

TARGET PRODUCT PROFILES (TPPs) FOR ANIMAL PLASMA-DERIVED ANTIVENOMS FOR TREATMENT OF SNAKEBITE ENVENOMING IN SUB-SAHARAN AFRICA

Overview

Snakebites are responsible for considerable mortality and morbidity throughout much of the world. The World Health Organisation (WHO) has convened a Technical and Scientific Advisory Group to generate public-sector Target Product Profiles (TPPs) for treatment of snakebite envenoming. With support from the Drugs for Neglected Disease Initiative (DNDi) the overall goal of this program is to ensure access to safe, effective, affordable, and accessible treatments for all patients in need.

Heterologous animal plasma-derived immunoglobulin preparations (“antivenoms”) have been the mainstay of treatment for snakebite envenoming for nearly 130 years¹ and are the most effective drugs currently available for treatment of snakebite envenoming. They are most commonly produced by immunising donor animals such as horses or sheep with small amounts of snake venoms and then purifying antibody fractions from the hyperimmune plasma for intravenous administration to snakebite envenoming victims. The quality, safety, and effectiveness of antivenoms is highly dependent upon the investment of producers in research and development, application of Good Manufacturing Practices (GMP) and rigorous quality control.

This first set of four TPPs focuses on animal plasma-derived antivenoms for sub-Saharan Africa. They provide guidance on conventional broad-spectrum Pan-African polyvalent antivenoms (*Bitis*, *Dendroaspis*, *Echis*, *Naja*), monovalent products (*Dispholidus typus*, *Echis romani*/*E. ocellatus*), and two important new product classes; Pan-African polyvalent antivenoms for treatment of envenoming dominated by neurotoxic effects., and Pan-African polyvalent antivenoms for treatment of envenoming dominated by procoagulant, haemorrhagic or cytotoxic effects.

At present there are no direct acting small-molecule or non-plasma-derived biological therapies approved for snakebite treatment, but some are in early stages of development. Specific TPPs for these products will be developed by WHO in 2022 but it may be several years before any are successfully commercialized and available for use.

Unmet Medical Need/Problem

WHO estimates that 5.4 million people worldwide are bitten each year, with 2.7 million envenomings. Snakebites are responsible for some 83,000-138,000 deaths per annum². An additional 400,000 people per year suffer from disabilities such as amputations, scarring leading to impaired limb function and post-traumatic stress disorder. In sub-Saharan Africa the number of snakebite cases is estimated to reach 435,000-500,000 per year with 20,000-32,000 deaths³. Victims are from some of the least-empowered, poorest, and most-marginalised communities; often agricultural workers, rural villagers, working children; in poorly constructed housing with very limited access to education and health care.

WHO has identified access to safe, effective, affordable, and accessible antivenoms as a key priority for addressing snakebite morbidity and mortality. Defining TPPs for antivenoms in this market is an essential early step towards improving the current manufacturing environment. It will help to end a vicious cycle dominated by poorly designed, ineffective, and weakly regulated products, and provide regulators, manufacturers, procurement agencies and medical professionals with essential

¹ World Health Organization. *Guidelines for the production, control and regulation of snake antivenom immunoglobulins*. Expert Committee on Biological Standardization. Technical Report Series no. 1004. Appendix 5. 2018.

https://www.who.int/bloodproducts/AntivenomGLrevWHO_TRS_1004_web_Annex_5.pdf

² World Health Organization. *Snakebite envenoming: A strategy for prevention and control*. 2019. <https://apps.who.int/iris/rest/bitstreams/1230920/retrieve>

³ Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, *et al*. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med*. 2008; 5(11): e218.

characteristics that define well-designed, quality-assured alternatives. Thus, it represents an opportunity to change the product landscape, drive innovation and development of improved antivenom products, and result in better treatment, and outcomes for the victims of this neglected tropical disease.

Background and Rationale

Snakebite envenoming can seem to be a complex disease to manage effectively. There are approximately 110 venomous snake species in Africa, but not all are medically important. Many of these species have very small geographical ranges and a low risk of human contact. Some of them have venom that is not considered dangerous to humans. Venoms are complex mixtures of multiple toxins and, depending on the type of toxins present in a venom, the physiological and pharmacological effects may vary considerably among and even within species. Fortunately, many of the toxins share broad immunological homogeneity such that neutralizing antibodies raised against one snake species is often effective against other species too.

To make the snakebite problems more manageable, some important intellectual and practical simplifications need to be considered.

WHO considers 24 species from 4 genera (*Bitis*, *Dendroaspis*, *Echis* and *Naja*) to be of highest (category 1) medical importance in sub-Saharan Africa and the major targets for antivenom products in the region¹. These are the venomous snakes that are most commonly encountered and the greatest potential threat to human life and wellbeing. A further 24 species are considered to be of secondary (category 2) medical importance, either because they are known to be highly venomous, but are either less frequently associated with serious snakebites, or have little epidemiological data available. The list of these species and their distributions have been published by WHO^{1,4}.

