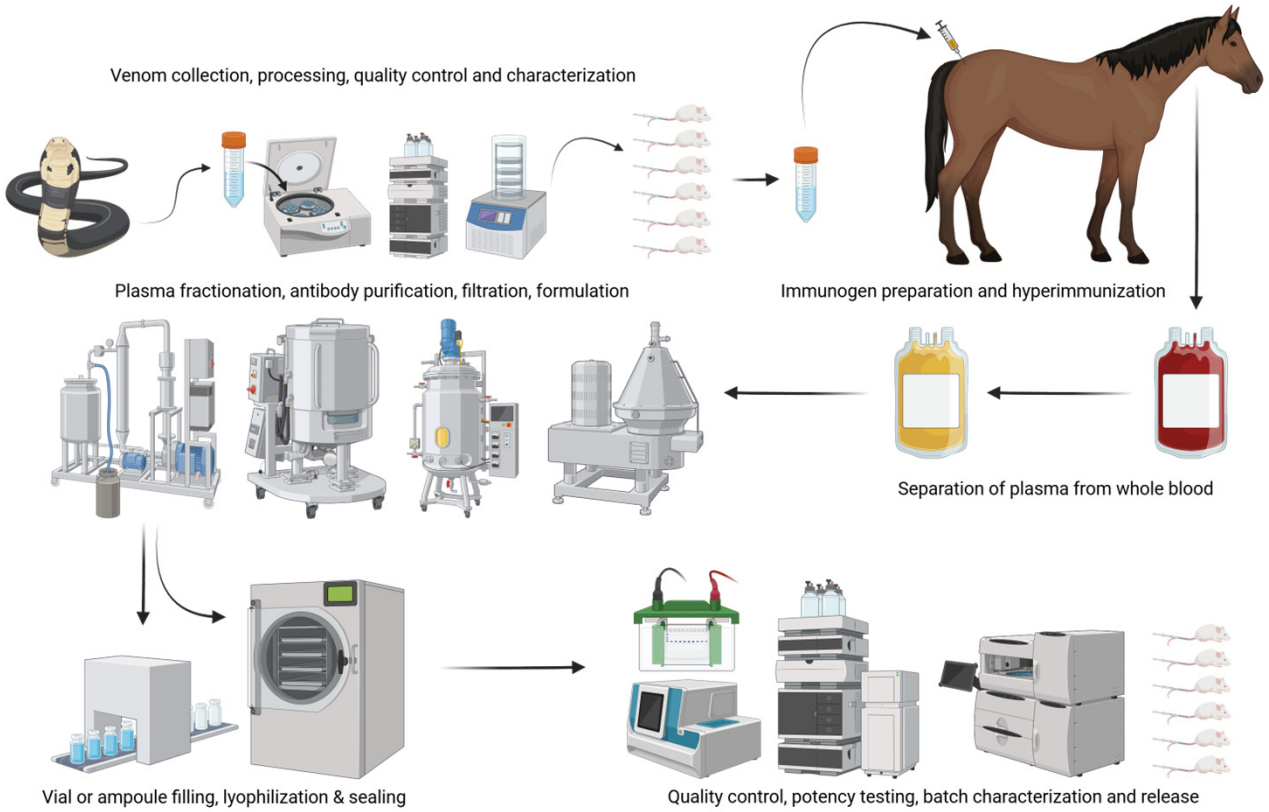
Overview and introduction:
WHO work on antivenoms

Dr David Williams
Scientist,
Vaccines & Immunization Devices, Prequalification Unit,
Regulation and Prequalification Department,
World Health Organization, Geneva, Switzerland

World Health Organization

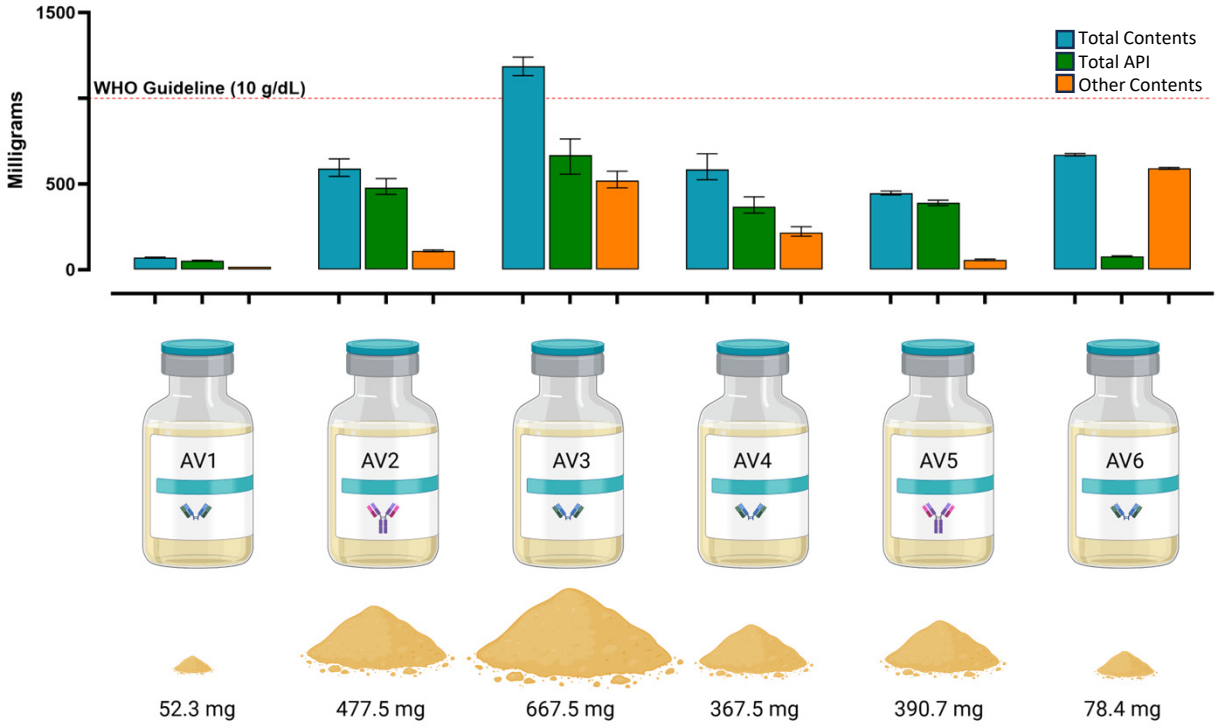
What is antivenom?

- 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

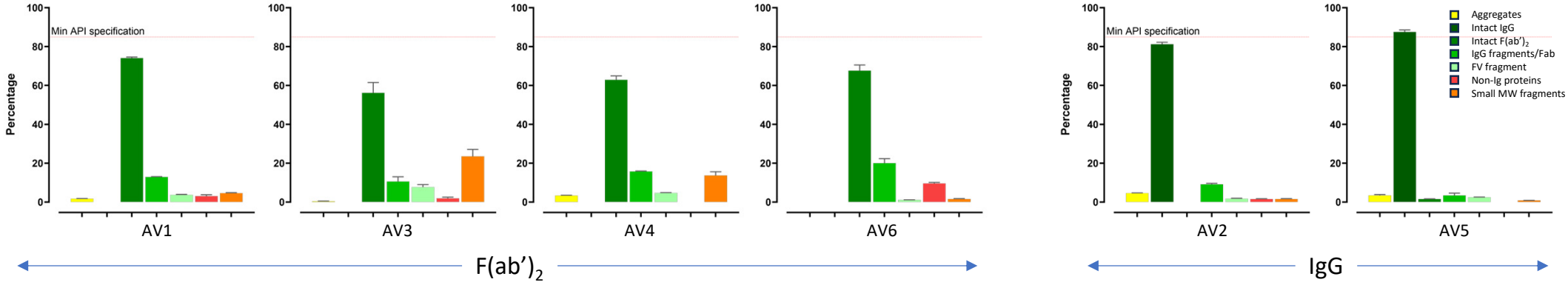
- There are substantial differences between different products, and even between different batch lots of the same product.
- Total protein, Active Pharmaceutical Ingredient (API), and other contents vary greatly between products, impacting efficacy and safety.
- The most important component is the API – 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

