
Third-generation antivenomic evaluation of venom: antivenom interactions





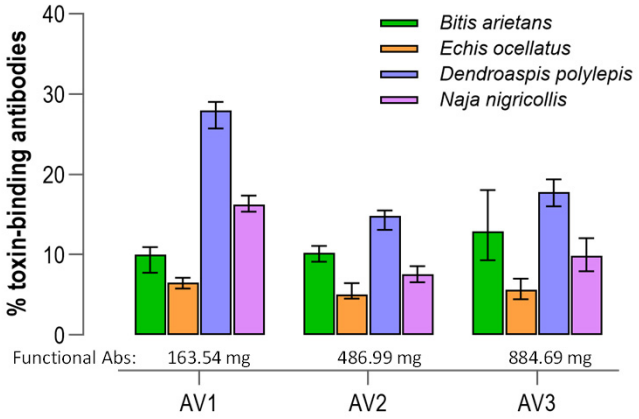
Description	Median (IQR)	Maximum
Toxin Immunorecognition (µg V/mg AV)	26.93 (22.40-30.59)	33.58
Bound by Intact F(ab')$_2$ (mg V/vial)	**1.41 (1.17-1.60)**	**1.76**
% Toxin-binding intact F(ab')$_2$	*21.89% (18.68-24.31%)*	*26.18%*
Toxin binding F(ab')$_2$ (mg intact F(ab')$_2$/vial)	*11.45 (9.77-12.71)*	*13.69*
Bound by other IgG$_F$ (mg V/vial)	**0.32 (0.26-0.36)**	**0.39**
% Other toxin-binding IgG$_F$	*24.29% (20.75-26.99%)*	*29.05%*
Other toxin-binding IgG$_F$ (mg IgG$_F$/vial)	*2.84 (2.43-3.16)*	*3.40*
Total venom bound (mg V/vial)	**1.73 (1.43-1.96)**	**2.15**
% Total toxin-binding antibodies	*20.36% (17.39-22.63%)*	*24.35%*
Total toxin-binding antibodies (mg Ab/vial)	*14.29 (12.20-15.87)*	*17.09*

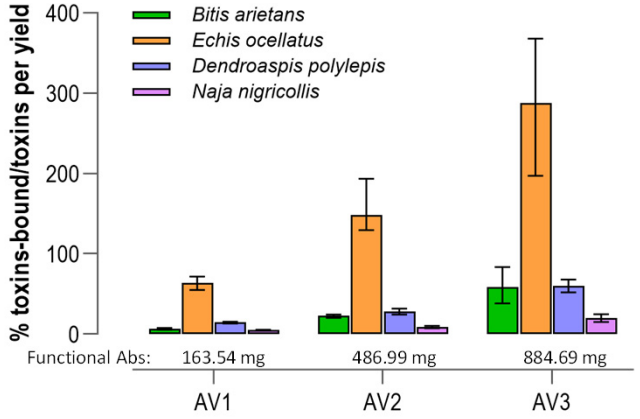




What can this data tell us about the quality and specificity of antivenoms

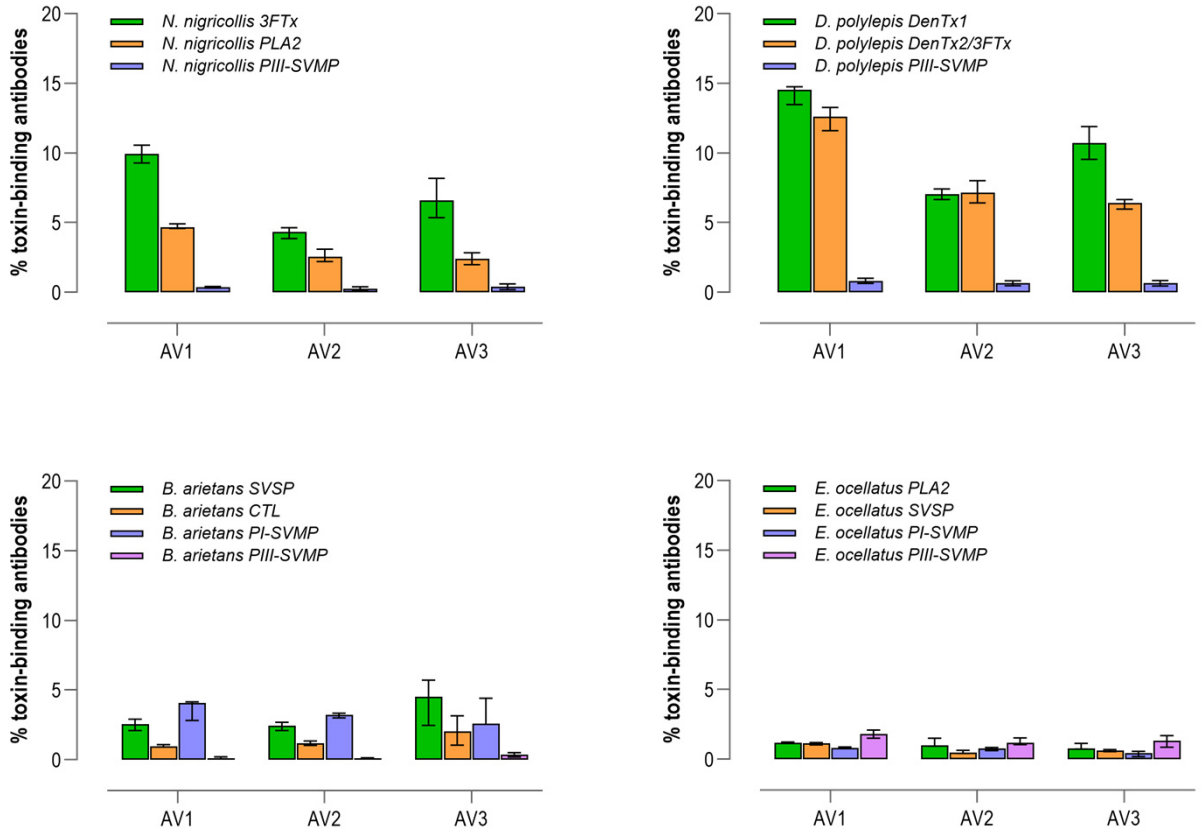
- By analyzing data, it possible to determine how much of each toxin present in any venom is immunorecognized and bound by the available antibodies.
- This in turn indicates:
  - Percentage of antibodies present that bind to specific snake venoms and can potentially contribute towards their neutralization.
  - What proportion of the average venom yield of a species is bound by the toxin-specific antibodies in a vial of a particular antivenom. For species with low venom yields there may be an excess of antibodies, but for those with high venom yields there will be a deficiency.
  - The number of vials that might minimally be needed to be able to bind all the toxins present in the average venom yield.
  - The number of mg of antibody that are needed to bind each mg of venom from a particular species.
  - Exactly which toxins are well-recognized by antibodies, and which are not. This can help to understand the *in vivo* potency or specific-activity neutralization data better.
- Cumulatively these data provide a rich understanding of venom: antivenom interactions and immunorecognition.
- This in turn can be used to improve existing designs, reformulate and increase the efficacy of antivenoms using an evidence-based approach.





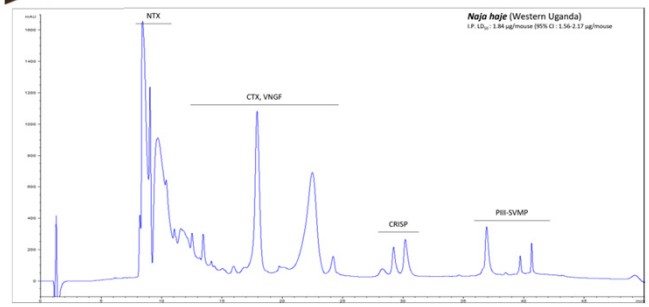
Immunogenicity of different types of toxins

- Widely stated in literature that the reason for ineffective neutralization of elapid venoms is due to the weak immunogenicity of small toxins in these venoms.
- Data show that antivenoms contain higher proportions of antibodies that recognize elapid 3-finger toxins (6-9 kDa) than those recognizing much larger toxins such as serine proteases (26.8 kDa), metalloproteinases (23-48 kDa) or C-type lectins (30 kDa).
- The reason for poor neutralization comes down to toxin abundance. On average there are 5-6 times more molecules of toxins in elapid venoms than in viper venoms, and the potential venom yields are often very much higher.
- Poor design and formulation result in products that do not contain sufficient ratios of toxin-specific antibodies to be clinically effective unless very large doses are given.
- Antivenoms should be formulated with venom yields and toxin composition considered as part of the design of the product, to ensure that adequate neutralizing antibodies are present in the initial dose.

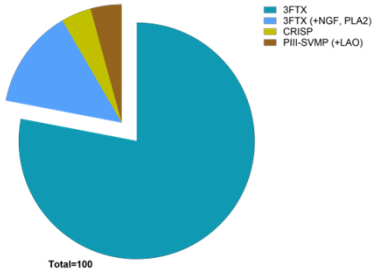


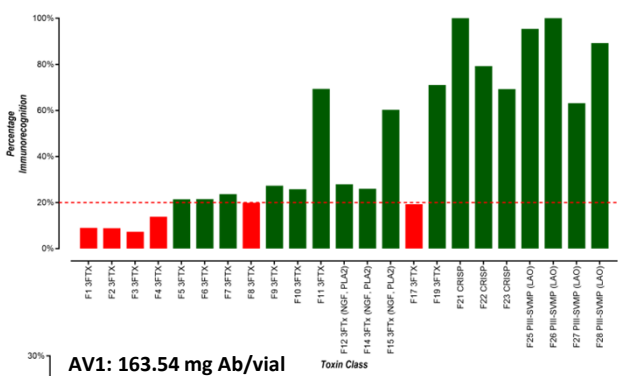
Percentage toxin-specific antibodies as a proportion of all functional antibodies per vial

Comparison of immunorecognition of venoms by different antivenoms



Egyptian cobra (*Naja haje*): Uganda

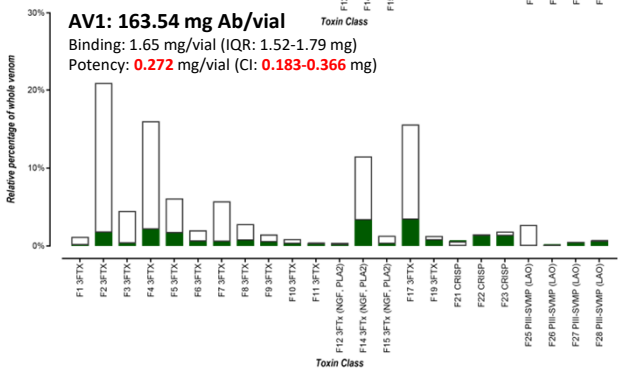


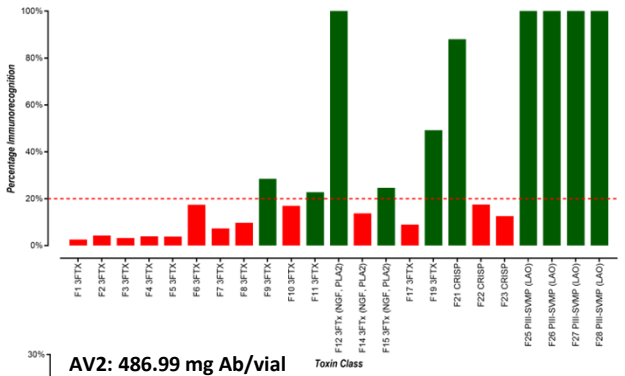


AV1: 163.54 mg Ab/vial

Binding: 1.65 mg/vial (IQR: 1.52-1.79 mg)

Potency: **0.272** mg/vial (CI: **0.183-0.366** mg)

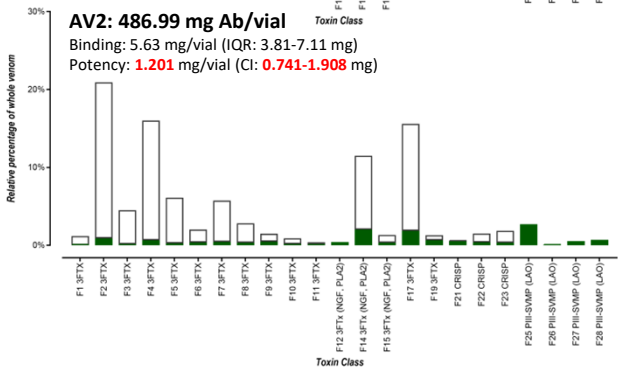




AV2: 486.99 mg Ab/vial

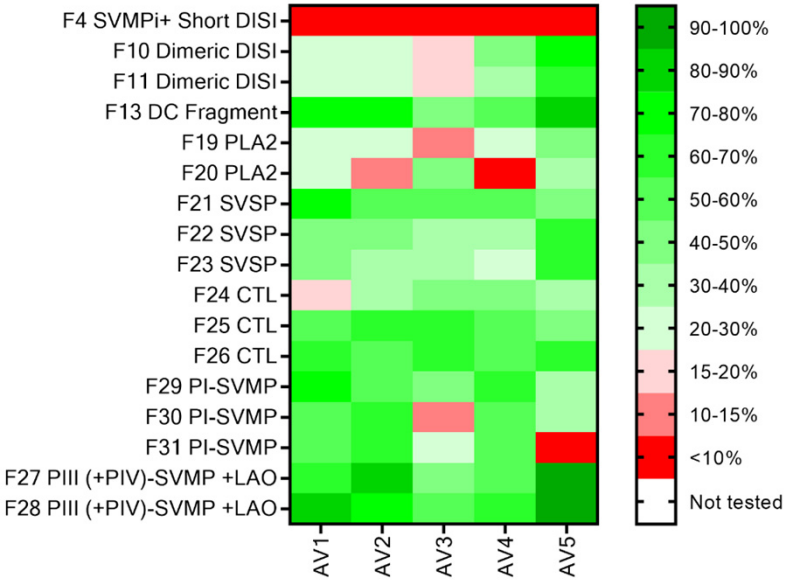
Binding: 5.63 mg/vial (IQR: 3.81-7.11 mg)