The clinical syndromes of envenoming in sub-Saharan Africa are well-defined and the syndromic grouping of species is potentially useful in the management of snakebites. WHO guidelines define six clinical syndromes⁵ of which the four most common are:

1. Marked local swelling with coagulable blood: typically caused by bites from cytotoxic spitting cobras (*Naja* spp.), puff adders (*Bitis arietans*) and (southern Africa only) Berg adders (*Bitis atropos*);
2. Marked local swelling with incoagulable blood and/or spontaneous systemic bleeding: most typically caused by bites from carpet vipers (*Echis* spp.) in sub-Saharan Africa or, in the Sahara Desert, by desert horned vipers (*Cerastes cerastes*). More uncommonly it may sometimes follow bites by bush vipers (*Atheris* spp.), puff adders (*B. arietans*) or gaboon vipers (*B. gabonica* and *B. rhinoceros*);
3. Progressive paralysis (neurotoxicity): due to bites by neurotoxic, typically non-spitting cobras (*Naja* spp.) and by mambas (*Dendroaspis* spp.);
4. Mild swelling alone: associated generally with bites by burrowing asps (*Atractaspis* spp.), night adders (*Causus* spp.) and by some species of dwarf, bush and desert vipers (*Bitis* spp., *Atheris* spp., and *Cerastes* spp.);

Administration of an appropriate antivenom requires the correct early diagnosis of symptoms and signs of snakebite envenoming. Syndromic assessment of patients can inform both the diagnosis and the selection of the right antivenom from those available. It also enables health workers to identify the type of species of snake that may be involved by distinguishing between neurotoxic, haemorrhagic, cytotoxic, or procoagulant effects. At present most of the antivenoms available in sub-Saharan Africa are Broad-spectrum, Pan-African polyvalent products that are designed to be used for bites by WHO category 1 *Bitis*, *Dendroaspis*, *Echis* and *Naja* species. These antivenoms negate the need for species level identification of the biting snake and can be effective in the geographical areas where those

⁴ https://www.who.int/teams/control-of-neglected-tropical-diseases/snakebite-envenoming/snakebite-information-and-data-platform/overview#tab=tab_1

⁵ World Health Organization. Regional Office for Africa. (2010). *Guidelines for the prevention and clinical management of snakebite in Africa*. World Health Organization. Regional Office for Africa. <https://apps.who.int/iris/handle/10665/204458>

snakes occur. These products sometimes have considerable paraspecific cross-neutralizing activity against venom from other species. One key problem however is that antivenoms designed for large numbers of species (and especially those that produce large volumes of venom) may lack specific potency for some of those species. This may result in a need for administration of very large doses of antivenom, and if this is not possible, the performance of the product may be poor. Reducing the number of venoms and taking a syndromic approach to antivenom design can lead to products of greater specificity and potency that are highly effective, safe, and more affordable.

Monovalent products are appropriate where one particular species or genus causes either a majority of snakebite cases in a defined geographical range or where the venom has specific activities that are not neutralized by available polyvalent antivenoms. A monovalent antivenom is manufactured in small volumes to treat relatively uncommon bites by the category 2 colubrid *Dispholidus typus*. Other monovalent antivenoms have been manufactured in large volumes for the very common bites caused by the category 1 carpet vipers *Echis romani*/*Echis ocellatus* in several west African countries. These products are highly effective and can be administered in low doses to counteract venoms that are themselves only produced by the snakes in small volumes. For species such as *Echis romani* or *Echis ocellatus* that cause large numbers of snakebites, the production of these products in large batches can make them very cost-effective. Conversely having small quantities of an effective antivenom available to treat infrequent bites by species such as *Dispholidus typus* that may otherwise have very high case fatality is essential, albeit at higher production cost for each life saved.

Use case scenarios

Taken collectively, these considerations have led us to propose four potential Use-Case scenarios:

1. Snakebite envenoming by an unidentified species of WHO category 1 or 2 sub-Saharan African snake
2. Snakebite envenoming by a known species of WHO category 1 or 2 sub-Saharan African snake
3. Snakebite envenoming by an unidentified species of WHO category 1 or 2 sub-Saharan African snakes that produces a clinical syndrome of envenoming dominated by neurotoxic effects.
4. Snakebite envenoming by an unidentified species of WHO category 1 or 2 sub-Saharan African snakes that produces a clinical syndrome of envenoming dominated by procoagulant, haemorrhagic or cytotoxic effects.

These in turn lead to four potential classes of antivenom products:

- A. Broad-spectrum Pan-African polyvalent antivenoms
- B. Monovalent antivenoms for specific use cases
- C. Syndromic Pan-African polyvalent antivenoms for neurotoxic envenoming
- D. Syndromic Pan-African polyvalent antivenoms for non-neurotoxic envenoming

General considerations

Production and evaluation

Animal plasma-derived antivenoms are described in several key pharmacopeia's, including those in the United States, United Kingdom, Europe, and India. Considering the biological nature of the product and its manufacture, stating explicitly a few principles that would be regarded as implicit for other type of drugs, is useful. Antivenom products should be manufactured and subjected to routine quality controls following Good Manufacturing Practice (GMP) standards. Pre-clinical testing and any additional assays should follow Good Laboratory Practice (GLP) to meet minimum standards for study conduct, personnel, facilities, equipment, quality assurance, and protocols, processes, and reports. Such requirements encompass the preparation of immunising venoms from snakes and the immunisation and collection of hyperimmune plasma from host animals¹. Clinical trials should comply with Good Clinical Practice (GCP) international standards as developed in the International Council for Harmonisation of Technical requirements for pharmaceuticals for human use (ICH)⁶ when

⁶ ICH Harmonised Guideline. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)* Current Step 4, 9 November 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