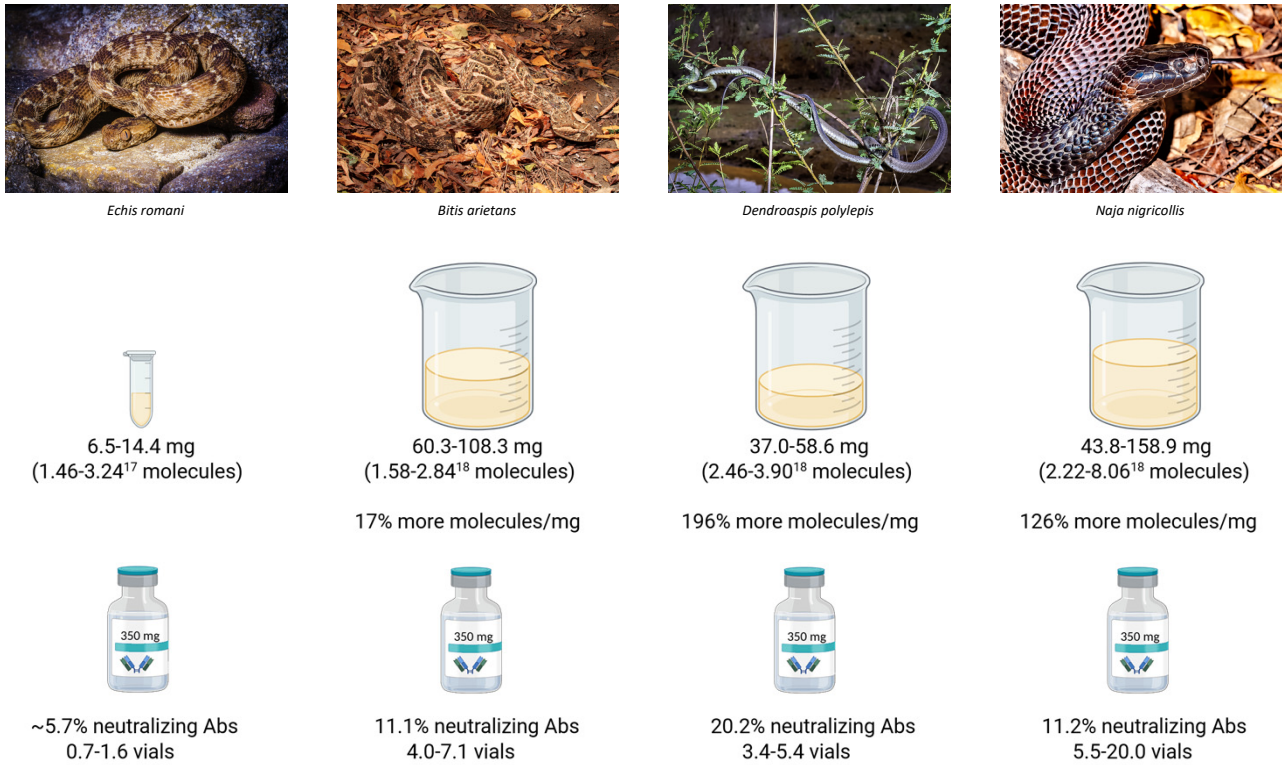
Not all antivenoms are the same

- 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.

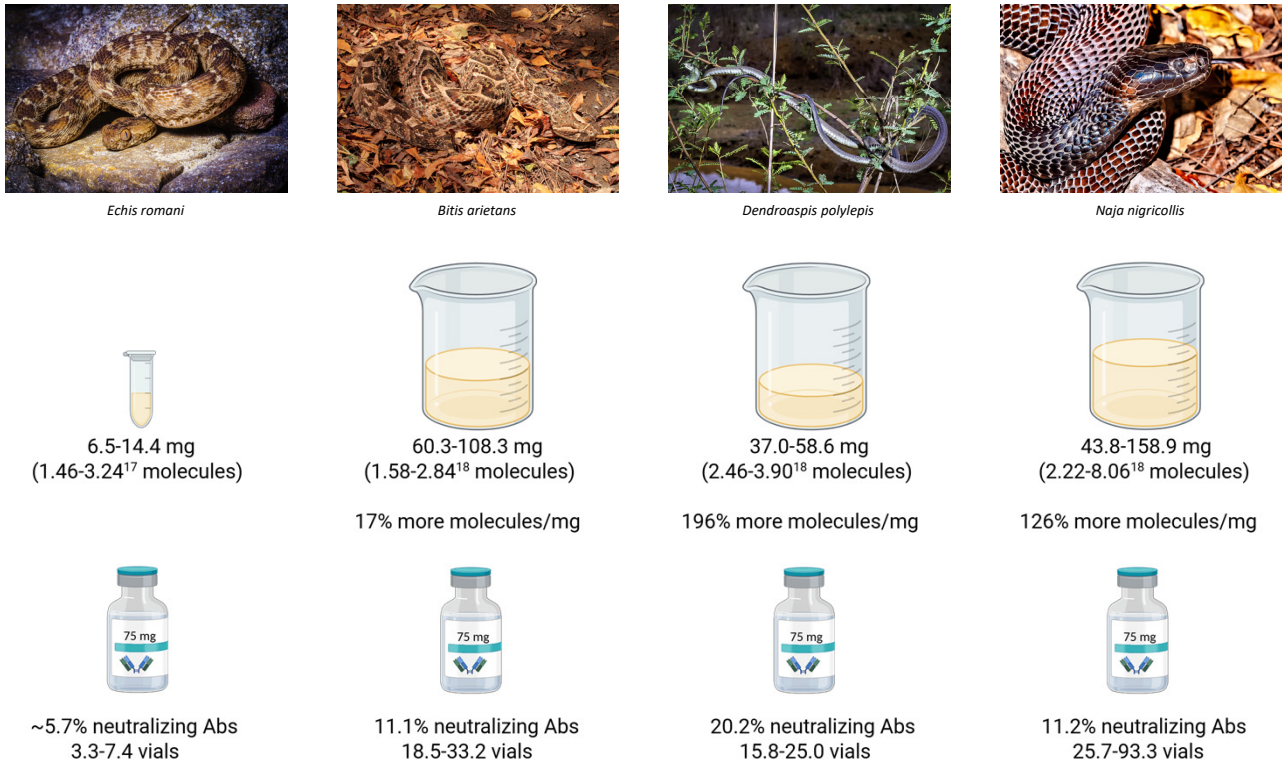


25-75 percentile interquartile range of venom yields following defensive strikes by *Echis romani*, *Bitis arietans*, *Dendroaspis polylepis*, and *Naja nigricollis* with approximate number of toxin molecules per yield. Compared to *Echis romani*, the number of molecules per milligram venom for *Bitis 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.

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.