Potency: **1.201** mg/vial (CI: **0.741-1.908** mg)

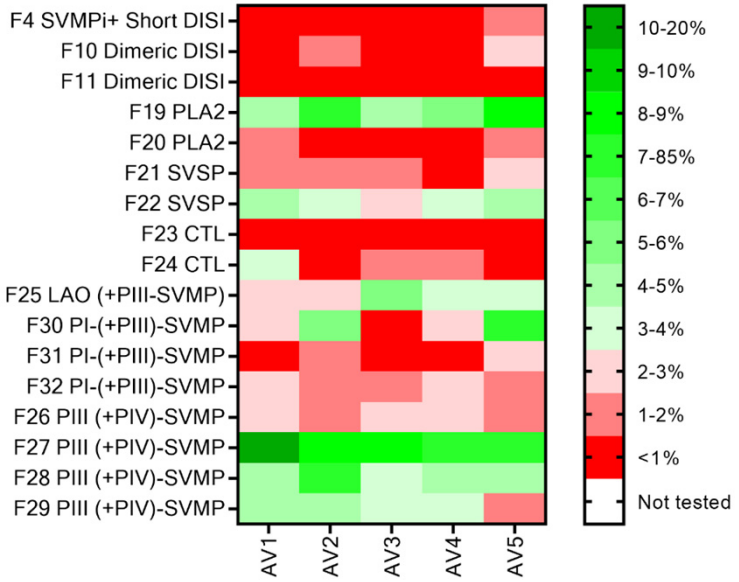


Understanding venom variation and implications for antivenom efficacy

Echis romani **(Cameroon)**



Echis ocellatus **(Ghana)**



Venom LD_{50}:
Cameroon: 34.77 µg/mouse
Ghana: 26.41 µg/mouse

Average venom yields:
Cameroon: 31.0 mg
Ghana: 11.2 mg

Can you guess which species manufacturers use to raise their antivenoms?

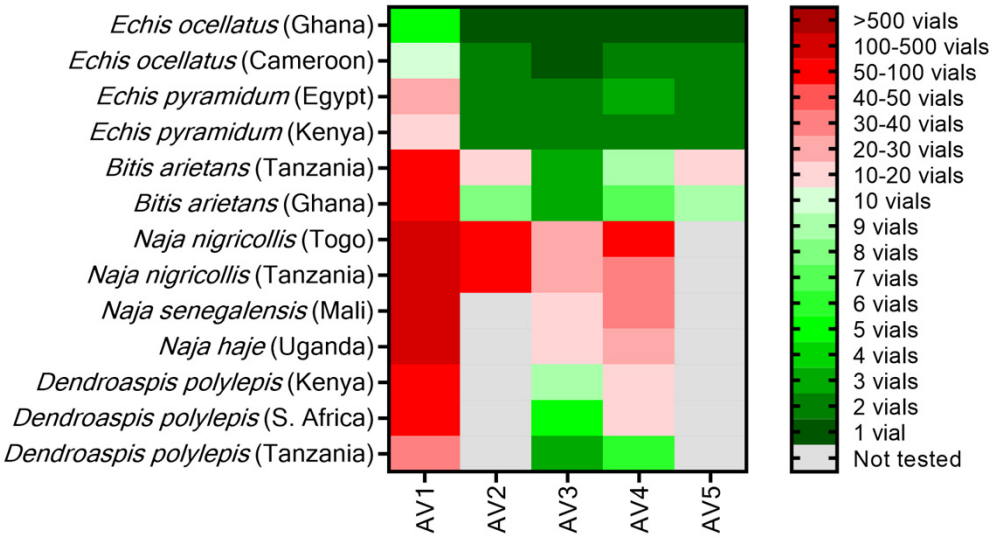
25 LD_{50} equivalents*:
Cameroon: 869.25 µg
Ghana: 660.25 µg

LD_{50} per venom yield
Cameroon: 891.6 (4 vials)
Ghana: 424.1 (2 vials)

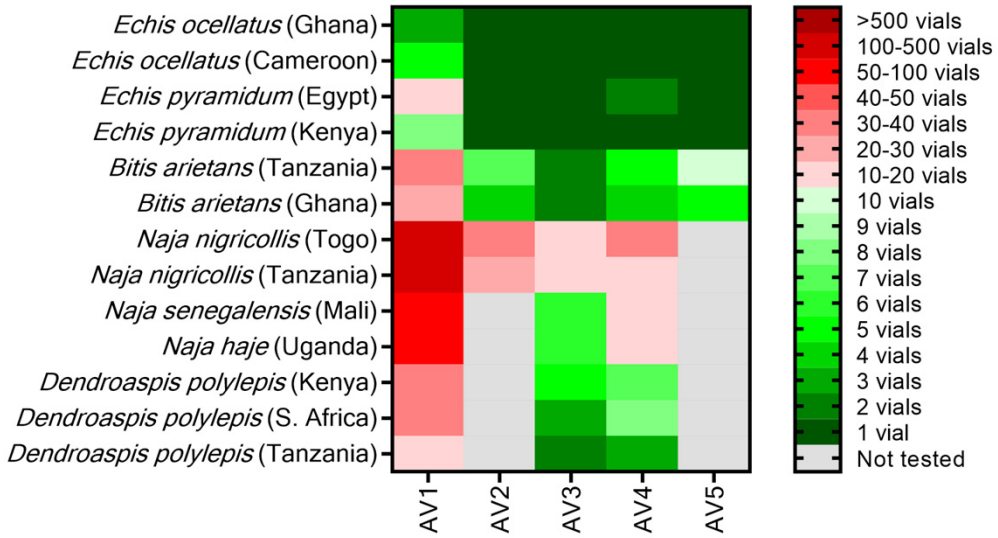
* Typical potency of antivenoms often poorly expressed as 25 LD_{50}/mL or 250 LD_{50}/vial. This arbitrary measure refers to the LD_{50} of venom used by manufacturers, which may be quite different to the LD_{50} of local populations of the same species and may affect the dose of antivenom needed.

3G antivenomics can provide an estimate of minimum theoretical dose

100% average venom yield dose prediction



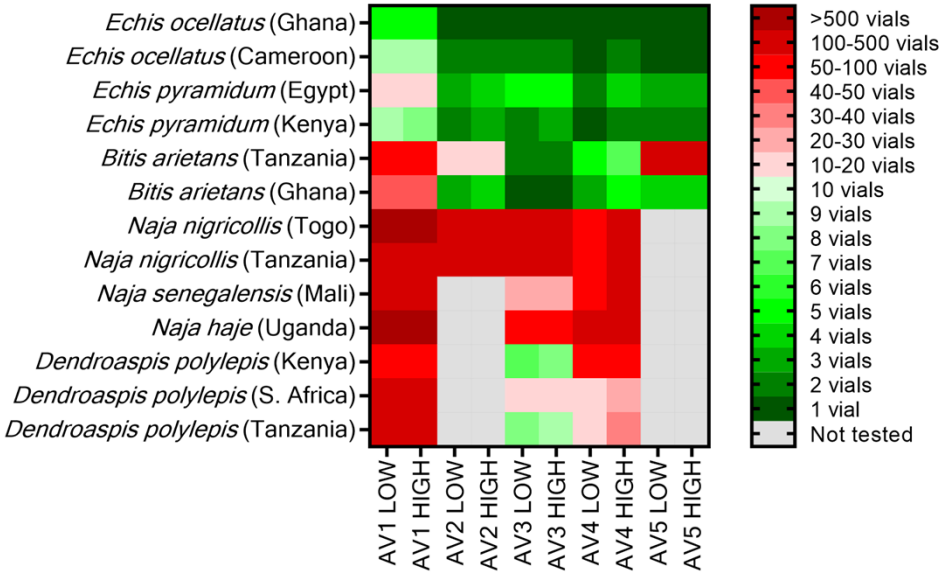
50% average venom yield dose prediction



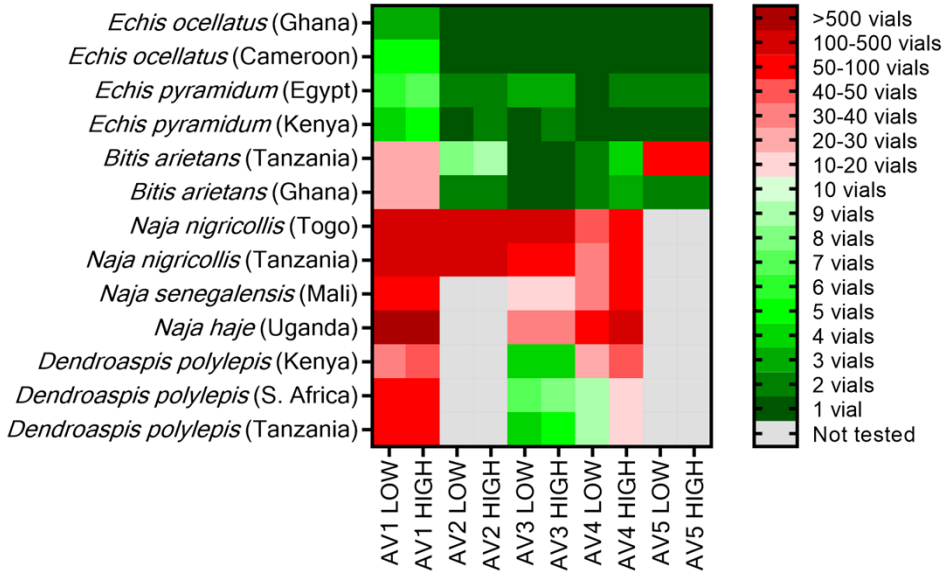
- Results of toxin-specific antivenomics combined to estimate the median, maximum and IQR ranges for toxin-binding, and potential dose required to neutralize specific amounts of venom.
- These provide an estimate, and *in vitro* results typically over-estimate the *in vivo* results!!
- Guides preliminary decision making on which products may be suitable for subsequent *in vivo* potency (e.g.: ED_{50}, potency) and specific toxin activity neutralization (e.g.: MND_{50}) assays.
- If a product fails to bind venom components *in vitro*, then it is extraordinarily unlikely that it will be effective in *in vivo* experiments!!

In vivo potency testing in mice – typically shows weaker efficacy.

100% average venom yield dose prediction

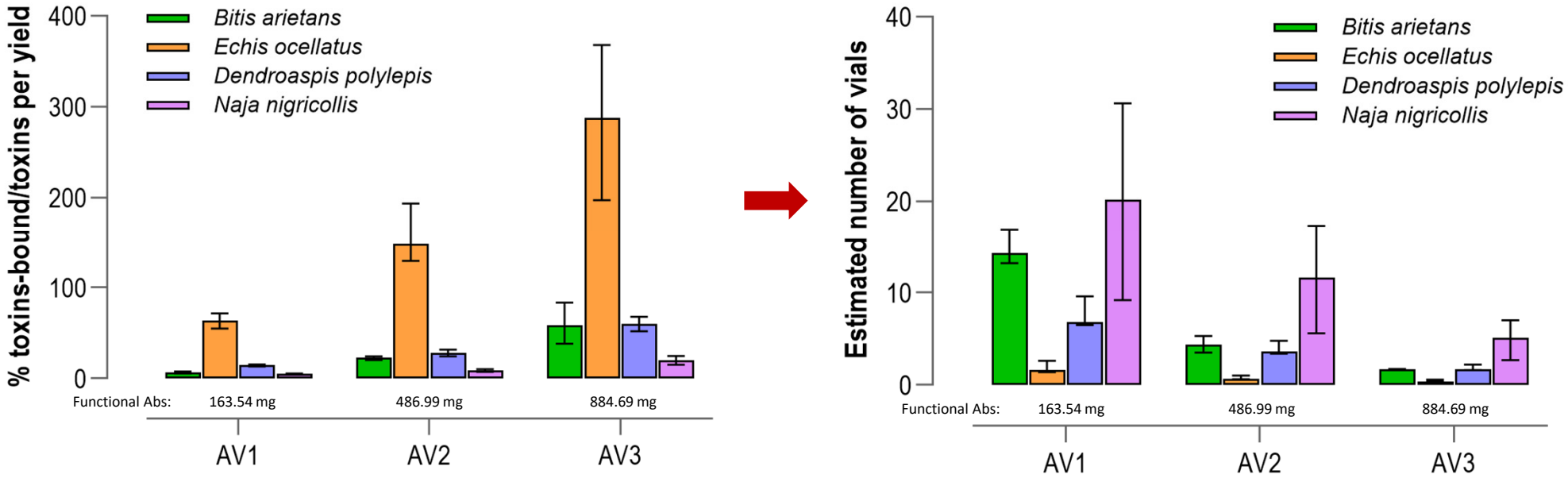


50% average venom yield dose prediction



- Potency [P] measures the amount of antivenom needed to completely neutralize the lethal effects of a snake venom and produce 100% survival, rather than just the 50% test animal survival achieved by conventional ED_{50} bioassays (e.g.: ED_{50} underestimates dose of AV needed).
- Results show consistent pattern to that of 3G antivenomic estimates of minimum dose but demonstrate that *in vivo* murine dose is higher than the *in vitro* minimum estimates based on immunorecognition alone.
- For human clinical use, the quantities needed will likely be higher again due to a range of additional factors, hence dose finding and safety studies are essential before products are introduced into new markets.