Clinical trials

Well-designed, pragmatic and transparently managed clinical trials of antivenom are essential, and these TPPs all recommend that antivenoms be carefully evaluated in both pre-clinical laboratory studies and in clinical trials prior to marketing authorization or licensing. Clinical trials need to adhere to the principles of Good Clinical Practice (GCP), an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Stakeholders including the World Health Organization have developed the [International Council for Harmonization \(ICH\) GCP Guideline](#) to provide a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

Clinical effectiveness

Much has been written about the lack of effectiveness of poorly designed and often untested antivenoms in sub-Saharan Africa. This largely negative narrative has given rise to substantial skepticism and concern over the usefulness of animal plasma-derived antivenoms in general^{7,8}. At the same time little recognition is given in commentaries to the clinical effectiveness of well-designed, diligently tested and monitored products. Such antivenoms can be highly effective, reducing mortality due to snakebite envenoming to less than 2%^{9,10}. Improved or new products, manufactured with characteristics set out in these TPPs should optimally exceed this rate of success, and maintain it at a minimum. These TPPs also propose optimally and minimally acceptable effectiveness characteristics for other clinical consequences of snakebite envenoming (e.g.: coagulopathy, amputation, tissue injury, etc.) that are pragmatically based on the performance of existing good quality products at a minimum.

Affordability and access

A core motivation for undertaking this work is the antivenom supply crisis in sub-Saharan Africa, characterized by the detrimental high market penetration of low-cost products of limited effectiveness and safety. Whilst it is tempting to indicate an acceptable unit price for an antivenom, we have not done so as the unit price is part of overall affordability which also includes considerations such as variations in clinical performance between products. Performance and cost-effectiveness data are not currently available across relevant products, so it is not currently possible to define desired prices or costs in absolute numbers. Until such time as cost-effectiveness studies are completed, principles of 'fair pricing' should guide discussions between buyers and sellers, sometimes referred to as the lowest possible sustainable price.

⁷ Harrison RA, Oluoch GO, Ainsworth S, Alsolaiss J, Bolton F, Arias AS, Gutiérrez JM, Rowley P, Kalya S, Ozwarra H, Casewell NR. (2017). Preclinical antivenom-efficacy testing reveals potentially disturbing deficiencies of snakebite treatment capability in East Africa. *PLoS Negl Trop Dis.* 11(10): e0005969.

⁸ Knudsen C, Ledsgaard L, Dehli RI, Ahmadi S, Sørensen CV, Laustsen AH. (2019). Engineering and design considerations for next-generation snakebite antivenoms. *Toxicon.* 167: 67-75.

⁹ Abubakar IS, Abubakar SB, Habib AG, *et al.* (2010). Randomised Controlled Double-Blind Non-Inferiority Trial of Two Antivenoms for Saw-Scaled or Carpet Viper (*Echis ocellatus*) Envenoming in Nigeria. *PLoS Negl Trop Dis.* 4(7): e767.

¹⁰ Ademola-Majekodunmi FO, Oyediran FO, Abubakar SB. (2012). Incidence of snakebites in Kaltungo, Gombe State and the efficacy of a new highly purified monovalent antivenom in treating snakebite patients from January 2009 to December 2010*. *Bull. Soc. Pathol. Exot.* 105: 175-178.

Animal plasma-derived antivenom TPP List

TARGET PRODUCT PROFILES FOR SUB-SAHARAN AFRICA

This document sets out four target product profiles (TPPs) for animal plasma-derived antivenoms intended for use against venoms from medically important snakes from sub-Saharan Africa:

TPP TITLE	USE CASE
Broad-spectrum Pan-African polyvalent antivenoms	Snakebite envenoming by an unidentified species of WHO category 1 or 2 sub-Saharan African snake
Monovalent antivenoms for specific use cases	Snakebite envenoming by a known species of WHO category 1 or 2 sub-Saharan African snake
Syndromic Pan-African polyvalent antivenoms for neurotoxic envenoming	Snakebite envenoming by an unidentified species of WHO category 1 or 2 sub-Saharan African snakes that produces a clinical syndrome of envenoming dominated by neurotoxic effects.
Syndromic Pan-African polyvalent antivenoms for non-neurotoxic envenoming	Snakebite envenoming by an unidentified species of WHO category 1 or 2 sub-Saharan African snakes that produces a clinical syndrome of envenoming dominated by procoagulant, haemorrhagic or cytotoxic effects.

Common Characteristics of Target Product Profiles

ALL SUB-SAHARAN AFRICAN ANIMAL PLASMA-DERIVED ANTIVENOMS

The following characteristics are common to the target product profiles of all animal plasma-derived antivenom products for use in sub-Saharan Africa. These should be read in conjunction with the specific TPP product characteristics of each of the four TPPs that are set out in the next section of this document.