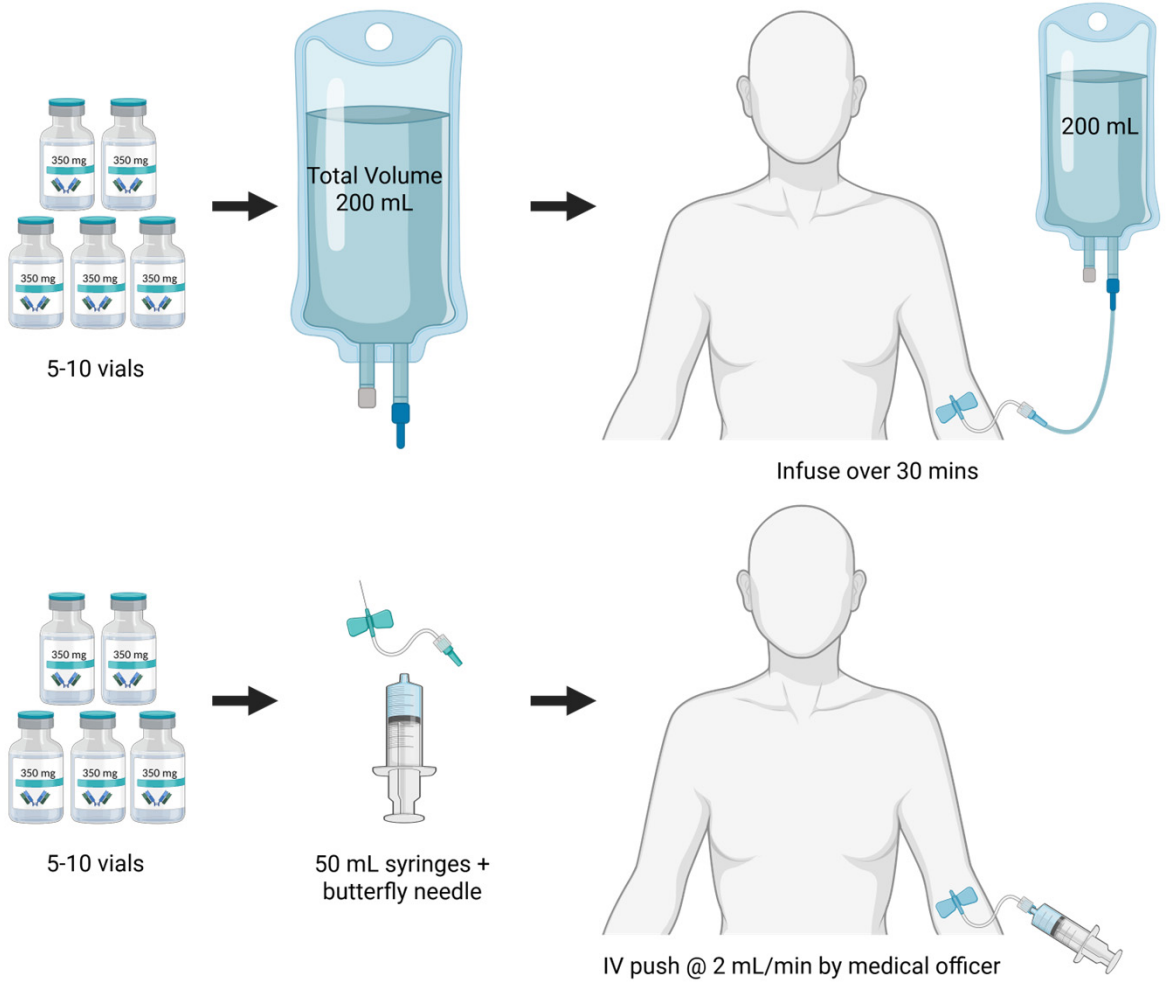


25-75 percentile interquartile range of venom yields following defensive strikes by *Echis romani*, *Bitis arietans*, *Dendroaspis polylepis*, and *Naja nigricollis* with approximate number of toxin molecules per yield. Compared to *Echis romani*, the number of molecules per milligram venom for *Bitis 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 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.

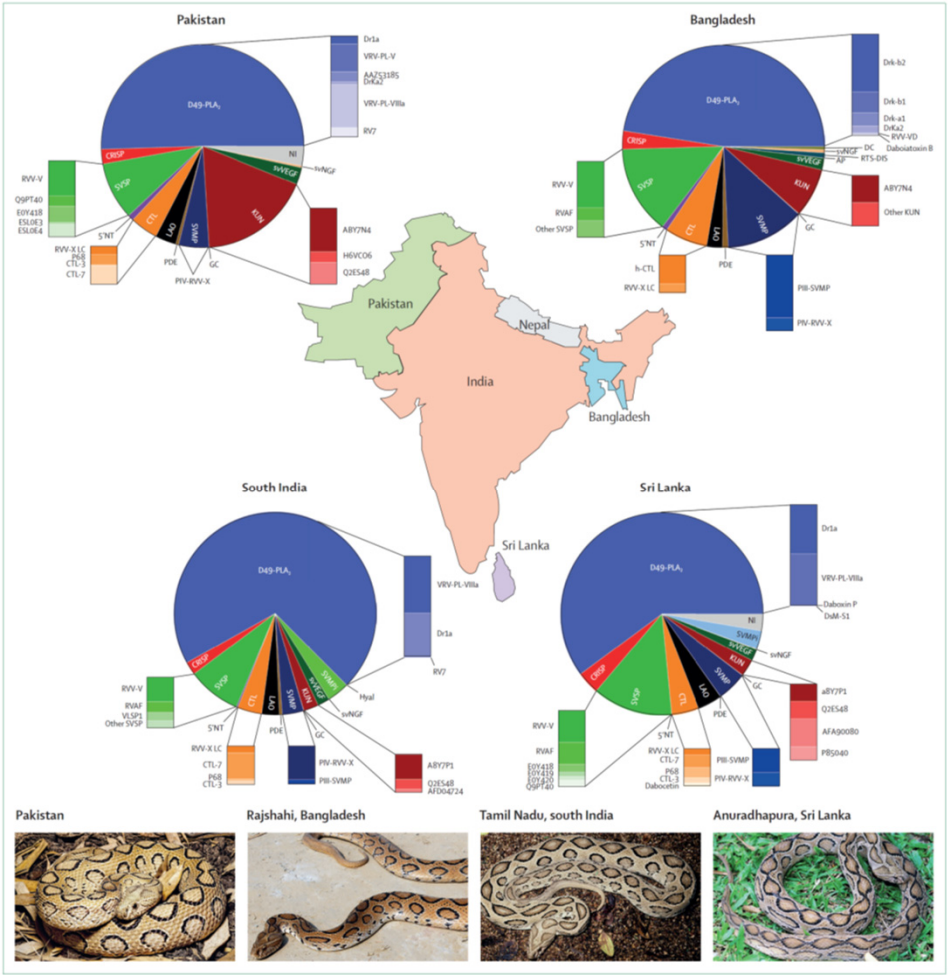
Administering antivenoms safely and effectively

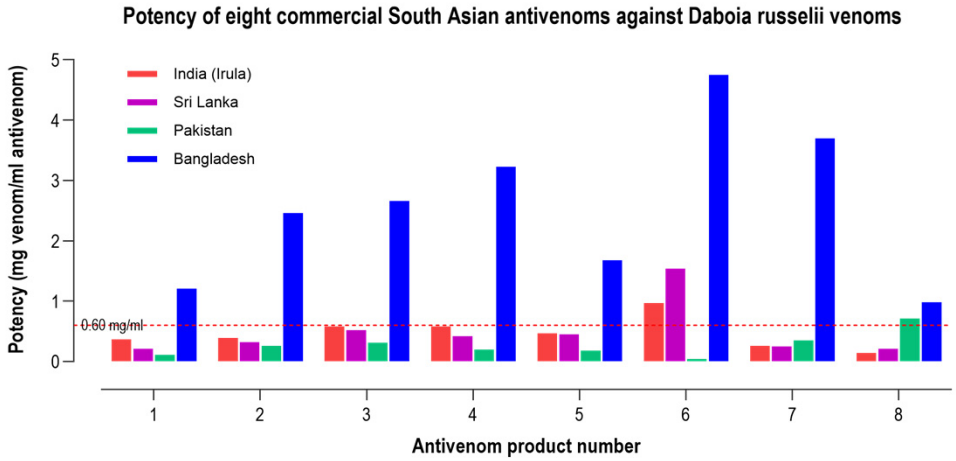
- Antivenoms need to be administered as soon as possible once signs of envenoming have been observed.
- They should be administered either as an intravenous infusion, or by intravenous push using a suitable needle and syringe.
- Guidelines on the use of premedication with subcutaneous adrenaline (0.25 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





- Venom variation is a critical issue in the design of antivenoms, due to the impact that it may have on efficacy.
- Only one antivenom tested by WHO met minimum specifications (min. 0.60 mg/ml) for potency against *Daboia rus*selii venoms from India and Sri Lanka.
- Only one antivenom met the same specification against Pakistani *Daboia russelii* venom.
- All eight antivenoms exceeded the minimum specifications against *Daboia russelii* venom from Bangladesh.
- Toxin-specific antivenomic data is being used to understand the reasons for these discrepancies. All but two antivenoms (6 & 8) are raised using venom sourced from the Irula Snake Catchers Industrial Cooperative Society.