Impact of toxin-specific antibodies on minimum vial estimates



3G antivenomic data are idealized, *in vitro* experimental data based on immunorecognition in a closed environment during preincubation of chromatography columns containing venom and antivenom. They may represent the best-case scenario for toxin/antibody interaction under these conditions, but in practice this is only useful to indicate a **minimum vial estimate** that might contain sufficient toxin-specific/venom-specific antibodies that immunorecognize the number of the toxins present in fixed quantities of each venom *in vivo*.

NB: These data should not be used for any purpose other than to find a starting point, above which a dose of antivenom to test in a clinical study might be identified. In real life a substantial excess of antibodies would be required to consider the biological and pharmacokinetic barriers to 100% binding of toxins by injected antivenom in human snakebite envenoming. Neither antivenomics or immunoassays reliably predict *in vivo* potency and should not be used as alternatives to *in vivo* methods specified by Pharmacopeia without robust validation in line with ICH Q2(R1) and other international guidance such as US FDA industry guidelines or WHO TRS 932 Annex 2.

WHO Snakebite Envenoming Strategy: Key pillars and priority areas

Engage and empower communities

- Active local community engagement and participation
- Improve SBE prevention, risk-reduction and avoidance
- Effective pre-hospital care and ambulance transport
- Accelerate development of pre-hospital treatments
- Improve health care-seeking behaviours
- Build understanding of socio-cultural and economic factors affecting outcomes

Ensure safe, effective treatment

- **Make safe, effective treatments available, accessible and affordable to all.**
- **Better control and regulation of antivenoms**
- **Prequalification of antivenoms**
- Invest in innovative research on new therapeutics
- Integrated health worker training and education
- Improved clinical decision-making, treatment, recovery, and rehabilitation

Strengthen health systems

- Strengthening community health services
- Facilitating research and policy development around health-care cost mitigation
- Improving infrastructure, services, and health facilities
- Country-level implementation via national and sub-national health plans
- Enhanced disease burden monitoring and surveillance
- Research on snakebite envenoming ecology, epidemiology, clinical outcomes, and therapeutics

Partnerships, coordination & resources

- Support governance and leadership
- Promote advocacy, effective communication, and productive engagement
- Enhancing integration, coordination, and cooperation
- Build strong regional partnerships and alliances
- Coordinated data management and analysis
- Establishing a strong, sustainable investment case

NTD listing (2017); WHA resolution 71.5 (2018); WHO strategic plan launched (2019)

Risk-benefit assessment of snake antivenoms

Goal: provide evidence-based evaluation of antivenoms to support the work of national regulators, ministries of health, procurement agencies, clinicians and other stakeholders.

Dossier Review

Product dossiers are reviewed by independent experts who evaluate the information, identify deficiencies, raise questions for clarification, and make preliminary recommendations on risk-benefit ratios

Lab Assessment

A minimum of two batches of product are subjected to a comprehensive physico-chemical evaluation followed by extensive *in vitro* and *in vivo* preclinical potency and specific toxin neutralizing activities.

GMP Inspections

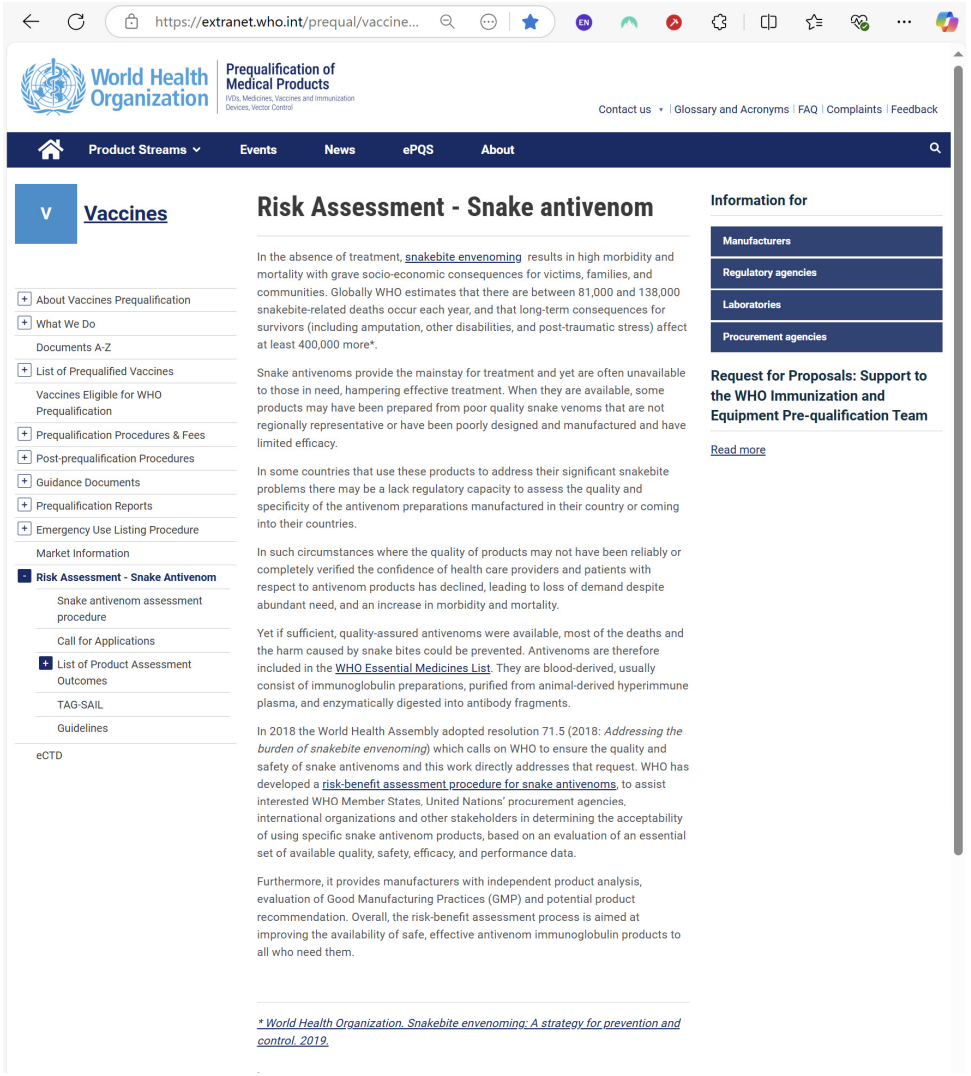
WHO inspectors visit each of the manufacturing sites and conduct a comprehensive GMP assessment of all activities, including snake venom and hyperimmune plasma production, and small animal use.

Product Listing

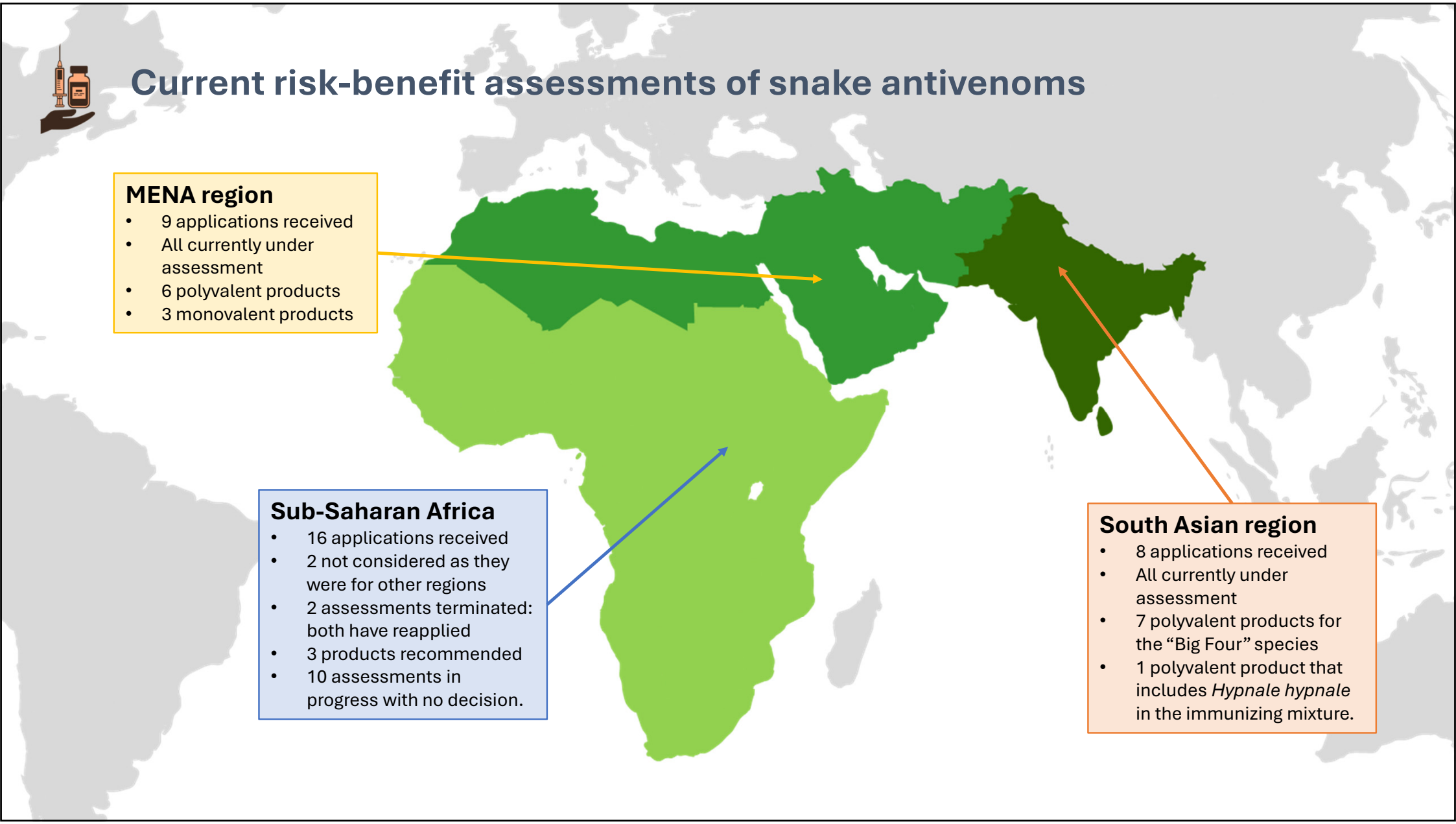
Products with an overall positive risk-benefit ratio may be recommended for procurement for specific use cases. Comprehensive reports are provided to manufacturers and public summary reports published.

Application procedure

- WHO publishes calls for expressions of interest in applying for risk-benefit assessment of products for specific markets, or indications.
- Eligibility criteria are defined in each call, and products must conform to these.
- All applications are made in writing, submitted electronically, and must be accompanied by a product dossier prepared in the ICH CTD format.
- Samples of each of the immunizing venoms (500 mg each) and the antivenoms (50 vials each from 2 different batch lots) are submitted to the WHO laboratory in parallel.
- Applications undergo initial screening by WHO technical unit prior to acceptance.
- Information from assessments will be published on WHO website and may be shared with NRAs and other relevant MS authorities or UN agencies.



Current risk-benefit assessments of snake antivenoms



MENA region
- 9 applications received
- All currently under assessment
- 6 polyvalent products
- 3 monovalent products

Sub-Saharan Africa
- 16 applications received
- 2 not considered as they were for other regions
- 2 assessments terminated: both have reapplied
- 3 products recommended
- 10 assessments in progress with no decision.

South Asian region
- 8 applications received
- All currently under assessment
- 7 polyvalent products for the “Big Four” species
- 1 polyvalent product that includes *Hypnale hypnale* in the immunizing mixture.