SCOPE

CHARACTERISTIC	OPTIMAL	MINIMAL
1. Target population	All individuals and age groups with signs and symptoms of snakebite envenoming caused by a WHO Category 1 or Category 2 Sub-Saharan African snake for which the antivenom was raised.	All individuals and age groups with signs and symptoms of snakebite envenoming caused by a WHO Category 1 Sub-Saharan African snake for which the antivenom was raised.
<i>Comments</i>	All of the people living in the countries within the sub-Saharan African region are potentially at risk of snakebite envenoming. Antivenoms are used to treat snakebites in men, women (including pregnant women), and children of all ages.	
2. Geographic working range	All sub-Saharan African countries: Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Equatorial Guinea, Eritrea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Republic of Tanzania, Republic of the Congo, Rwanda, Sao Tome and Principe, Senegal, Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Togo, Uganda, Zambia, Zimbabwe,	
<i>Comments</i>	These sub-Saharan African countries all have indigenous populations of venomous terrestrial snakes.	
3. Level of implementation in the healthcare system	The product is capable of being deployed at all levels of the health system that meet minimal criteria for infrastructure and can be administered by trained health workers under direct or indirect supervision of an appropriately qualified medical doctor.	The product is deployed to all levels of the health system that meet optimum criteria for infrastructure and can be administered by trained health workers under the direct supervision of an appropriately qualified medical doctor.
<i>Comments</i>	Antivenom is a time-critical emergency biotherapeutic drug and should ideally be available as close to the communities in which people are at risk of snakebite envenoming as is possible. Products defined by this TPP should have safety profiles that make them amenable to being deployed to primary health care facilities that have health workers who have been trained in the diagnosis and emergency treatment of snakebite envenoming. While it is minimally preferable that antivenom will be administered under the direct supervision of an appropriately qualified and experienced medical doctor, the use of antivenom under indirect (e.g.: following telephone consultation, radio communication or other “telemedicine” engagement with the medical doctor) supervision should	

	<p>be encouraged as the optimal case for expanding accessibility to safe, effective antivenoms for the majority of the population.</p> <p>Minimal clinical skills for health workers administering antivenoms should include: ability to detect criteria for antivenom treatment (clinical signs of envenoming, perform and interpret bedside tests such as 20WBCT), gain intravenous access, and detect signs of anaphylaxis and treat with adrenaline/epinephrine.</p>
4. Intended end-users	End users include procurement agencies and health care professionals
<i>Comments</i>	While patients will ultimately be the recipients of antivenoms, procurement agencies and health care professionals are the major “end-users” rather than patients themselves.

MANUFACTURING CONSIDERATIONS

CHARACTERISTIC	OPTIMAL	MINIMAL
5. 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.
<i>Comments</i>	<p>Antivenoms are currently available as intact (whole) immunoglobulins or F(ab')₂ (or more rarely Fab) fragments.</p> <p>Optimal antivenom preparations are intact immunoglobulins on the basis of:</p> <ul style="list-style-type: none"> • Higher yield of specific intact IgG compared to F(ab')₂ or Fab fragments. • Consistently higher purity and minimal non-API content compared to F(ab')₂ fragment products. • Robust contribution of caprylic acid treatment to the inactivation of lipid-enveloped viruses • Favourable pharmacokinetic profiles. • Good safety and tolerability profiles with evidence that retention of the Fc region does not induce increased complement activation or adverse drug reactions. <p>Clinical studies have provided evidence that intact immunoglobulins produced under GMP are safe, well tolerated, effective in neutralizing various types of venoms, with good clinical effectiveness.</p>	
6. Finished Product Form	Either liquid or lyophilized final product forms are acceptable.	
<i>Comments</i>	<p>Both types of preparations have advantages and limitations.</p> <p>Current liquid preparations dispensed in the final container under GMP-compliant conditions are easier to use clinically but require the guarantee of storage and transportation under conditions maintaining a cold chain (typically 2-8°C).</p> <p>Lyophilised formulations may usually be transported and stored at a temperature not exceeding 25°C and are of interest for distribution to areas where the cold chain cannot be guaranteed, such as in many tropical regions of the world. However, lyophilization is an expensive and complex manufacturing operation that should be carefully validated and</p>	

<p>operated to maintain the quality of the product. Faulty lyophilization can result in denatured protein that is difficult to solubilize.</p> <p>Many of the countries where these products are deployed are considered to be ICH climatic zone III, IVa or IVb. Temperature tolerance of at least $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ at relative humidity of up to $75\% \pm 5\%$ should be the goal of efforts to improve the thermostability of both liquid and lyophilized product forms.</p>		
<p>7. Specific Immunoglobulin Content (Active Pharmaceutical Ingredient [API] content)</p>	<p>Not less than 90% ($\pm 5\%$) of the total protein content must consist of intact active pharmaceutical ingredient [e.g.: intact (whole) IgG or F(ab')₂ fragments of IgG]. Total API content to be included in vial labelling.</p>	<p>Not less than 85% ($\pm 5\%$) of the total protein content must consist of intact active pharmaceutical ingredient [e.g.: whole IgG or F(ab')₂ fragments of IgG]. Total API content to be included in vial labelling.</p>
<p><i>Comments</i></p> <p>Specific immunoglobulin content refers to the amount of the defined active pharmaceutical ingredient (API) for the product, which typically will either be intact (whole) IgG or alternatively F(ab')₂ fragments of IgG. Currently most manufacturers specify that products contain not less than 85% API (e.g., whole IgG or F(ab')₂ molecules). A number of products assessed by WHO fell short of this specification in independent laboratory assessments.</p> <p>The purity of antivenom is intrinsically linked to product safety and tolerability and reducing the proportions of non-immunoglobulin proteins in antivenoms will improve safety.</p> <p>For this reason, $85\% \pm 5\%$ was considered to be the absolute minimum acceptable specification for specific API whether it be F(ab')₂ or intact (whole) IgG. Smaller fragments such as F(ab'), Fab or scFV should not be included in the measurement of this specification. Optimally higher purity is desirable with $90\% \pm 5\%$ being recommended.</p> <p>The amount of total protein, the amount of API and the specific amounts of any other vial contents (e.g.: aggregates, non-API immunoglobulins, other proteins, etc.) should be included on vial labels and other packaging.</p>		