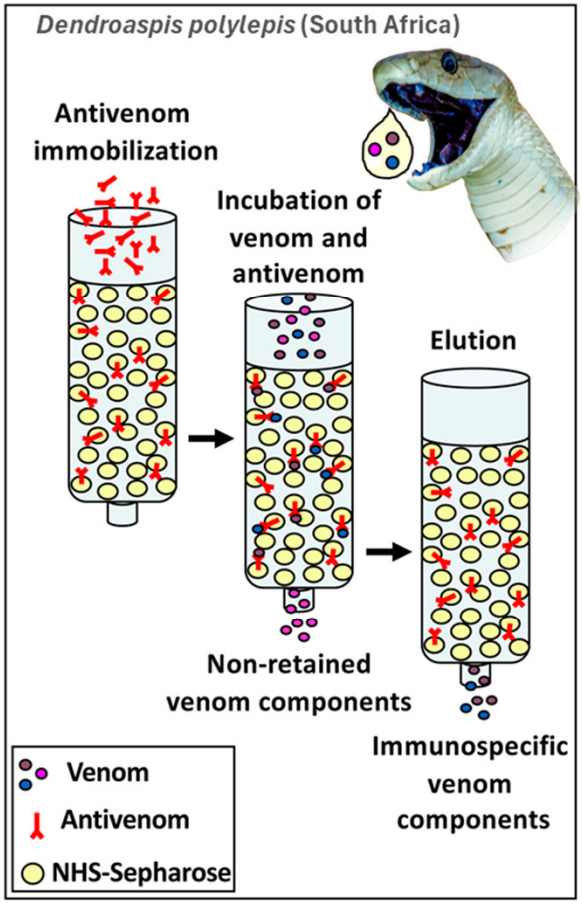
Venom yield, like potency, is critical to the design of effective antivenoms

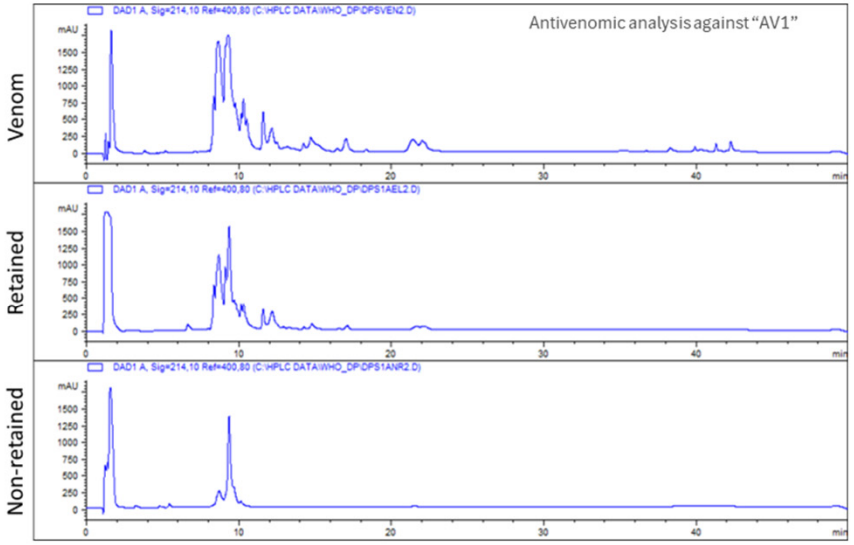
Species	Conventional Manual Venom Extractions		Simulated Defensive Snakebites (single strikes)	
	Median [mg]	*IQR (Maximum) [mg]*	*Median [mg]*	*IQR [mg]*
Bitis arietans	89.9	64.5-149.9 (310.0)	84.4	60.3-108.3
Echis ocellatus	10.1	6.5-13.7 (14.4)	8.14	6.5-14.4
Dendroaspis polylepis	74.4	57.5-94.6 (338.2)	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.

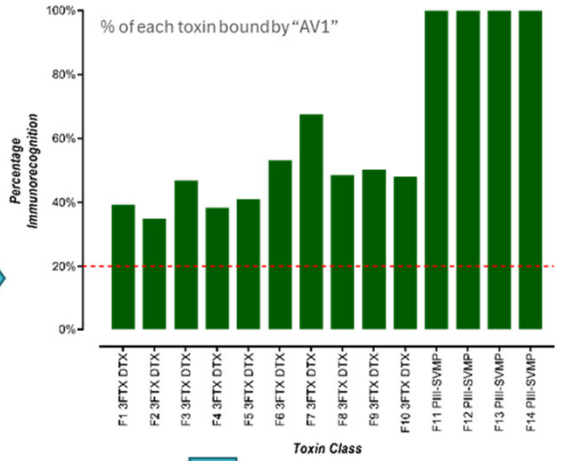
- For antivenom to be effective it must be administered in a dose that provides sufficient neutralizing antibodies to counter the clinical effects of the mass of injected venom.
- Different species produce different quantities of venom, and each snake has control over how much venom it injected under 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.

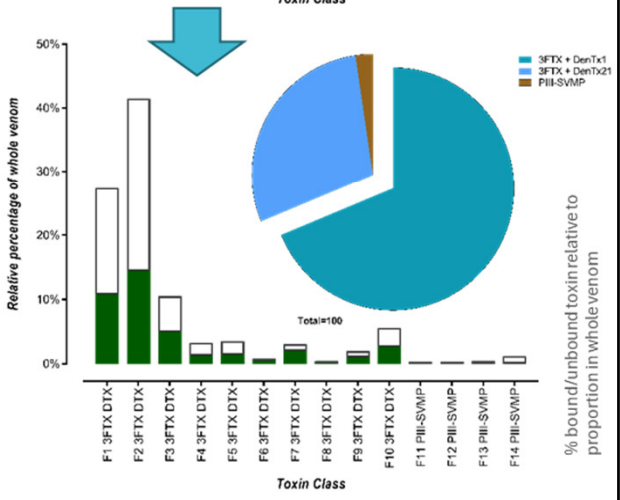
Third-generation antivenomic evaluation of venom: antivenom interactions





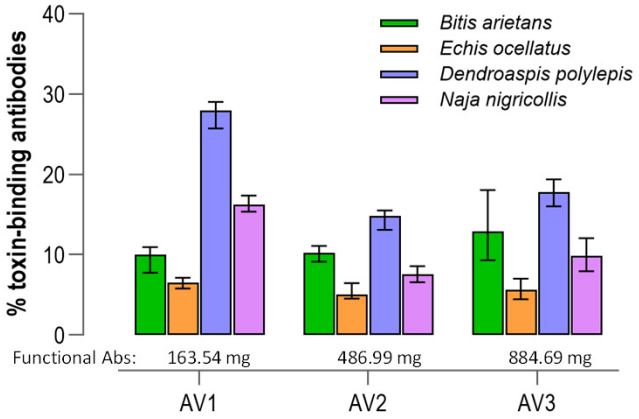
Description	Median (IQR)	Maximum
Toxin Immunorecognition (µg V/mg AV)	26.93 (22.40-30.59)	33.58
Bound by Intact F(ab')$_2$ (mg V/vial)	**1.41 (1.17-1.60)**	**1.76**
% Toxin-binding intact F(ab')$_2$	*21.89% (18.68-24.31%)*	*26.18%*
Toxin binding F(ab')$_2$ (mg intact F(ab')$_2$/vial)	*11.45 (9.77-12.71)*	*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*