Risk-benefit assessment workflow

Laboratory evaluation and GMP assessments are undertaken simultaneously. For each product, the goal is to complete the risk-benefit assessment within 24 months, but this may vary, particularly where GMP compliance has not been established.

30–60 days

Dossier Review

Internal assessment with summary prepared for review by TAG-SAIL.

Laboratory Evaluation

Products moves through each of the four key phases sequentially, the duration depends on product design.

6–9 months

12–18 months

GMP Assessment

Inspection through to final decision subject to specific circumstances of each manufacturer.

TAG-SAIL Recommendation

TAG-SAIL meets to review data, request further information and make recommendations to Secretariat.

30 days

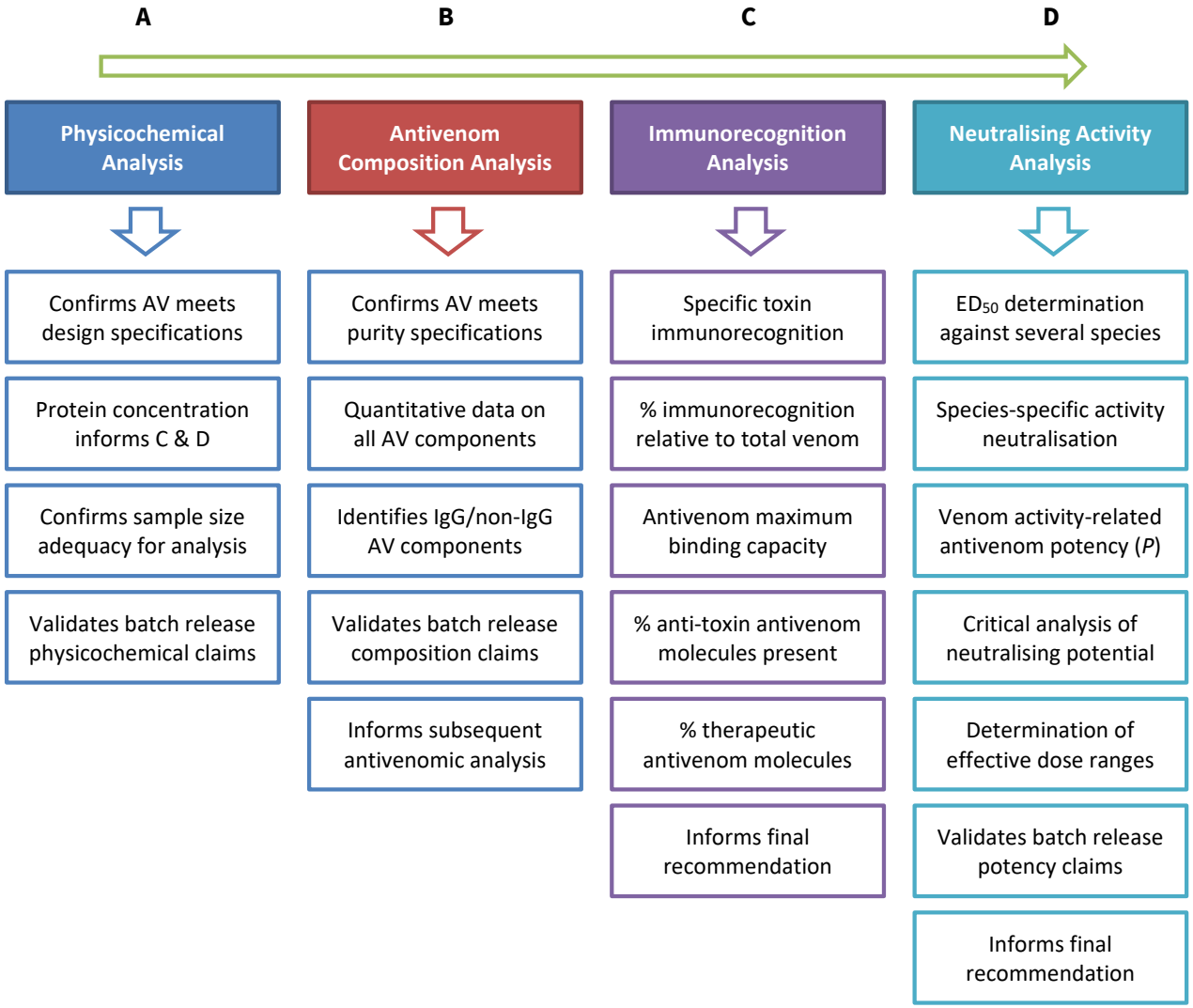
30–90 days

Notification

Manufacturers are provided 30 days to raise questions after decision is notified before publication.

Laboratory workflow

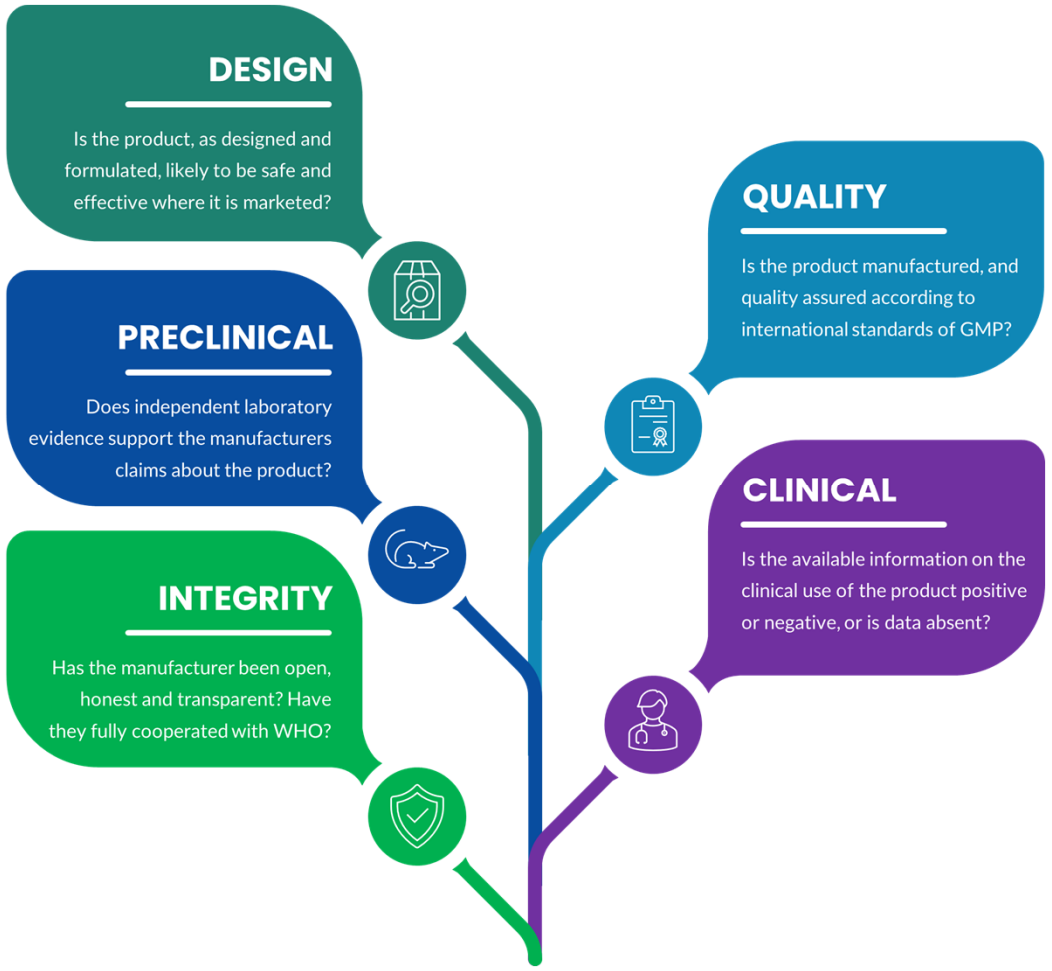
- Samples from 2 batches of each product are analyzed in an independent WHO contract laboratory.
- Stepwise analysis of:
  - Physicochemical properties
  - Antivenom composition
  - Immunorecognition
  - Neutralizing activity
- WHO ECBS-endorsed quality control and preclinical efficacy assays, including a range of specific toxin neutralization bioassays from *WHO Guidelines for Production, Control and Regulation of Snake Antivenom Immunoglobulins*
- Goal is to validates manufacturer batch release claims, comprehensively assess each product and inform the final recommendations based on evidence.




EchiTAb Study Group Nigeria
EchiTAbG
Ovine Echis ocellatus antivenom
Box contains five ampoules of 10ml each
Immunoglobulin solution for intravenous injection
Minimum of 23mg immunoglobulins per ampoule
Minimum of 35mg specific antibody per ampoule
BN: EOG 002120 Expiry: Nov-2023
Store at 2 to 8°C. Do not freeze.
MicroPharm Ltd., Station Road, Newcastle Emlyn, SA38 9BY, UK Licence Number: MIA 8794
NAFDAC Registration Number: A6-0078
STORE UPRIGHT
Snake Venom Antiserum I.P.
נסיוב כנגד ארס אפעה
(מקור סוס)
Echis coloratus Antiserum
(Equine source)
For intravenous use only
Solution for Infusion
Contents:
1 Single-use vial of 10mL Antiserum
1 Sterile single-use filter needle
Store refrigerated at 2-8°C.
Do Not Freeze.
Store in the Original Container in order to Protect from Light.
Keep Out of Reach of Children.
Sterile, non-pyrogenic.
Use immediately after opening.
Discard unused portion.
Dosage and administration: see package insert.
10mL
נסיוב כנגד ארס צפע א"י
(מקור סוס)
Vipera palaestinae Antiserum
(Equine source)
100 PD50/mL, 10mL
KAMADA
Manufacturer: Kamada Ltd., Beit Kama, Israel.
SnaFab
www.padraserum.com
BIG PAC

What does the process establish, and what does this mean?

- Risk-benefit assessment is not the same as WHO prequalification.
- The overall objective is to establish, whether on balance of evidence, **are any risks that may be associated with use of a product outweighed by the benefits of use to patients**.
- A positive assessment means that the antivenom and manufacturing processes have been evaluated and WHO has determined that it is:
  - Manufactured in compliance with WHO GMP.
  - Preclinically effective to the extent shown by the WHO laboratory analysis.
  - Considered likely to be clinically beneficial at the dose ranges shown in the final WHO assessment.
  - Can be recommended for procurement in accordance with the conditions of the WHO decision.
- There may still be risks associated with use and these should still be considered when making procurement decisions.



Technical advisory group (TAG-SAIL)

- WHO has established a technical advisory group on snake antivenom immunoglobulin product listing (TAG-SAIL).
- The group includes members with expertise in:
  - Veterinary medicine.
  - GMP production, quality control and regulation of hyperimmune plasma.
  - Biochemistry, snake venoms and preclinical quality assessment of snake antivenoms.
  - Clinical medicine with regional and global experience in treatment of snakebite envenoming.
  - Biological standardization of toxins, vaccines and antitoxins
  - Clinical and quality assessment of biologicals.
  - Production and purification of therapeutic antibodies.
  - Design and conduct of clinical trials of antivenoms.
- The key function of TAG-SAIL is to evaluation risk-benefit assessment findings and make final recommendations to WHO secretariat on which products may be listed for procurement.

WHO will announce a new call for additional TAG-SAIL nominations from NRAs, NCLs and Academic institutions in 2025.

Risk-benefit assessment progress for sub-Saharan African antivenoms

ASSESSMENT COMPLETED

- EchiTAbG™
  MicroPharm Limited
- Antivipmyn Africa® *Laboratorios Silanes, S.A. de C.V.*
- PANAF™ Premium
  Premium Serums & Vaccines

ASSESSMENT IN PROGRESS

- EchiTAb-plus-ICP
  Instituto Clodomiro Picado
- BeAfrique-10 (Pan African), Be Afrique-6 (Central Africa), and BeAfrique-1 (*Echis ocellatus*)
  Biological E Limited
- SAIMR Polyvalent Antivenom
  South African Venom Producers
- Snake Venom Antiserum (Afriven) I.H.S. (Lyophilised)*, Snake Venom Antiserum (*Echis*), Boomsven, and Afriven-S
  VINS Bioproducts Limited
- Inoserp™ PAN-AFRICA*
  Inosan Biopharma S.A.

** Previously terminated. Resubmitted for assessment in 2022 and 2023, respectively. The assessments are ongoing, and no decisions have been made.*

Risk-benefit assessments of snake antivenoms

World Health Organization

WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control)

Contact us | Glossary & Acronyms | FAQ

PRODUCT STREAMS | EVENTS | NEWS | ABOUT

V Vaccines

- About Vaccines Prequalification
- What We Do
- Documents A-Z
- List of Prequalified Vaccines
- Vaccines Eligible for WHO Prequalification
- Prequalification Procedures & Fees
- Post-prequalification Procedures
- Guidance Documents
- Prequalification Reports
- Emergency Use Listing Procedure
- Market Information
- Risk Assessment - Snake Antivenom

Risk Assessment - Snake antivenom

In the absence of treatment, snakebite envenoming results in high morbidity and mortality with grave socio-economic consequences for victims, families, and communities. Globally WHO estimates that there are between 81,000 and 138,000 snakebite-related deaths occur each year, and that long-term consequences for survivors (including amputation, other disabilities, and post-traumatic stress) affect at least 400,000 more*.