PERFORMANCE

CHARACTERISTIC	OPTIMAL	MINIMAL
<p>8. Pre-clinical efficacy (Including potency of the antivenom)</p>	<p>Preclinical potency and toxin-specific activity bioassays demonstrate the potential of the antivenom to neutralize in vivo at least the average adult venom yield of each species by the recommended initial dose of the product.</p>	<p>Preclinical potency bioassays demonstrate the potential of the antivenom to neutralize in vivo at least the average adult venom yield of each species by the recommended initial dose of the product.</p>
<p><i>Comments</i></p> <p>Potency [P] is derived from ED₅₀ and LD₅₀ and is the amount of venom neutralised (in mg) per mL of antivenom [mg V neutralised/mL antivenom]) using the equation^{11,12}:</p>		

¹¹ Wagstaff SC, Sanz L, Juarez P, Harrison RA, Calvete JJ. Combined snake venomomics and venom gland transcriptomic analysis of the ocellated carpet viper, *Echis ocellatus*. *J. Proteomics* 2009; 71:609-623.

¹² Morais V, Ifran S, Berasain P, Massaldi H. Antivenoms: potency or median effective dose, which to use? *J. Venom. Anim. Toxins incl. Trop. Dis.* 2010; 16:191-193.

$$P = \frac{(n - 1)LD_{50}}{ED_{50}}$$

Where “n” is the number of LD₅₀ used in the determination of the ED₅₀, P is the amount of venom (V) that is completely neutralised per unit volume of antivenom (antivenom), and would protect 100% of mice, as opposed to ED₅₀ which is the amount that protects 50% of them. The expression “(n-1) LD₅₀” is used instead of the total amount of venom (n LD₅₀) because at the endpoint of the neutralisation assay, one LD₅₀ (n=1) remains unneutralized and causes the death of 50% of mice. To transform the neutralisation activity from ED₅₀ to P, LD₅₀ should be expressed as [mg venom/mouse] and ED₅₀ in [mL antivenom/mouse]. Potency enables estimation of the amount of antivenom required to provide complete neutralisation of a given quantity of venom. This is more relevant the ED₅₀, since it estimates the dose for complete neutralization of lethality (and protection of all the test animals) rather than just protection of 50% of the test animals.

9. Safety and tolerability	Incidence of anaphylaxis <2.0%. Incidence of other early adverse drug reactions or late-presenting serum sickness of <10%. No requirements for laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc.).	Incidence of anaphylaxis <5.0%. Incidence of other early adverse drug reactions or late-presenting serum sickness of <20%. No more than clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes etc.).
<i>Comments</i> Here, anaphylaxis is minimally defined as the occurrence of one or more of the following clinical events: shock and other cardiovascular effects, bronchospasm, upper airway obstruction and/or angioedema.		
10. Interactions with other medicinal products	There are no interactions with other medicinal products.	There are no serious interactions with other medicinal products, and minimal minor interactions.
<i>Comments</i> Potential interaction due to hypersensitization from previous exposure to equine or ovine (exogenous) immunoglobulin products.		
11. Dose regimen	All patients, regardless of age, sex or body weight should receive the same dose. An initial dose should optimally be sufficient to neutralize 100% of the average adult venom yield of each of the species for which it is intended regardless of the specific activity of the venom. The specific volume of the initial dose, and its clinical effectiveness and safety will have been established through well-designed and administered randomized controlled trials (RCTs) that have been published and peer-reviewed. Additional doses may be administered based on the observed	All patients, regardless of age, sex or body weight should receive the same dose. An initial dose should optimally be sufficient to neutralize 100% of the average adult venom yield of each of the species for which it is intended regardless of the specific activity of the venom. The specific volume of the initial dose, and its clinical effectiveness and safety will have been established through well-designed and administered clinical dose-finding and safety studies that have been published and peer-reviewed. Additional doses may be