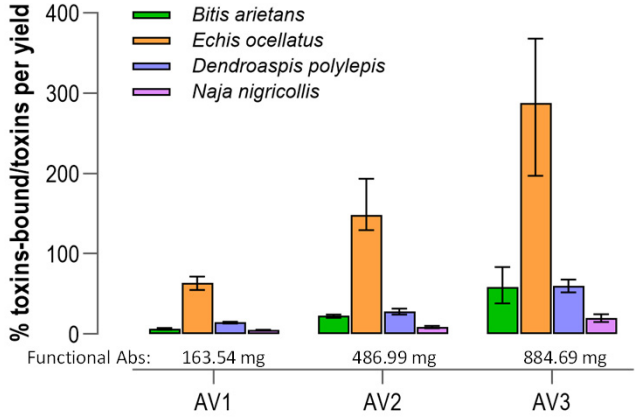




What can this data tell us about the quality and specificity of antivenoms

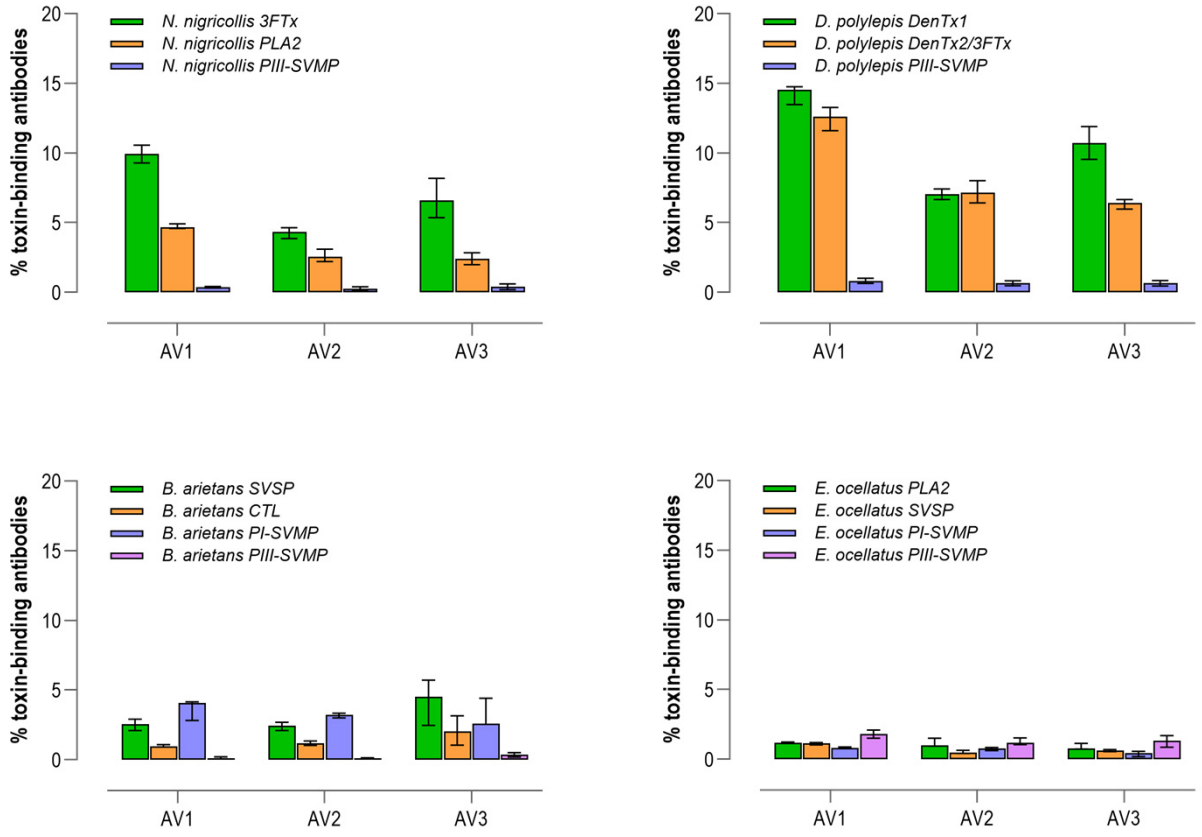
- By analyzing data, it possible to determine how much of each toxin present in any venom is immunorecognized and bound by the available antibodies.
- This in turn indicates:
  - Percentage of antibodies present that bind to specific snake venoms and can potentially contribute towards their neutralization.
  - 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.





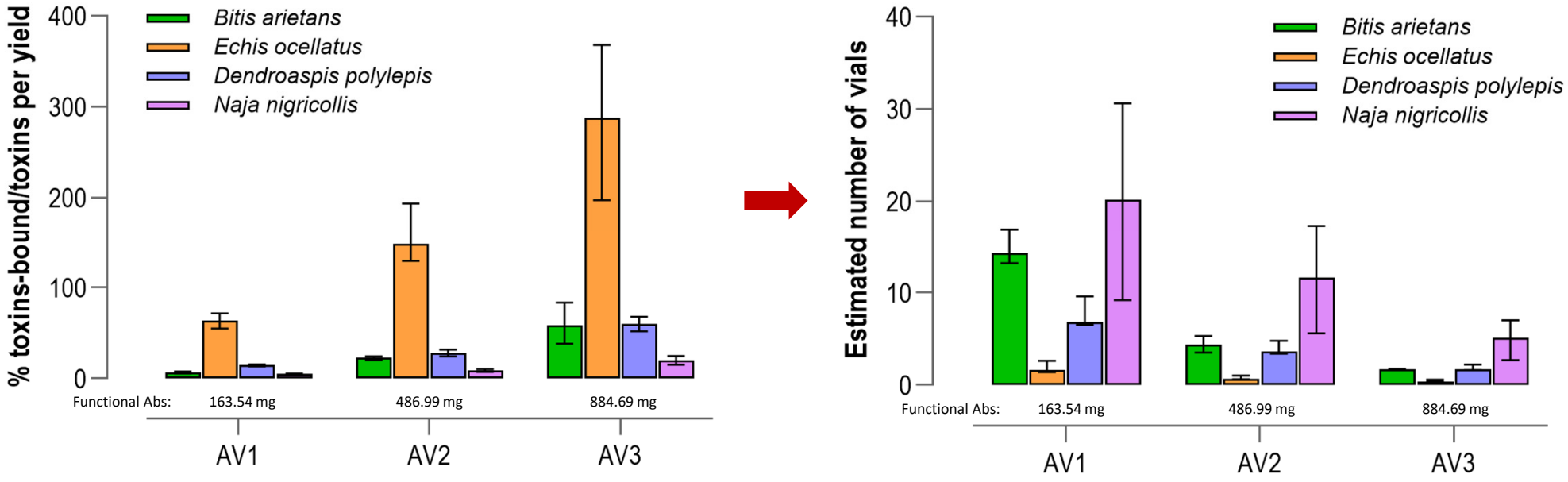
Immunogenicity of different types of toxins