Despite this high burden, snake antivenoms are often unavailable to those in need, hampering effective treatment. When they are available, they may have been prepared from poor quality snake venoms that are not regionally representative or have been poorly designed and manufactured and have limited efficacy.

In some countries that use these products to address their significant snakebite problems there may be a lack regulatory capacity to assess the quality and specificity of the antivenom preparations manufactured in their country or coming into their countries.

In such circumstances where the quality of products may not have been reliably or completely verified the confidence of health care providers and patients with respect to antivenom products has declined, leading to loss of demand despite abundant need, and an increase in morbidity and mortality.

Information for

- Manufacturers
- Regulatory agencies
- National control laboratories
- Procurement agencies

Call for applications

Risk-Benefit Assessment of Snake Antivenom Immunoglobulins

Polyvalent antivenoms intended for use in the treatment of snakebite envenoming by Bungarus caeruleus, Daboia russelii, Echis carinatus and Naja naja in Pakistan, India, Nepal, Bangladesh, Bhutan, or Sri Lanka

WHO listed products which have received a positive risk-benefit assessment are published on the PQ website: https://extranet.who.int/prequal/vaccines/risk-assessment-snake-antivenom

This site also includes details of products with assessments still pending completion, or which have had assessments completed without a positive assessment. This information is provided to assist countries in selecting products which are suitable for use in their jurisdictions, that have already been robustly assessed by WHO for both quality, preclinical efficacy, and for compliance with Good Manufacturing Practices (GMP).

EchiTAbG
Monovalent liquid antivenom recommended by WHO for bites by Carpet vipers (*Echis ocellatus*, *E. romani*, *E. pyramidum*).

Requires cold chain storage and transport.

PANAF Premium
Polyvalent lyophilized antivenom recommended by WHO for bites by 24 species of African vipers and elapid snakes, including Carpet vipers (*Echis* spp.), African adders (*Bitis* spp.), cobras (*Naja* spp.) and mambas (*Dendroaspis* spp.).

Can be stored at room temperature (<30°C)

Antivipmyn Africa
Polyvalent lyophilized antivenom recommended by WHO for bites by Carpet vipers (*Echis ocellatus*, *E. romani*, *E. pyramidum*) and puff adders (*Bitis arietans*). Under review for wider recommendation for elapid envenoming.

Can be stored at room temperature (<30°C)

Recommended PAN-African polyvalent antivenom: PANAF-Premium™

World Health Organization

PANAF-Premium™
Combipack of Snake Venom Antiserum with Sterile Water for Injection (Pan Africa)

PRODUCT OVERVIEW	
Type:	Snake Antivenom for sub-Saharan Africa
Commercial Name:	PANAF-Premium™ Combipack of Snake Venom Antiserum with Sterile Water for Injection (Pan Africa)
Manufacturer:	Premium Serums and Vaccines Pvt. Ltd.
Country:	India.
URL:	https://www.premiumserums.com/
Responsible NRA:	Central Drugs Standards Control Organization (CDSCO)
Country:	India
URL:	https://www.cdsco.gov.in

PRODUCT DESCRIPTION	
Pharmaceutical Form:	Injectable solution
Presentation:	Lyophilized powder (vial) with diluent (SWFI) for reconstitution (ampoule).
Number of Doses:	1 (10 mL upon reconstitution)
Route of administration:	Intravenous
Shelf Life:	48 months
Storage temperature:	Store below 30°C, no refrigeration required.
Immunoglobulin content:	Not more than 10% w/v.
Packaging configuration:	Box containing one (1) vial lyophilized PANAF-Premium™, one (1) ampoule of diluent (SWFI), and instructions for use.

WHO RECOMMENDATION

Based on the results of a comprehensive risk-benefit assessment, this product can be used, at the dose ranges indicated in **Schedule 1**, for the treatment of envenoming by snake species listed in **Schedule 2**.

The recommendation is subject to terms and conditions imposed by WHO upon the manufacturer, which include the implementation (within one year) of a post-marketing surveillance strategy to monitor the use of the product and the clinical outcomes, including reporting of deaths, disabilities and adverse drug reactions.

WHO reviews all recommendations annually, and considers all new data that becomes available, and may renew, revoke, or amend these recommendations, based on the information available at the time of the review.

SCHEDULE 1: INITIAL DOSES

Dose recommendations below are based on the recognition of the variable composition of snake venoms leading to differences in potency within and between species. They also recognize the wide variation in the amount of venom that may be injected by individual specimens, particularly by large cobras (*Naja*) and mambas (*Dendroaspis*). These dose recommendations may be updated as new data based on clinical practice or clinical trials experience becomes available, and subject to review and approval by WHO.

Species Group	Genus	Recommended Initial Dose
African adders	*Bitis*	3-6 vials
African carpet vipers	*Echis*	1-3 vials
African mambas	*Dendroaspis*	10-25 vials
African cobras	*Naja*	20-40 vials

SUPPORTIVE TREATMENT:

Antivenom alone cannot be relied upon to reverse neurotoxicity or prevent its progression to respiratory paralysis. It is essential that close attention be given to protecting and maintaining airway and breathing. Basic airway management and assisted breathing is lifesaving. Appropriate interventions such as Guedel airways, laryngeal mask airways, supplementary oxygen, bag-mask ventilation and if available endotracheal intubation and initiation of mechanical ventilation should be implemented as soon as indicated. For bites by neurotoxic cobras the use of anticholinesterase drugs like Neostigmine can temporarily reverse paralysis, but these drugs are not safe or appropriate for treatment of mamba bites. When used for cobra bites the co-administration of atropine is essential to block potentially serious muscarinic effects, such as bradycardia, bronchospasm, and an increase in secretions. Two anticholinergic drugs are available for this purpose, namely, atropine and glycopyrrolate. Atropine or glycopyrrolate may be used as anticholinergic agents.

After reconstitution, each ml of PANAF-Premium neutralizes the following number of murine median lethal doses (LD_{50}) and micrograms of venom neutralized, at a minimum–

Bitis arietans	≥ 25 LD_{50} (338 ug)	*Bitis gabonica*	≥25 LD_{50} (458 ug)
Bitis nasicornis	≥ 20 LD_{50} (529 ug)	*Bitis rhinoceros*	≥ 25 LD_{50} (615 ug)
Echis leucogaster	≥ 25 LD_{50} (872 ug)	*Echis ocellatus*	≥ 25 LD_{50} (556 ug)
Echis carinatus	≥ 25 LD_{50} (384 ug)	*Naja haje*	≥25 LD_{50} (152 ug)
Naja melanoleuca	≥20 LD_{50} (204 ug)	*Naja nigricollis*	≥ 20 LD_{50} (552 ug)
Dendroaspis polylepis	≥25 LD_{50} (168 ug)	*Dendroaspis viridis*	≥ 25 LD_{50} (310 ug)
Dendroaspis jamesoni	≥ 25 LD_{50} (277 ug)	*Dendroaspis angusticeps*	≥ 25 LD_{50} (796 ug)

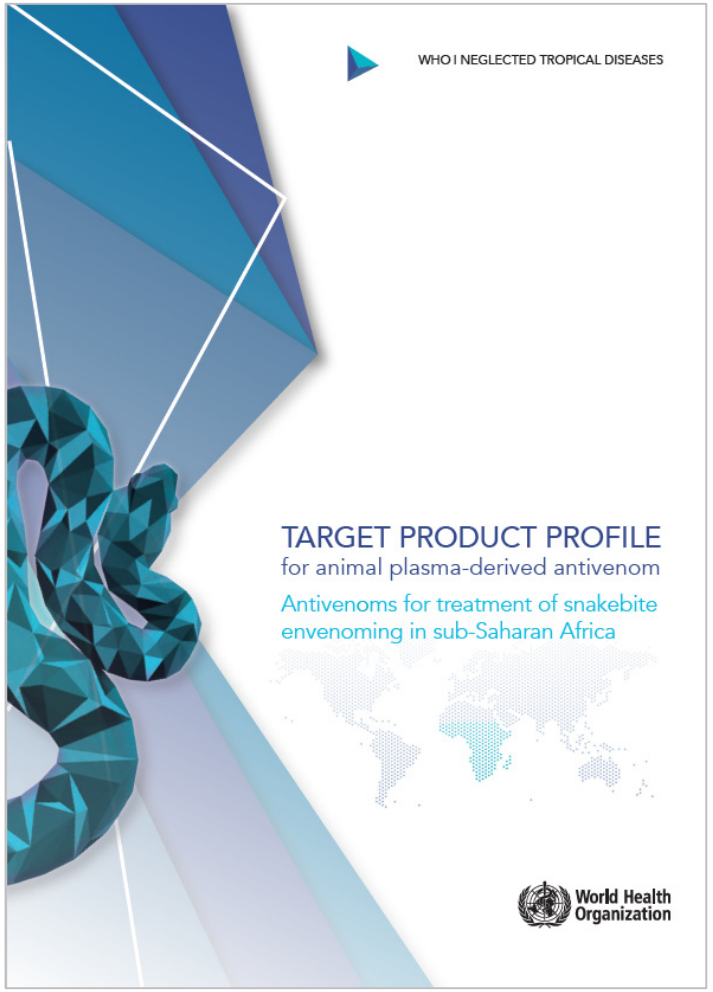
Cresol (Preservative) NMT 0.25% v/v
Glycine B.P stabilizer, Sodium Chloride B.P excipient

https://extranet.who.int/prequal/vaccines/risk-assessment-snake-antivenom

Target product profiles for antivenoms and other treatments

- Several public-benefit TPPs are in development for:
  - Conventional animal plasma-derived antivenoms
  - Small molecule inhibitors
  - Engineered antibody therapeutics.
- Aimed at providing guidance to researchers, manufacturers, regulators and other stakeholders.
- Developed by an 18 member Technical and Scientific Advisory Group (TSAG) comprising a broad range of expertise, and according to the WHO TPP methodology.
- Drafts are published on WHO website for public comment prior to finalization.
- Final documents published on website as PDFs for download with first finalized TPPs on conventional antivenoms for Sub-Saharan Africa now online:

https://www.who.int/teams/control-of-neglected-tropical-diseases/snakebite-envenoming/target-product-profiles



Clinical trials of snake antivenoms

TRS 1004 Annex 5 Ch. 20:

- *Antivenoms are unusual among pharmaceutical agents in that they have been used in human patients since 1896 with little attention being paid to clinical trials of their effectiveness and safety. However, since the 1970s it has been clearly demonstrated that it is possible to carry out dose-finding and randomized controlled trials (RCTs) in human victims of snake-bite envenoming. These studies have yielded invaluable information, as in the case of clinical trials of other therapeutic agents for which clinical trials are generally regarded as the essential basis for regulatory approval.*
- *The conventional pathway for clinical evaluation of new therapeutic products is:*
  - *Phase I: healthy volunteer studies – detection of unanticipated adverse events;*
  - *Phase II: limited effectiveness and safety studies, often dose-finding;*
  - *Phase III: full-scale clinical evaluation, often using blinded RCTs to avoid potential introduction of bias;*
  - *Phase IV: post-marketing surveillance.*
- *So far, most antivenoms have been registered without prior clinical studies. This situation should not persist: it is desirable, first, to collect the existing clinical data on antivenoms already marketed, and second to promote Phase II or III clinical trials before registering new antivenoms.*

While this is desirable, the key question we need to ask is – are such clinical trials feasible and affordable.

For an impartial appraisal see:

Potet J, Smith J, McIver L (2019). Reviewing evidence of the clinical effectiveness of commercially available antivenoms in sub-Saharan Africa identifies the need for a multi-centre, multi-antivenom clinical trial. PLoS Negl Trop Dis 13(6): e0007551.

From the literature...