	clinical picture and considering the natural time course for reversal of functional and physiological disturbances.	administered based on the observed clinical picture and considering the natural time course for reversal of functional and physiological disturbances.
<i>Comments</i>	<p>Venomous snakes do not meter the dose of injected venom according to the size or weight of bitten persons, and it is currently not possible to quantitatively measure the concentration of injected venom in patients at the bedside to inform dosing decisions. Hence all patients need to receive the same, standardized initial dose of antivenom, one which is adequate to neutralize all injected venom.</p> <p>Current dose recommendations on package inserts of available products are rarely based on results of well-designed clinical dose finding studies or clinical trials yet this should be a fundamental minimum requirement for all antivenom products seeking registration and marketing approval.</p>	
12. Frequency of administration	Administration of a single dose of antivenom. This dose should be sufficiently potent to neutralize 100% of the average adult venom yields of each of the snake species for which the product is intended. Additional doses may be given based on the observed clinical picture over time, but ideally the initial dose should be adequate to neutralize all the injected venom, without the need for re-dosing.	
<i>Comments</i>	<p>Snakebite is a time-critical emergency, and the sooner that a fully effective dose of an appropriate antivenom is administered, the better the chance that the patient will have a good outcome with minimal sequelae. This is best achieved by ensuring that every patient who has clinical signs and symptoms sufficient to warrant administration of antivenom receives a primary (initial) dose that is able to neutralize all of the injected venom. Since data is lacking on the masses of venom injected in real cases of snakebite envenoming, the most appropriate, available proxy (and one that is used elsewhere in the world) is average adult mass by weight of venom collected from specimens of each species during manual venom extraction. WHO should coordinate collection of data on average adult venom yields and include this data in its Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins.</p>	
13. Route of Administration	Administered by controlled intravenous infusion (regulated iv drip or mechanical infusion pump). Antivenom may be diluted further with an appropriate volume of isotonic fluid to a total volume of not more than 200 millilitres, infused over a period of up to 60 minutes.	Administered undiluted by slow-push intravenous injection at a maximum rate of no more than 5.0 mL/minute, and with a total volume of not more than 200 millilitres given over a period of up to 60 minutes.
<i>Comments</i>	<p>Both intravenous infusion and intravenous injection have advantages and disadvantages.</p> <p>Infusion of antivenom diluted in isotonic fluid is safe, easy, and convenient, but equipment and consumables add additional cost in resource-poor settings. Venous access can be maintained for administration of other drugs or for ongoing fluid management. A risk is that patients may be left unattended during administration at a time when there is a risk of evolution of adverse drug reactions and with the risk of unobserved and uncontrolled infusion rate. An additional risk is that antivenom will be incorrectly diluted in a large quantity of intravenous</p>	

	<p>fluid (e.g., 1 L) and wrongly given over a protracted time period at a maintenance rate.</p> <p>Intravenous slow-push injection requires the attending health worker to remain at the bedside and uses minimal equipment. It may however be uncomfortable for patients, and poor technique can lead to local trauma and infiltration into tissue rather than the circulation. If not undertaken carefully with aseptic technique, there is a risk of introducing contaminants with either technique. Dilution of antivenom with isotonic fluid prior to administration can potentially lead to contamination of sterile products, dosing errors, or administration errors so care and vigilance are essential.</p>	
14. Product Stability	At least 5 years in conditions up to and including ICH climatic zone IVb (temperature of 30°C ± 2°C and relative humidity of up to 75% ± 5%).	For lyophilized products: At least 3 years in conditions up to and including ICH climatic zone IVb (temperature of 30°C ± 2°C and relative humidity of up to 75% ± 5%). For liquid products: At least 3 years in conditions up to and including ICH refrigerated zone (temperature of 5°C ± 3°C).
<i>Comments</i>	Countries in sub-Saharan Africa have climates that range from ICH climatic zone III to IVb. Products deployed in these regions should be able to tolerate the maximum threshold (IVb). Longer shelf lives are preferred. Both real-time and accelerated stability studies should be considered to establish the thermal tolerances of antivenoms.	
15. Storage	Room temperatures at up to 30°C ± 2°C and relative humidity of up to 75% ± 5%.	Room temperatures at up to 30°C ± 2°C and relative humidity of up to 75% ± 5% or refrigerated cold-chain storage at 2-8°C.
<i>Comments</i>	Preference would be to antivenom both liquid and lyophilized products that are thermostable at ICH climatic zone IVb.	
16. Presentation	A single container (e.g.: vial, ampoule, or intravenous infusion bag) that holds sufficient active pharmaceutical ingredient to neutralize 100% of the average adult venom yields of each of the snake species for which it is intended.	A single container (e.g.: vial, ampoule, or intravenous infusion bag) that holds sufficient active pharmaceutical ingredient to neutralize 100% of the average adult venom yield of the neurotoxic species, and 50% of the non-neurotoxic species for which it is intended.
<i>Comments</i>	<p>The presentation of antivenoms in vials or ampoules that do not contain a complete therapeutic dose contributes to the systematic under-dosing of patients in many settings, but especially in those where out-of-pocket spending remains the main source of funding for antivenom treatment.</p> <p>In order to ensure that all patients receive an effective therapeutic dose of antivenom as early as possible, and to minimize the possibility that economic pressure contributes to under-dosing, especially in situations where the cost is borne by the patient, presenting the antivenom as a single effective therapeutic dose (e.g.: in 50-100 ml vials or sterile infusion bags) can achieve these objectives.</p>	

	The amount of total protein, the amount of API and the specific amounts of any other vial contents (e.g.: aggregates, non-API immunoglobulins, other proteins, etc.) should be included on vial labels and other packaging.
17. Packaging	Each outer package (e.g.: box or carton) should contain one complete initial dose, presented in a single container (e.g.: vial, ampoule, or intravenous infusion bag). Lyophilized presentations should be accompanied by an adequate volume of isotonic fluid or sterile water for injection (WFI) to ensure complete reconstitution of the product. Package inserts should be provided in the language of the country where the product is being marketed. Inserts should meet the requirements of internationally accepted guidelines (e.g., ICH, WHO) and national regulations in the country of manufacture and the country where the product will be marketed. Information on the total protein content and the total active pharmaceutical ingredient (API) content should be included on vial labels and package inserts.
<i>Comments</i>	In line with the characteristics for product presentation as a single vessel dose, outer packaging should clearly indicate single use/single dose. Solutions provided for reconstitution of lyophilized antivenoms must be produced in competent GMP environments, be sterile, appropriately packaged and correctly labelled.