- 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

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

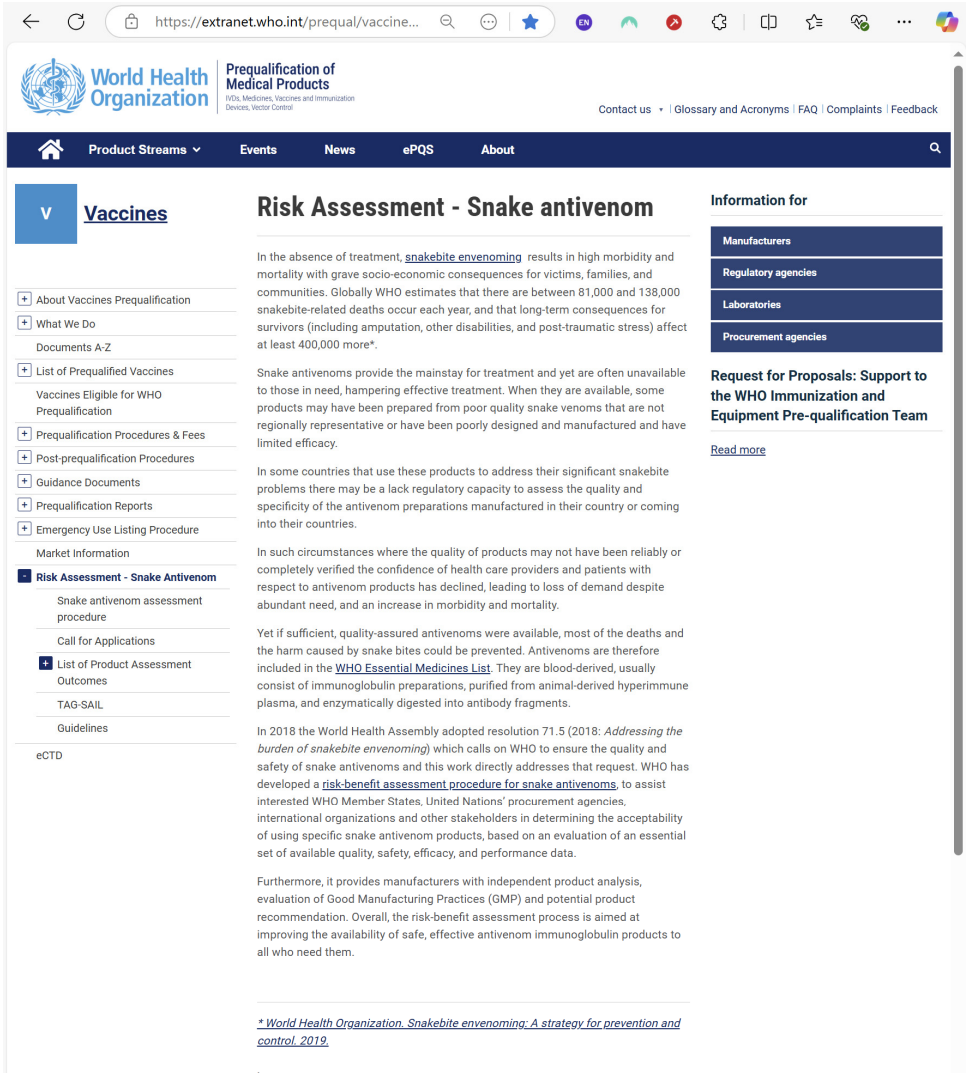
WHO inspectors visit each of the manufacturing sites and conduct a comprehensive GMP assessment of all activities, including snake venom and hyperimmune plasma production, and small animal use.

Product Listing

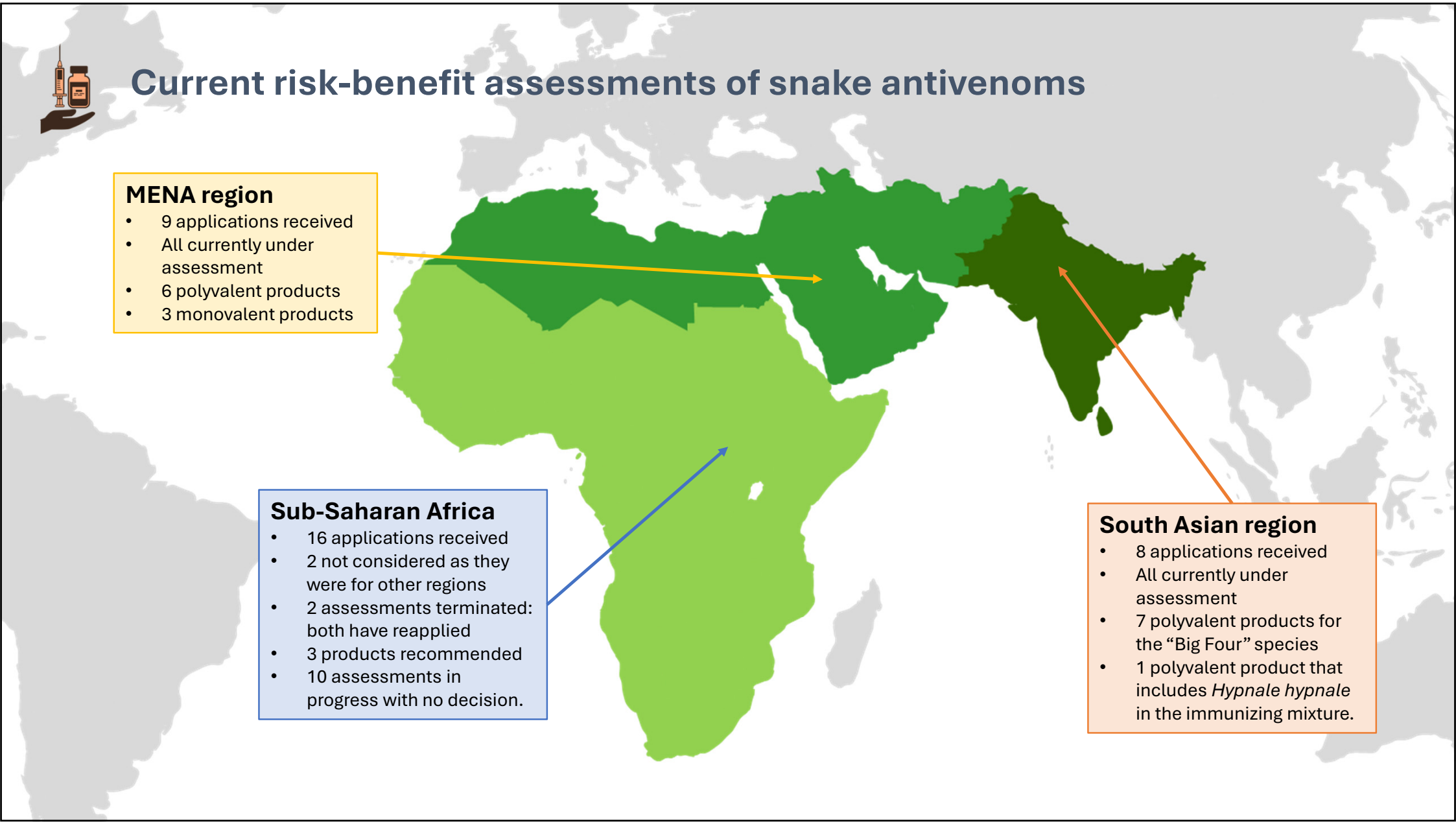
Products with an overall positive risk-benefit ratio may be recommended for procurement for specific use cases. Comprehensive reports are provided to manufacturers and public summary reports published.

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.


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

Antivenoms under risk-benefit assessment for South Asian “Big 4”

Product	Manufacturer	Country of Origin
Snake Venom Antiserum (Lyophilised)	Bharat Serums & Vaccines	India
Snake Antivenin (Polyvalent) I.P. (Liquid), 10 mL Vial Presentation	Biological E Limited	India
Snake Antivenin (Polyvalent) I.P. (Lyophilised), Combipack with 10 mL Sterile Water for Injection (Ampoule)	Biological E Limited	India
Snake Antivenin I.P.	Haffkine Bio-Pharmaceutical Corporation	India
Polyvalent Antivenom Immunoglobulins (Liquid Purified)	National Institutes of Health	Pakistan
Combipack of Snake Venom Antiserum with Sterile Water for Injection	Premium Serums and Vaccines Pvt Ltd.	India
Combipack of Snake Venom Antiserum with Sterile Water for Injection – Sri Lanka	Premium Serums and Vaccines Pvt Ltd.	India
Snake Venom Antiserum I.P.	VINS Bioproducts Limited	India