Potet et al:

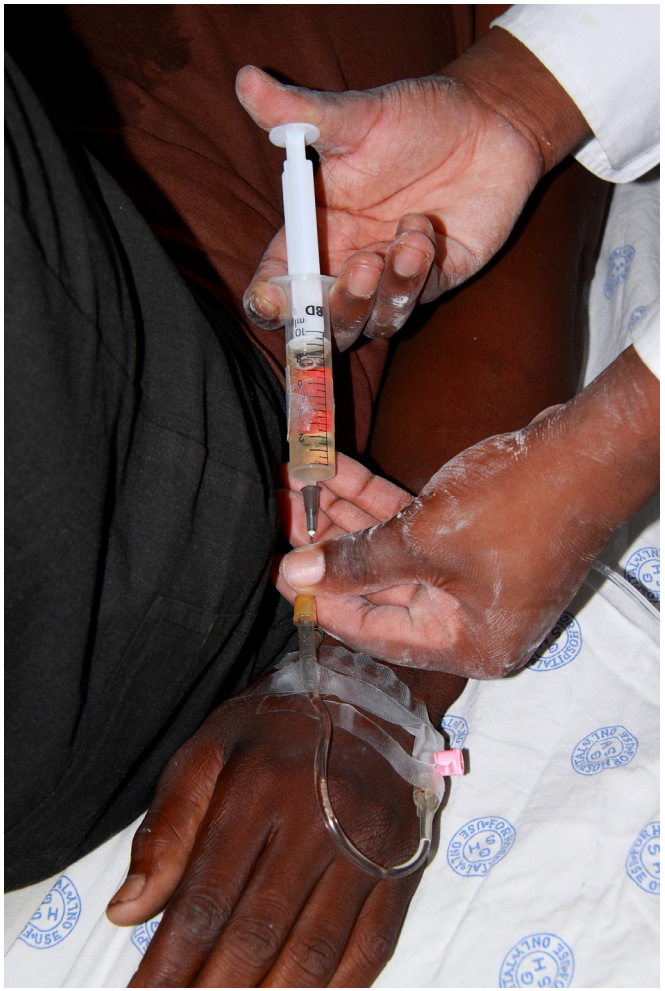
- 26 studies identified in SS Africa between 1974-2018:
  - 2 RCT's – both in Nigeria
  - 5 non-randomized comparative clinical studies
  - 11 observational cohort studies
  - 8 anecdotal clinical reports
- Heterogeneous design, endpoints, dose regimens, and products.
- Quality of reporting inconsistent, often without information on time interval from bite to hospital and severity of envenoming.
- Only three products were supported by good-quality clinical studies that found them to be effective for bites by carpet vipers.
- Quality of data for any product against other species poor.
- Multi-centre clinical trial approach was recommended as being urgently needed, with a comparative approach to compare safety and effectiveness of different products.
- Conclusion:

For as long as anti-venom treatment is distributed in sub-Saharan Africa without adequate supporting clinical data, the safety and effectiveness of such treatment cannot be ascertained. Urgent investments in research are required to more accurately determine the regional specificity of existing forms of antivenom treatment.

From TRS 1004 Annex 5:

Chapter 20.2:

- Clinical studies of antivenoms primarily address three main issues:
  - assessment of the optimal initial dose of antivenom;
  - assessment of effectiveness of the antivenom;
  - assessment of the safety of an antivenom, particularly the incidence and severity of early and late reactions.
- 20.2.1 outlines approaches to initial dose-finding and safety studies to establish optimum initial doses of antivenom in patients with different degrees of severity of envenoming.
- 20.2.2 discusses non-placebo Phase III RCTs based on random allocation to treatment groups according to the “intention to treat” principle to avoid concealing poor outcomes through study dropouts.
- 20.2.3 considered effectiveness endpoints, which should be pragmatic, measurable, and defined a priori with objectivity in mind.
- 20.2.4 deals with safety endpoints.
- 20.2.5 talks about the practical challenges, noting that they are expensive (especially for multi-centre studies), logistically challenging, and subject to variable protocol compliance.



From manufacturers product CTDs:

"No Clinical studies are conducted in general for Immunosera Products including Anti Snake Venom, as the [product name redacted] should be administered as soon as the snakebite happens."

"Administration of the Anti Snake Venom should not await bacteriologic confirmation of the diagnosis since the condition of the patient may be fatal and can deteriorate rapidly."

"No volunteers or patients will be available for conducting any clinical trials."

"Human clinical data is not available"

"Unusually for a human medicine, clinical trials are not a pre-requisite for antivenom approval, licensing and use in patients."

"This is a historical product widely used for the treatment of African snake bites ... and its safety and efficacy has been well established. Therefore, we have not performed any Controlled and/or Uncontrolled Phase-I/II/III clinical studies and hence reports of Data analyses for these studies are not available with us."

These are not acceptable excuses for a lack of clinical evidence of safety and effectiveness

At a time when millions of people are vulnerable, thousands are dying, and many more are being left with disabilities due to a chronic lack of safe, effective and affordable antivenoms…

"What if we don't change at all ...
and something magical just happens?"

Can we really afford the luxury of expensive, complex and risky clinical trials?

Monitored emergency use authorization of snake antivenoms

Goal: facilitate rapid access to existing, new or experimental treatments, and improve capacity to regulate products based on accumulated clinical evidence and expert ethical oversight.

MEURI: Monitored emergency use of unregistered and experimental interventions

A proven framework

- First proposed in 2014 during Ebola Virus Disease (EVD) crisis in West Africa.
- An adapted model based on the MEURI ethical framework under development to facilitate the emergency use authorisation of new snakebite treatments or existing treatments for which clinical data is lacking.
- Similar approach to compassionate use authorization schemes for experimental, investigational, or unregistered medicines by Europe's EMA and US FDA.

Prerequisites

- Agreement of national government to issue an emergency use authorization and provide national ethics committee oversight.
- Robust preclinical data, approved treatment protocol, informed consent, compulsory case reports to independent DSMB for progressive review.

Goals

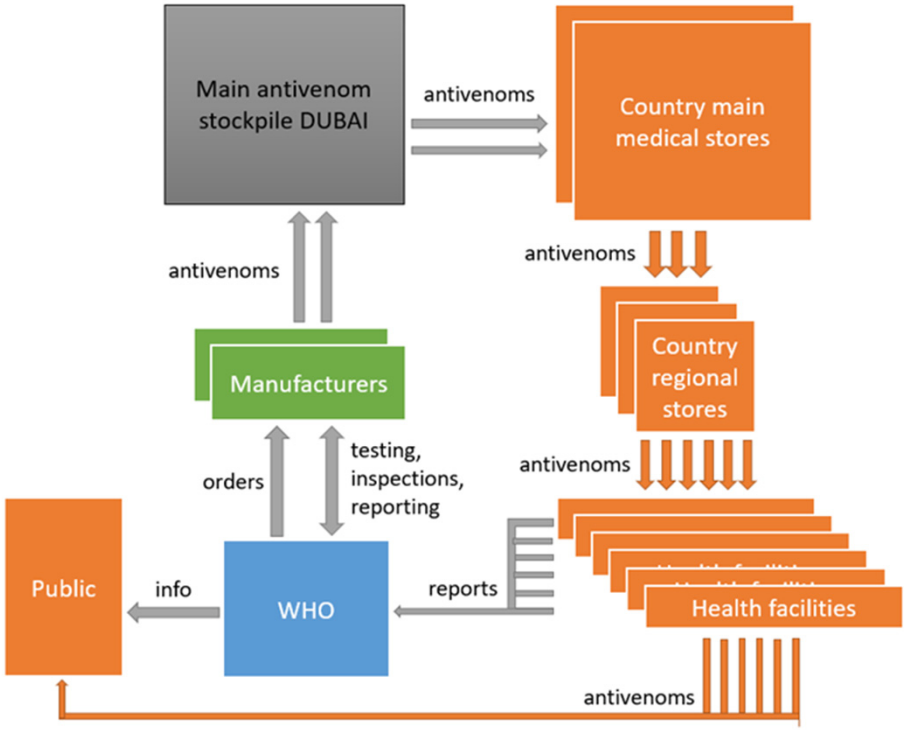
- Facilitate rapid access to existing, new and experimental treatments.
- Improve the oversight of antivenoms, particularly in countries where no current provision for clinical trials is encased in regulatory requirements for authorization.

Application of MEURI criteria to snakebite envenoming

Criteria	Can snakebite envenoming qualify?
No proven effective treatment exists.	Demonstrably effective antivenoms often absent.
It is not possible to initiate clinical studies immediately.	This can be demonstrated.
Data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee based on a favourable risk–benefit analysis.	WHO risk-benefit assessments can demonstrate evidence of preclinical efficacy and safety for some products, and the TAG-SAIL can recommend products as being suitable for MEURI evaluation.
The relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use.	This requires agreement from countries, and availability of qualified national ethics committees.
Adequate resources are available to ensure that risks can be minimized.	A collaborative effort on the part of manufacturers, clinical researchers, MOH, NRA and other partners could ensure this.
The patient's informed consent is obtained.	This can be done.
The emergency use of the intervention is monitored, and the results are documented and shared in a timely manner with the wider medical and scientific community.	Local DSMB and ethics committees can monitor the studies, and data can be shared through a variety of means, including peer-reviewed publication and community sensitization.

Antivenom pooled procurement project

Goal: Create a sustainable, trusted source of quality-assured antivenoms for African nations.



Flow chart showing flow of product from main stockpile in Dubai to countries' medical stores system and hospitals, as well as information flow back to WHO.

Products

- Minimum of three WHO-recommended and quality assessed antivenom products, with additional products added over time.

Process

- Products listed in WHO Procurement Catalogue with long-term supply agreements in place with manufacturers.
- WHO assistance to establish forward needs assessments based on surveillance data, snake distributions and other information.
- Countries place orders through WHO Catalogue with supplies shipped by WHO from central hub every quarter.
- Shipments delivered to countries by WHO within 60 days of order.
- Countries reimburse WHO for products that they procure.
- Additional emergency facility will be available for urgent resupply in disasters such as flooding events at any time.

Data Driven

- WHO expert-derived consensus snake distribution models.
- Human population, activity & risk of contact models for all medically important species informing health care accessibility models.
- Epidemiological, health facility, supply chain, infrastructure, health economics and logistics data.
- Risk-benefit assessments for new products and annual product quality and safety reviews of currently listed products by WHO PQT.
- Implementation and outcomes monitoring and reporting.

Partnerships

- Collaboration with government, AFRO, local experts, civil society and implementation partners. Work in countries carried out by local organizations with WHO and MOH support, training and coordination.

What a pooled procurement program will deliver

Goal: reduce the unit cost of antivenoms, increase supply volumes, distribution and surveillance.

- A pooled procurement process for countries based on supply through WHO of risk-benefit assessed antivenoms at a pre-negotiated price on a scheduled quarterly basis. Access to the scheme will be open to all countries in sub-Saharan Africa.
- Establishment of an emergency stockpile of the same antivenoms for rapid deployment in the event of health emergencies.
- New procurement products that include consumables packs to support (a) diagnosis, (b) safe antivenom administration, and (c) secondary wound care of snakebite patients.
- Improved supply chain management to reduce costs and wastage and to expand access to effective antivenoms and other snakebite treatments as they become available.
- A stabilized market that enables manufacturers to plan better.
- An environment that can stimulate development of new antivenoms and capacity for local manufacturing.

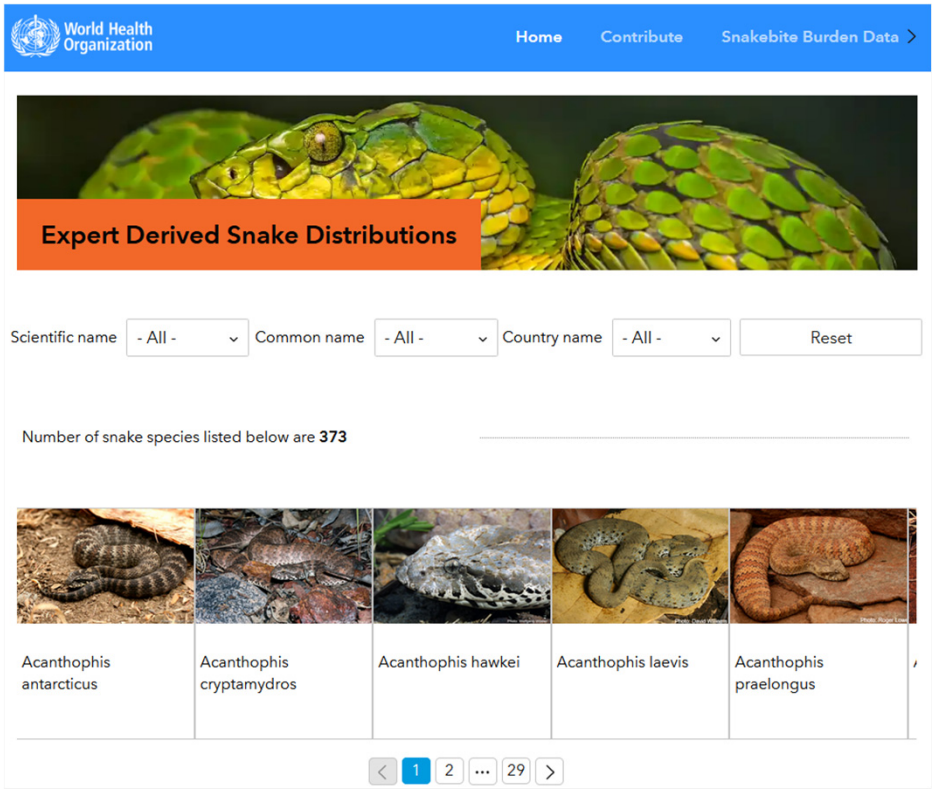
Local capacity building in parallel with improved antivenom supply

Goal: provide a holistic package of interventions to support reductions in mortality and morbidity.