OPERATIONAL CHARACTERISTICS

18. Costs	A cost effectiveness study is conducted and demonstrates that antivenom is highly cost-effective.	If cost effectiveness studies can't be performed, evidence to support fair pricing of antivenom is requested. Once the cost effectiveness study is performed, antivenom is found cost effective.
<i>Comments</i>	WHO considers that a “fair price” is one that is affordable for health systems and patients and at the same time provides sufficient market incentive for industry to invest in innovation and the production of medicines. In other words, fairness here implies positive incentives and/or benefits for all stakeholders. ¹³	
19. Supportive and adjunctive therapy	Essential ancillary drugs and consumables include adrenaline/epinephrine, anti-H1-histamine blockers, antibiotics, paracetamol and other non-NSAID analgesics, corticosteroids (for serum sickness), iv fluids, iv giving sets, burettes, syringes, needles, iv cannulas and related consumables. The monitoring of basic vital signs (heart rate, blood pressure and respiratory rate) is essential in all cases. Pulse oximetry is desirable.	
<i>Comments</i>	The items listed should be available for potential use with all patients who present with a suspected snakebite. The items shown are an essential list for any setting in which antivenom is being administered. Depending on individual case presentation some patients will need to be managed in facilities with substantially greater resources.	
20. Training & education needs	Knowledge of common local snake species including non-venomous ones, history and clinical examination, criteria for antivenom treatment, monitoring vital signs (including orthostatic BP), POC tests (20WBCT, urine reagent sticks), resuscitation of shocked patients, nursing sick patients	

¹³ www.who.int/medicines/access/fair_pricing/en/

	(positioning), iv access, iv cannula placement, management of iv infusion, criteria for use of/administration of adrenaline/epinephrine and other ancillary drugs.
<i>Comments</i>	There is a need for improved clinical training of health workers in the diagnosis, treatment, and management of patients with real or suspected snakebite envenoming. Medical schools, nursing, and health worker training colleges should be encouraged and supported to incorporate more detailed teaching on snakebite envenoming into curricula, countries should work with professional bodies and subject matter experts to develop standardized national or regional guidelines.

Specific Characteristics of Target Product Profiles

1. BROAD-SPECTRUM PAN-AFRICAN POLYVALENT ANTIVENOMS

SCOPE

CHARACTERISTIC	OPTIMAL	MINIMAL
21. Indication	For the treatment of snakebite envenoming by an unidentified WHO Category 1 or Category 2 Sub-Saharan African snake; to be used in conjunction with other treatment support interventions to address disease manifestations.	For the treatment of snakebite envenoming by an unidentified WHO Category 1 Sub-Saharan African snake; to be used in conjunction with other treatment support interventions to address disease manifestations.
<i>Comments</i>	Current Pan-Africa products are designed for treating bites by WHO Category 1 species from the genera <i>Bitis</i> , <i>Dendroaspis</i> , <i>Echis</i> and <i>Naja</i> . The TPP slightly broadens this to include the possibility of also including immunizing venoms from Category 2 species such as <i>Dispholidus typus</i> to broaden the coverage further.	
22. Contraindication	None	None
<i>Comments</i>	There are no absolute contraindications to treatment of snakebite envenoming with antivenom.	

MANUFACTURING CONSIDERATIONS

23. Immunizing venoms	Immunizing venoms should meet the specifications of corresponding WHO reference venoms ¹⁴ 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.
<i>Comments</i>	<p>Venoms should be representative of each of the WHO Category 1 genera. Minimally this would involve the use of at least two different <i>Bitis</i>, <i>Echis</i> and <i>Dendroaspis</i> species, two species of cytotoxic <i>Naja</i> and two species of neurotoxic <i>Naja</i> species (e.g.: proposed WHO reference standard venoms). Additional venoms, including those from Category 2 (e.g., <i>Dispholidus typus</i>) could be used by a manufacturer at their discretion. Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met.</p> <p>The venoms used should be a pool from specimens from across the geographic range of each species, including male and female juveniles, sub-adults and adults. Venom from each individual geographic population should</p>	

¹⁴ WHO has proposed the initial development of venom reference standards for *Bitis arietans*, *Dendroaspis polylepis*, *Echis ocellatus*/*E. romani*, *Naja haje* and *Naja nigricollis*. A process for developing these materials will be established in 2022.

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.

An ideal immunizing venom pool should exhibit minimal compositional redundancy. Also ideally, all the toxins present in the pool should have similar "opportunity" to elicit an immune response. The immunogenic surface area presented by a toxin depends on the molecular mass of the toxin. Thus, ideally pooled venoms should contain compositionally similar toxins, and when possible, also LD₅₀. Manufacturers tend to immunize different horses with different venom pools (e.g., viperid venom pool, elapid venom pool) and then combine the different hyperimmune plasma into a single product, a better approach is to immunize groups of horses with different venom pools. The different hyperimmune plasma pools should be fractionated and purified separately, and the specific immunoglobulins combined proportionally to yield the final formulation.

At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.