Antivenoms under risk-benefit assessment for MENA region

Product	Manufacturer	Country of Origin
Snake Venom Antiserum Polyvalent Liquid	Vacsera / Egyvac	Egypt
NORAF™ Premium	Premium Vaccines & Serums	India
SnaFAB5	Padra Serum Alborz	Iran
SnaFAB6	Padra Serum Alborz	Iran
Hexavalent Snake Antivenom Immunoglobulin (Equine)	Razi Vaccine & Serum Research Institute	Iran
Snake Venom Antitoxin I.H.S., Lyophilised (Biosnake)	VINS Bioproducts Limited	India
Echis coloratus Antiserum (Equine source)	Kamada Limited	Israel
Vipera palaestinae Antiserum (Equine source)	Kamada Limited	Israel
EchiTAbG™	MicroPharm Limited	United Kingdom

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

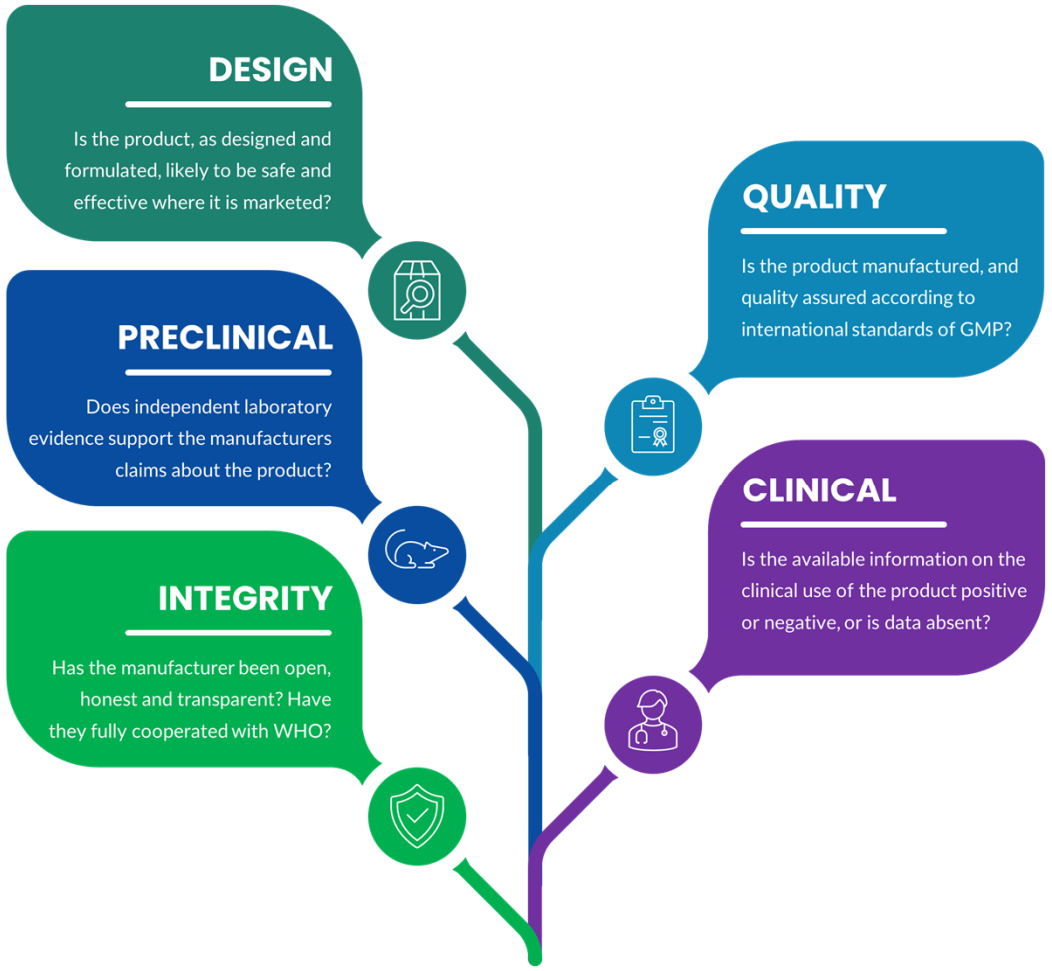
ASSESSMENT IN PROGRESS

- 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.*

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 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

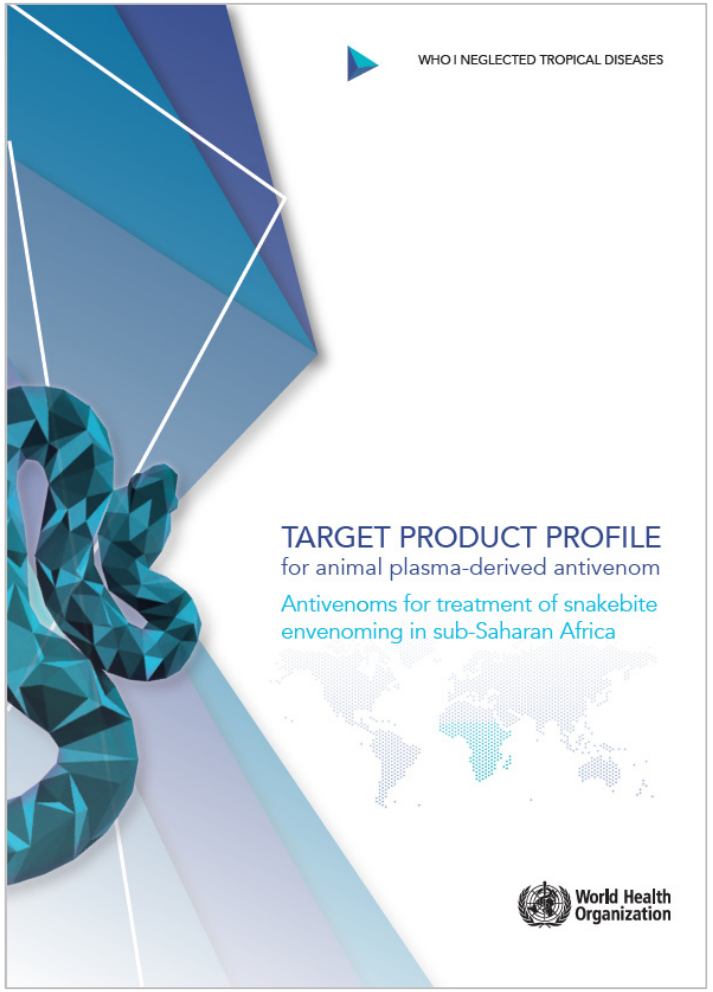
Polyvalent antivenoms intended for use in the treatment of snakebite envenoming by Bungarus caeruleus, Daboia russelii, Echis carinatus and Naja naja in Pakistan, India, Nepal, Bangladesh, Bhutan, or Sri Lanka

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



TPP features

Areas covered	Examples
Scope	Target populations, geographic working ranges, indications for use, contraindications, level of implementation in health systems, intended end users
Manufacturing Considerations	Immunizing venoms, active pharmaceutical ingredient (API), finished product form, specific immunoglobulin content, total protein content
Performance	Preclinical efficacy, clinical effectiveness, safety and tolerability, drug interactions, dose regimen, frequency of administration, route of administration, product stability, storage, presentation, packaging
Operational Characteristics	Costs, supportive and adjunctive therapy, training and education needs

Immunizing venoms and active pharmaceutical ingredients (APIs)

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
5. Immunizing venoms	In addition to minimal requirements, immunizing venoms should meet the specifications of corresponding WHO reference venoms[3] for each species of snake included in the immunizing mixture for the product.	Immunizing venoms should be selected based on a detailed analysis of the composition of venoms from specimens across the geographic range of each species, to ensure that all medically important toxin groups are represented in the immunizing venom pool for the product. Pooled venoms should be designed to have minimal compositional overlap and broad geographic representation of venom variants.
6. Active Pharmaceutical Ingredient (API)	Intact (whole) IgG immunoglobulin molecules obtained through appropriate technology	Either intact (whole) IgG immunoglobulin molecules or $F(ab')_2$ immunoglobulin molecule fragments obtained through appropriate technology.