- Training workshops for procurement, supply and distribution agencies to improve their knowledge of products, procurement decision-making, needs assessment, inventory management, supply and distribution strategies and tools, post-use surveillance and evaluation.
- Better trained health care workers who can correctly diagnose and treat snakebite envenoming with greater confidence and better patient outcomes.
- Training workshops for national regulatory agencies and national control laboratories to improve and enhance their capacity to evaluate product registration applications, perform product risk-benefit assessments, and monitor the use, safety and effectiveness of products.
- Local community-based initiatives that improve awareness of snakebite mitigation measures, knowledge of safe first aid interventions and correct health care seeking behaviors.
- Technical products to improve snakebite surveillance and epidemiology.
- Engagement with local stakeholders for the supply of implementation research activities and for program monitoring, review and evaluation.

WHO Snake Information and Data Platform

Goal: share data that can functionally inform policy and practice with stakeholders to improve decision-making and inform resource allocation.



Understanding the human-animal interface

- ArcGIS-driven core geospatial database that integrates data on human and animal ecology, environments and climate, health systems, infrastructure and public health records.

Integrating a toolkit of solutions to support interventions

- A range of tools including snakebite modules for DHIS2, AccessMod5 and CostIt, dedicated apps
- Support for rational antivenom distribution planning and MRE
- Venomous snake habitat suitability and climate change impact mapping.

Centralizing collection of critical data

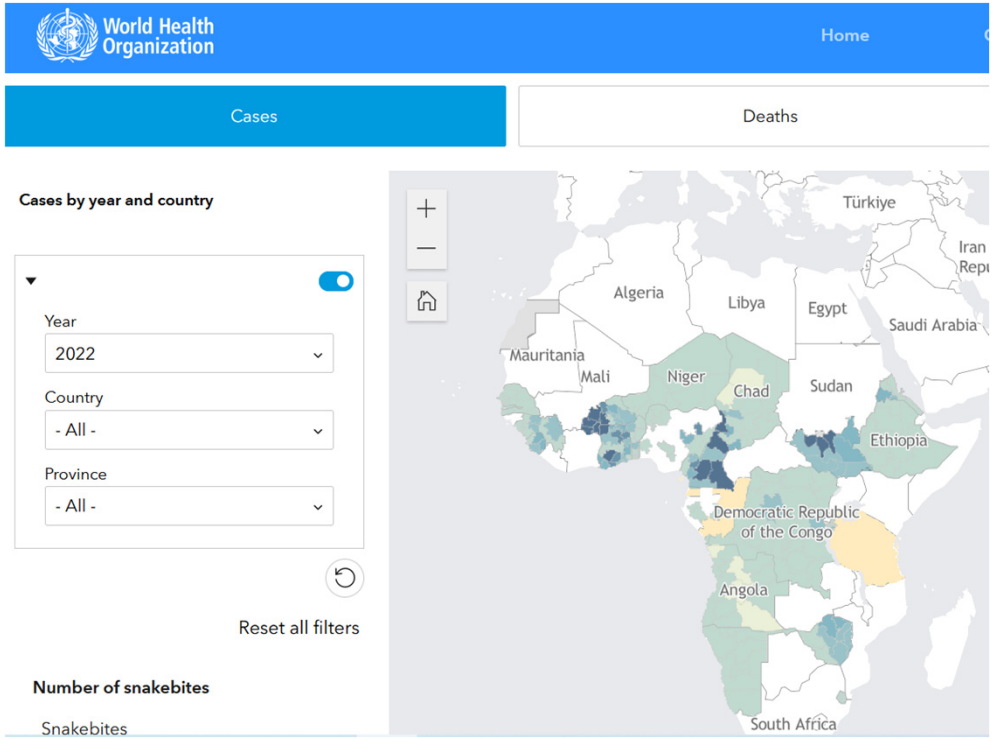
- National and regional hospital- and community-acquired data will be centralized and made accessible to users through the platform.

Enabling collaboration and cooperation

- Designed to enable broad collaboration and participation.
- Users will be able to contribute data and make use of all the data, either individually or as part of collaborative teams working on common problems.

WHO DHIS2 reporting module for snakebite envenoming

Goal: standardize reporting of epidemiological data within countries and to WHO and facilitate more accurate and timelier national and regional analysis and interpretation of findings.



Collection of baseline hospital-acquired data

- DHIS2-based data submission of admin level 1 and 2 data using Excel forms.

Data reveals major gaps in surveillance

- Some countries undertake no data collection for this NTD.
- We would encourage all countries to work with us to fill voids in data and endeavor to establish a baseline for the whole continent.

Reporting of data

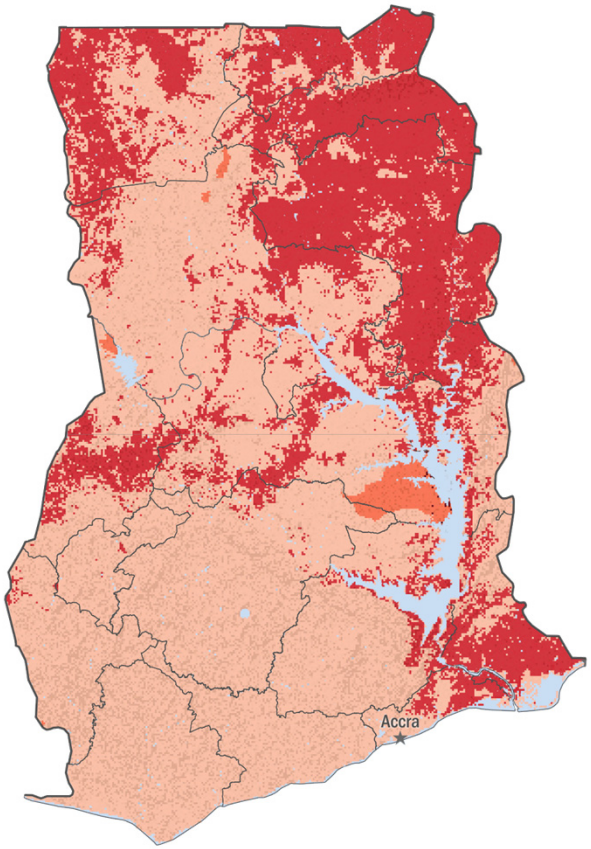
- Data shared with WHO is visible via the SIDP website.
- Report on 2020 cases from 14 countries published in the WHO WER journal.
- Future analyses will also be published to build better regional profile of epidemiology and burden of snakebites in Africa.
- Still time to submit 2020-2022 data to WHO.

https://snbdatainfo.who.int

Technical products to support countries

Goal: support participating countries to implement robust systems to support decision-making.

- Standardized tools to enhance epidemiological surveillance and measurement of the burden of disease and facilitate regional and national resource planning and priority setting.
- Antivenom forward needs forecasting tools to support the rational, evidence-based planning of future supply and distribution activities.
- Technical products to support the resourcing of health care facilities with a minimum package of health services, equipment, medicines, consumables, infrastructure and human resource capabilities to ensure adequate standards of care for patients throughout health systems.
- Standardized post-use product safety and efficacy evaluation tools.
- Tools for assessment of health care accessibility and identification of high-risk areas for contact with venomous snakes and estimation of burden at high resolution.
- Ongoing annual product reviews and random testing of product batch lots to ensure compliance with specifications and quality standards.

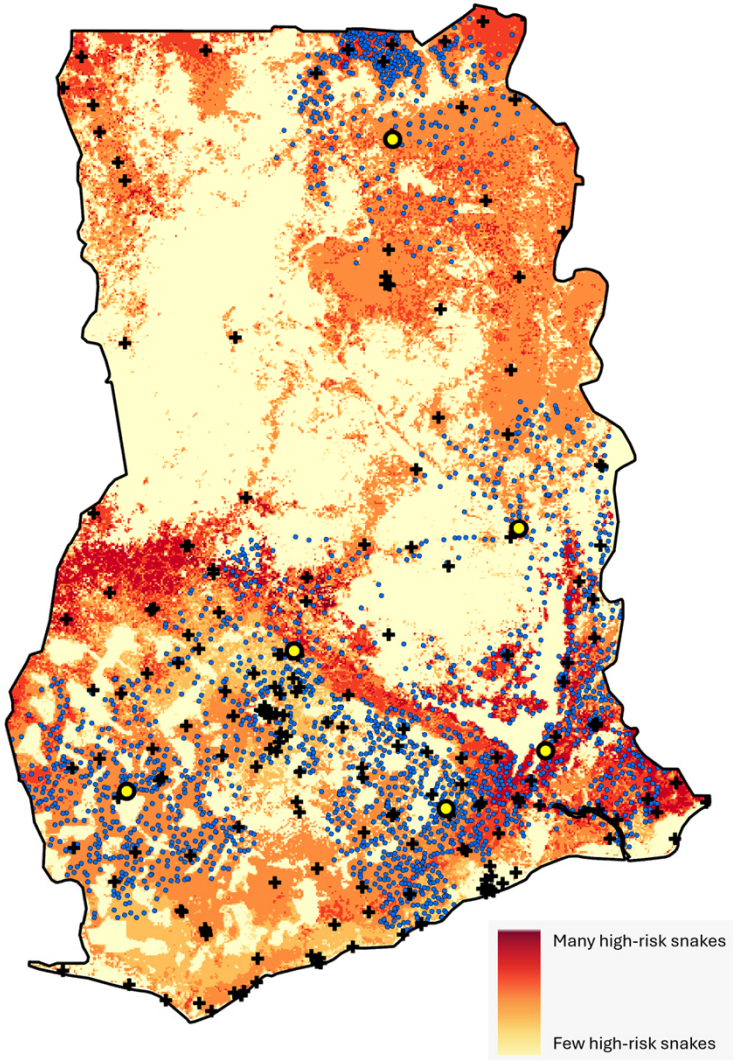


Human populations at risk of carpet viper envenoming

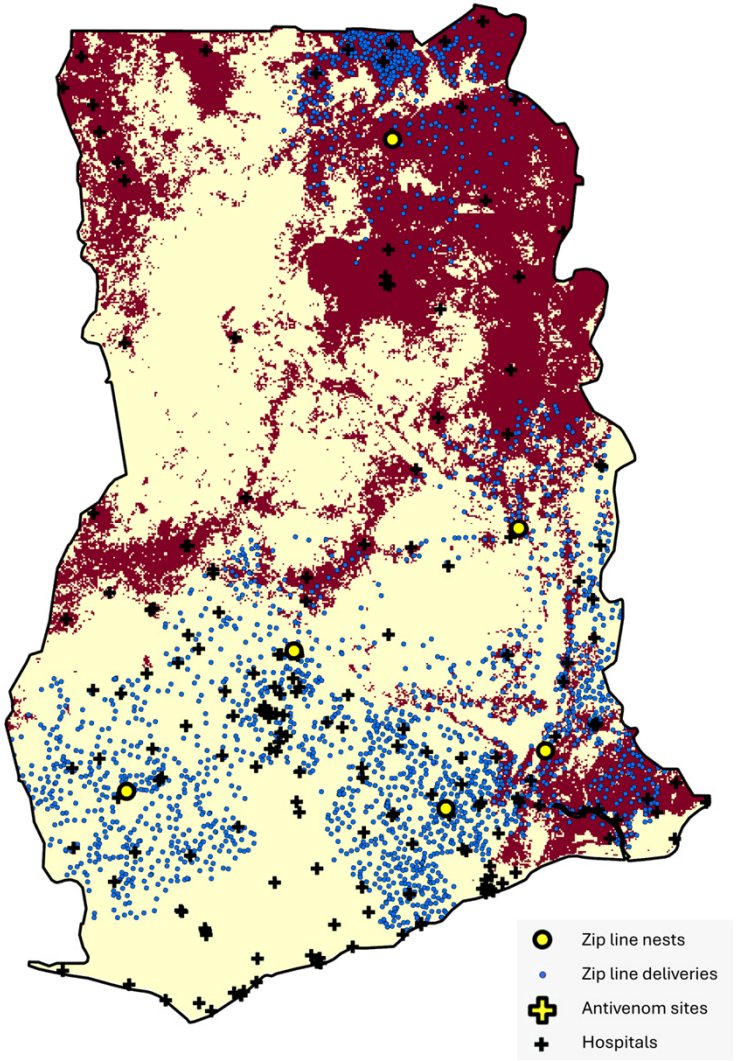
Map showing populations at risk of envenoming by *Echis* spp. who are either within or outside 6 hours of a health facility in Ghana.

- In the high-risk area, there are ~**4,245** people outside 6 hours of a health facility.
- In the high-risk area, there are ~**7,408,221** people within 6 hours of a health facility.
- In the low-risk area, there are ~**24,853** people outside 6 hours of a health facility.
- In the low-risk area, there are ~**22,994,002** people within 6 hours of a health facility.

Occurrence of all venomous snake species

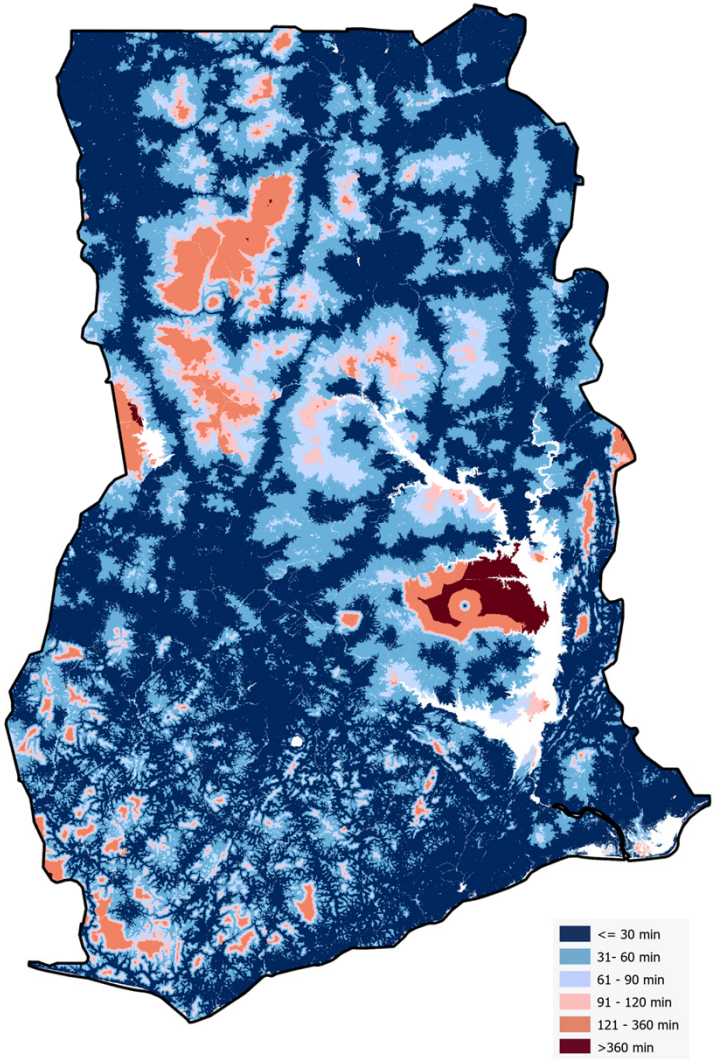


Occurrence of carpet viper species

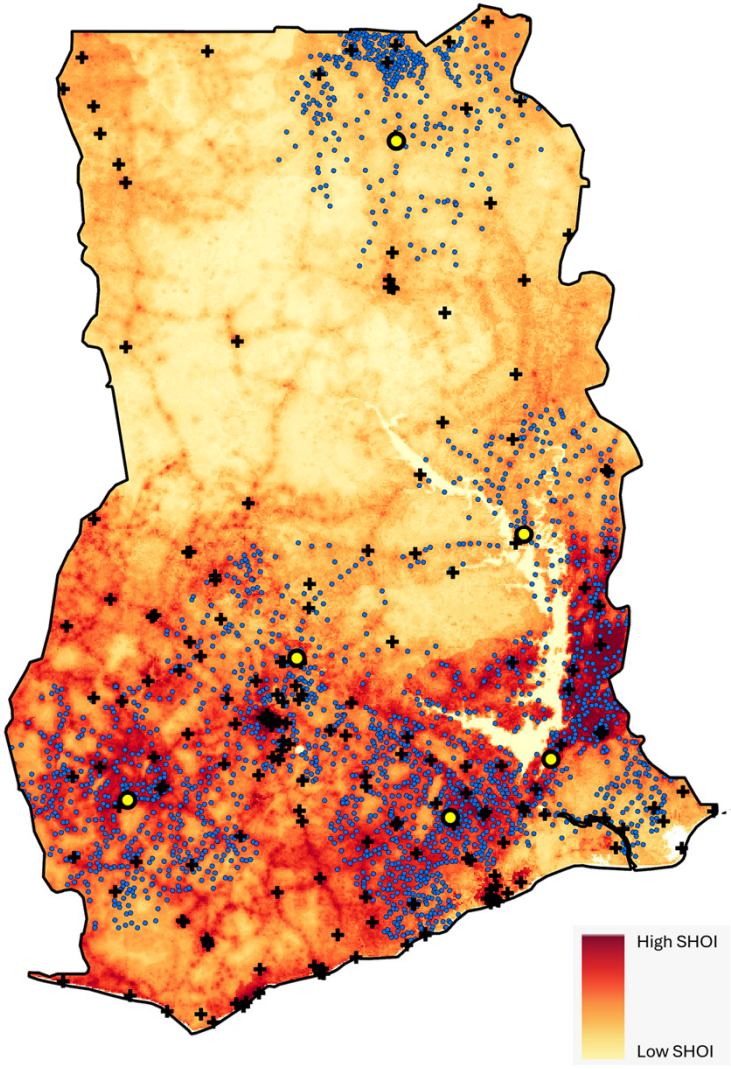


Modeling of snake species distributions against locations where antivenom is supplied, all hospitals, current drone delivery base stations, and health facilities serviced by drone delivery reveal opportunities of expanded access to antivenoms, and research into the benefits of novel supply logistics platforms versus conventional supply using both pull and push mechanisms. Where species richness is high, access to Pan African polyvalent antivenoms is essential.

Travel times to health care facilities



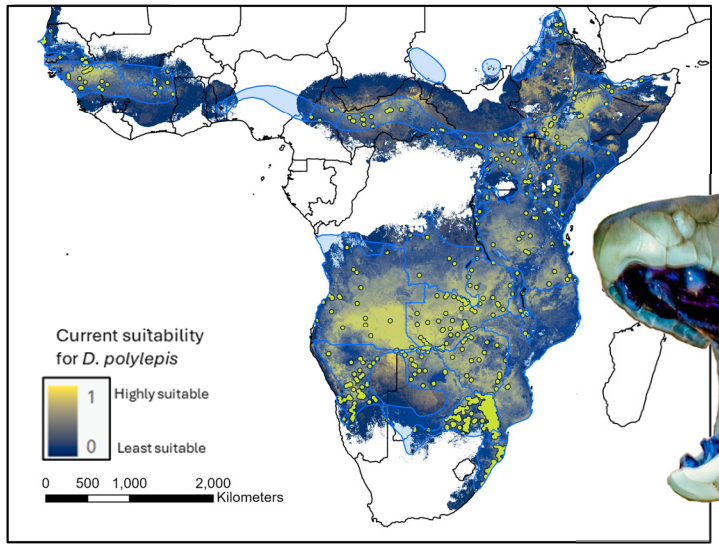
Snake-Human Exposure Index

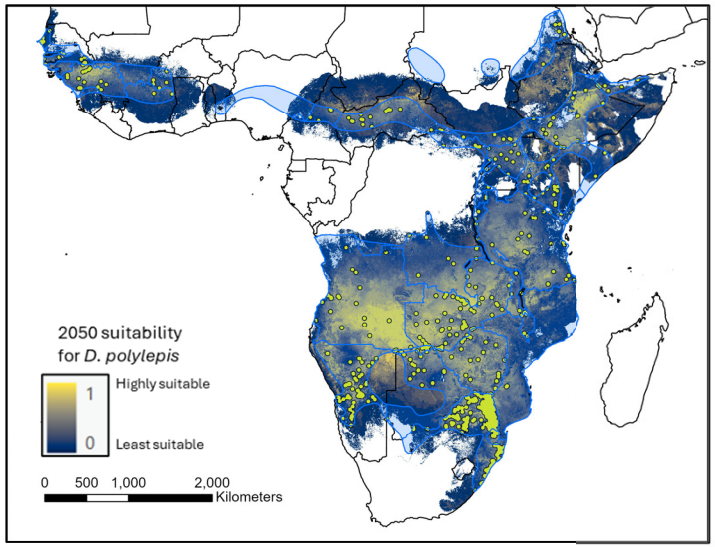


Decentralizing antivenom access can greatly reduce patient travel times to less than 2 hours across many areas of Ghana. Travel time analysis can also identify areas where delayed presentation for treatment is an additional risk factor for poor outcomes.

In parallel combining snake distribution data with human population and land use data makes it possible to establish a snake-human exposure index to assess relative risk of contact with venomous snakes. This supports identification of areas of high relative risk, where additional resources and capacity may be needed.

Understanding snake ranges and the impacts of climate change

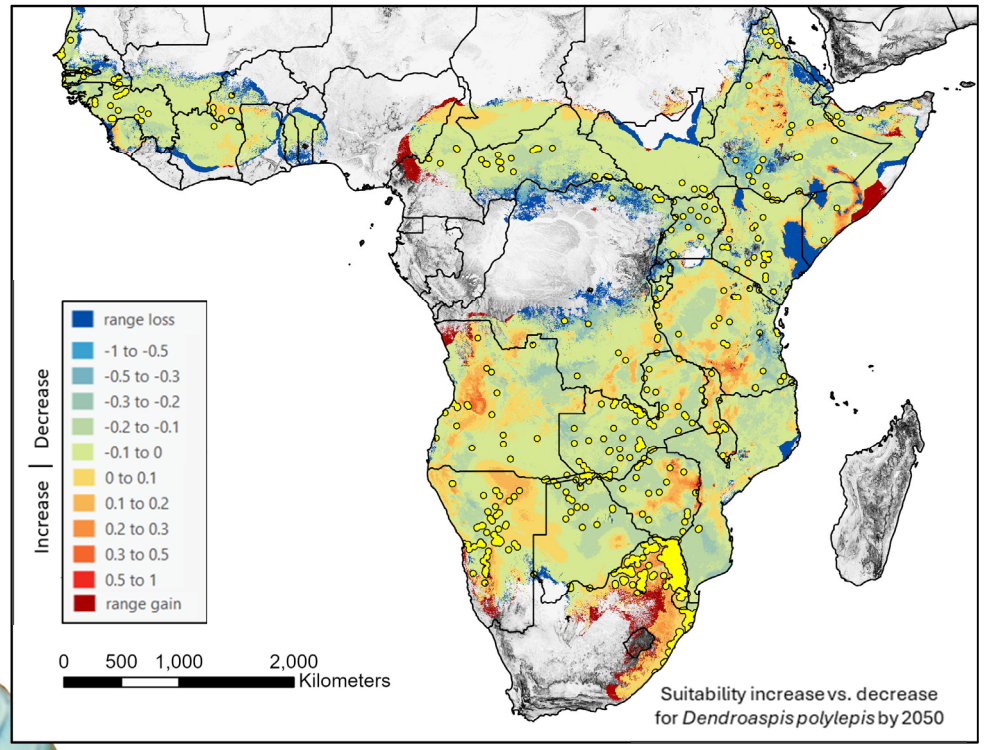




Changes in climate will impact the future range of venomous snakes and reduce risk of contact in some areas while increasing it in others.

This has important implications for future health care resource planning, particularly the distribution of treatments and community education

Habitat suitability data for all the world's medically important snakes is being analysed against human population and land use data to identify present and future hot spots.



Current (A) and future (B; 2050) habitat suitability and change in habitat suitability (C) for Black Mambas (*Dendroaspis polylepis*) across Africa.

Habitat suitability was modelled using MaxEnt software based on climate (minimum & maximum radiation, minimum humidity, minimum & maximum temperature, temperature & precipitation seasonality, precipitation of the driest & warmest quarter; WorldClim), mean and range of vegetation greenness (FAPAR; Copernicus), soil type (ISRIC), land use (ESA), and human population density (WorldPop) after selecting variables with >1% permutation importance from a candidate variable dataset. Future suitability shows the median across 7 global circulation models (CanESM5-CanOE (Canada); CMCC-ESM2 (Italy); EC-Earth3-Veg-LR (Europe); FIO-ESM-2-0 (China); INM-CM4-8 (Russia); INM-CM5-0 (Russia); MPI-ESM1-2-LR (Germany)). Change in suitability (C) shows the difference between A & B as well as predicted range expansions (dark red) and contractions (dark blue) on a background of topographic ruggedness.

Minimum health facility specifications, and procurement kits

Goal: provide countries with guidance on the minimum infrastructure, human resource and commodities requirements to manage snakebites, and access to essential commodities.

- To help countries better understand what is needed to be able to effectively treat snakebite envenoming WHO has engaged with experts from affected countries to develop a draft guidance document on minimum infrastructure, equipment, medicines and commodities requirements at different levels of health systems that admit snakebite patients, along with core health worker capabilities and training needs.
- Next step will be to map health facility capabilities to these criteria so that gaps and deficiencies, especially in high-risk areas are identified.
- In tandem we have worked with these and other experts to design two essential commodity procurement packs:
  - Package of essential consumables and ancillary drugs needed for the safe administration of antivenoms in rural health facilities and management of early adverse reactions.
  - Package of essential wound care for the treatment of snakebite-related necrotic wounds and other wounds such as Buruli ulcer.
- These packages would be added to the WHO Procurement Catalogue within the next year, so that countries can order and deploy them. Support from donors will be essential to enable an initial supply of these materials to be made available, with subsequent sustainable production secured by payments received from countries.

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