*There was no significant difference (P = 0.51) in the incidence of early adverse reactions to antivenom administration (28.9% for patients of group A [**F(ab')$_2$**] and 20.6% for patients of group B) [**IgG**], most of the reactions being mild, mainly cutaneous.*

Otero-Patiño et al. Comparative study of the efficacy and safety of two polyvalent, caprylic acid fractionated [IgG and F(ab')2] antivenoms, in Bothrops asper bites in Colombia **doi: 10.1016/j.toxicon.2011.11.017**. Epub 2011 Nov 29.

Caprylic acid fractionation allows the production of antivenoms of relatively high purity and with a low protein aggregate content, because the immunoglobulins are not precipitated during the process. The yield may reach up to 60–75% of the activity in the starting plasma, depending upon the particular procedure and/or the equipment used. The effectiveness and safety profiles of caprylic acid-fractionated antivenom immunoglobulins have been demonstrated in clinical trials (89, 93, 94).

WHO Guidelines for the Production, Regulation and Control of Snake Antivenom Immunoglobulins, TRS 1004, Annex 5, 2017.

New product types defined: broad-spectrum polyvalent antivenoms

TPPs for animal plasma-derived antivenoms: Antivenoms for treatment of snakebite envenoming in south Asia

Broad-spectrum south Asian polyvalent antivenoms

Products that are intended for all the major genera of WHO Category 1 medically important venomous snakes throughout south Asia.

Venoms should be representative of each of the WHO Category 1 genera. Minimally this would involve the use of venoms from *Bungarus caeruleus, Daboia russelii, Echis carinatus* and *Naja naja* (e.g.: proposed WHO reference standard venoms), but optimally it should include additional species of Category 1 medical importance for which current polyvalent antivenoms do not provide effective neutralization.

Examples of additional Category 1 species that could be used:

- *Bungarus: B. niger, B. sindanus, B. walli*
- *Echis: E. c. sochureki*
- *Hypnale: H. hypnale*
- *Macrovipera: M. lebetina*
- *Naja: Naja kaouthia, Naja oxiana*
- *Trimeresurus: T. erythurus, T. septentrionalis*

Other combinations, or additional venoms, including those from Category 2 (e.g., *B. ceylonicus, B. lividus, Ophiophagus hannah, T. malabaricus, T. septentrionalis*) could be used by a manufacturer at their discretion. The goal should be to select venoms from species that will induce the broadest possible immune response in plasma donor animals, resulting in polyvalent antivenom with the ability to neutralize as wide a range of venoms across as large a geographical area as possible. Venoms used should be a pool from across the geographic range of each species, including male and female juveniles, sub-adults, and adults. Venom from each individual geographic population should be characterized and selected to ensure that the broad range of intraspecific variation likely in that species is incorporated into the final immunizing venom pool.


Photo: Vishal Santra


Photo: Wolfgang Wüster

New product types defined: monovalent antivenoms

TPPs for animal plasma-derived antivenoms: Antivenoms for treatment of snakebite envenoming in south Asia

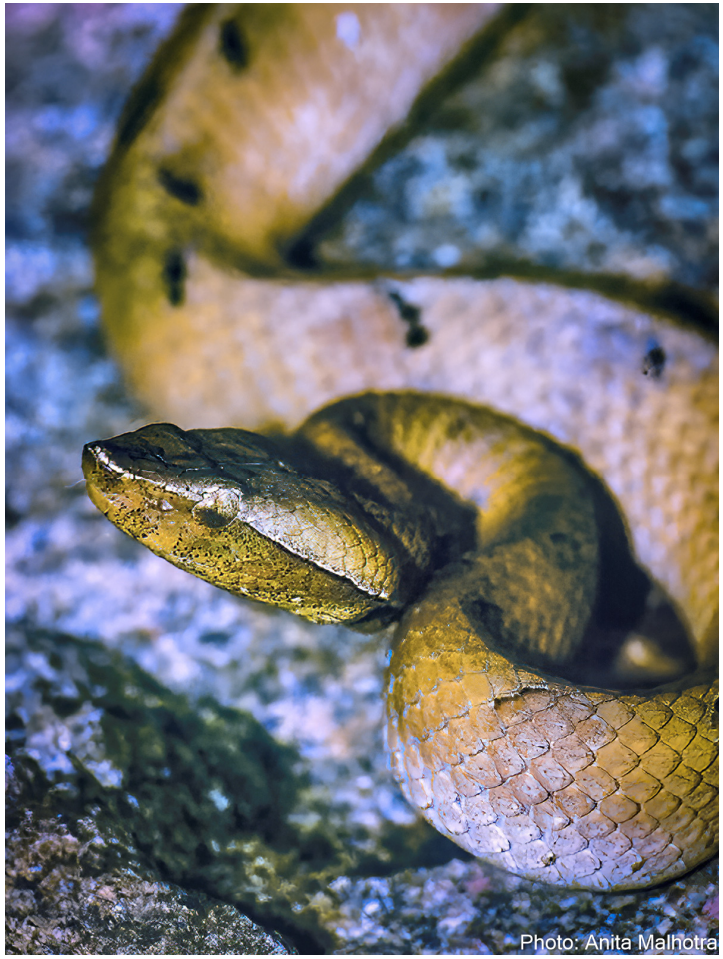
South Asian monovalent antivenoms

Products that are intended for either a single widespread species, a single genus, or species that are important causes of snakebite envenoming in a defined area.

Examples of species for which new monovalent antivenoms might be raised:

- Species specific: *Ophiophagus hannah* – rare presentation
- Genus specific: "green" pit vipers from the genera *Trimeresurus/Craspedocephalus*, other genera of vipers such as *Hypnale* or *Protobothrops*
- Locally important species: *Gloydius himalayanus* or *Ovophis monticola* in Nepal and north-west India, *Echis c. sochureki* in Rajasthan

Venoms should be representative of geographical range of the Category 1 or 2 species or genus against which the product is being raised.



New product types defined: syndromic polyvalent antivenoms

South Asian polyvalent antivenoms for neurotoxic envenoming

Products that are intended for use in treating snakebites that produce clinical syndromes defined by the presence of neurotoxic signs and symptoms.

Venoms should be representative of each of the WHO Category 1 or 2 genera that have neurotoxicity as the dominant action of the venom. Minimally this would involve the use of venoms from species in the genus *Bungarus* and *Naja* but might also include *Ophiophagus hannah*.

Examples of species that could be used:

- *Bungarus: B. caeruleus, B. ceylonicus, B. fasciatus, B. lividus, B. niger, B. sindanus, B. walli*
- *Naja: N. kaouthia, N. naja, N. oxiana, N. sagittifera*
- *Ophiophagus: O. hannah*

TPPs for animal plasma-derived antivenoms: Antivenoms for treatment of snakebite envenoming in south Asia

South Asian polyvalent antivenoms for non-neurotoxic envenoming

Products that are intended for use in treating snakebites that produce clinical syndromes defined by the presence of haemorrhagic, cytotoxic or procoagulant signs and symptoms, and the absence of any signs or symptoms of neurotoxicity.

Venoms should be representative of each of the WHO Category 1 or 2 genera that lack neurotoxic activity and instead have haemotoxicity or cytotoxicity as the dominant actions of their venoms. Minimally this would involve the use of *Daboia russelii*, *Echis carinatus* and *Hypnale hypnale* venoms. Optimally it might also include *Macrovipera lebetina* and one or more *Trimeresurus/Craspedocephalus* or other viper venoms.

Examples of species that could be used (both regional and local species):

- *Daboia: D. russelii*
- *Echis: E. carinatus*
- *Eristicophis: E. macmahonii*
- *Gloydius: G. halys, G. himalayanuss*
- *Hypnale: H. hypnale, H. nepa, H. zara*
- *Macrovipera: M. lebetina*
- *Protobothrops: P. jerdonii, P. mucrosquamatus*
- *Trimeresurus/Craspedocephalus: C. gramineus, C. malabaricus, C. trigonocephalus, T. erythrurus, T. tibetanus, T. salazar, T. septentrionalis*

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.