Examples of species to be used:

- *Bitis*: *B. arietans*, *B. gabonica*
- *Echis*: *E. romani/ocellatus*, *E. pyramidum*
- *Dendroaspis*: *D. polylepis*, *D. viridis*
- *Cytotoxic Naja*: *N. nigricollis/mossambica*, *N. katiensis*
- *Neurotoxic Naja*: *N. haje/senegalensis*, *N. annulifera*, *N. nivea*, and at least one species from the *Naja melanoleuca* clade.

24. Total Protein content	Not less than 7.5% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	Not less than 5.0% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.
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Comments Current pharmacopeia and WHO guidelines recommend upper limits for total protein but make no provision for minimum quantities. Broad-spectrum polyvalent antivenoms have to be capable of neutralizing large quantities of venom from several species, and while the average adult venom yield of some species (e.g.: carpet vipers, *Echis* spp.) may be as little as 10-30 mg, the average adult yields from large spitting cobras (*Naja* spp.) can exceed 1200 mg, and average adult yields from mambas (*Dendroaspis* spp.) can exceed 120 mg. WHO has found that products with very low total protein content simply cannot contain adequate Active Pharmaceutical Ingredient (API) at the minimum specifications to effectively neutralize these types of venom volumes.

PERFORMANCE

CHARACTERISTIC	OPTIMAL	MINIMAL
25. Clinical effectiveness (Including selected outcome measures)	When administered within 6-8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces: <ul style="list-style-type: none"> • case fatality rate (CFR) to <1% 	When administered within 4-6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:

	<ul style="list-style-type: none"> • amputations to <1%; • persistence of coagulopathy at 24 hours post-antivenom to <3%; • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <5%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <2%. 	<ul style="list-style-type: none"> • case fatality rate (CFR) to <2% • amputations to <2%; • persistence of coagulopathy at 24 hours post-antivenom to <6%; • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <10%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <5%.
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<p><i>Comments</i></p>	<p>The clinical effectiveness of an antivenom can only be assessed under the following conditions:</p> <ol style="list-style-type: none"> 1. It is used for treatment of envenoming by a snake species whose venom was used in its production (i.e., it is specific for that species) 2. It is given in an appropriate initial dose, that is optimally based on findings of clinical trials, or at a minimum, the results of independent pre-clinical testing by a competent laboratory and has been accepted and is recommended by national regulators, or in national/regional guidelines. 3. It is given within an acceptable time frame after the bite (i.e.: optimally within not more than 4-6 hrs; minimally within not more than 6-8 hrs). <p>Characteristics for minimal parameters were defined based on published reports of the performance of past and present antivenoms such as FAV-Afrique, IPSEr-Africa, EchiTAb-G, EchiTAb-Plus-ICP, Schlangengift Immunserum and SAIMR polyvalent antivenom.</p> <p>Characteristics for optimal performance aim for an improvement over and above what is currently best-in-market performance of at least 50%, based on adoption of TPPs into manufacturing on new or improved products</p> <p>Refer to Appendix 1 for additional information.</p>
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Specific Characteristics of Target Product Profiles

2. SUB-SAHARAN AFRICAN MONOVALENT ANTIVENOMS

SCOPE

CHARACTERISTIC	OPTIMAL	MINIMAL
26. Indication	For the treatment of snakebite envenoming by a known species of WHO Category 1 or 2 Sub-Saharan African snake; to be used in conjunction with other treatment support interventions to address disease manifestations.	
<i>Comments</i>	<p>Monovalent antivenoms are most appropriate for species that fulfil one or more of the following conditions:</p> <ul style="list-style-type: none"> • Very common and dominating snakebite epidemiology in at least parts of their range • Rare but potentially lethal, with venoms that are difficult to source in large amounts, and cannot be neutralized by other antivenoms <p>Current monovalent African products are designed for treating bites by WHO Category 1 or 2 species such as <i>Echis romani</i>/<i>E. ocellatus</i> and <i>Dispholidus typus</i>. Interest in raising monovalent antivenoms for some other species such as <i>Naja nigricincta</i>, <i>N. ashei</i> or <i>N. mossambica</i> has been expressed.</p>	
27. Contraindication	None	None
<i>Comments</i>	There are no absolute contraindications to treatment of snakebite envenoming with antivenom.	

MANUFACTURING CONSIDERATIONS

CHARACTERISTIC	OPTIMAL	MINIMAL
28. Immunizing venoms	Immunizing venoms should meet the specifications of corresponding WHO reference venoms ¹⁵ 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.
<i>Comments</i>	<p>Venoms should be representative of geographical range of the Category 1 or 2 species or genus against which the product is being raised. Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met.</p> <p>The venoms used should be a pool from specimens from across the geographic range of each species, including male and female juveniles,</p>	

¹⁵ WHO has proposed the initial development of venom reference standards for *Bitis arietans*, *Dendroaspis polylepis*, *Echis ocellatus*/*E. romani*, *Naja haje* and *Naja nigricollis*. A process for developing these materials will be established in 2022.

	<p>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.</p> <p>At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.</p> <p>Examples of species for which monovalent antivenoms might be raised:</p> <ul style="list-style-type: none"> • <i>Dispholidus typus</i> • <i>Echis</i>: <i>E. romani</i>/<i>E. ocellatus</i>, <i>E. leucogaster</i>, <i>E. jageri</i>, <i>E. pyramidum</i> • <i>Naja</i>: <i>N. nigricincta</i>, <i>N. ashei</i>, <i>N. mossambica</i>
29. Total Protein content	Minimum depends on the species and the average adult venom yield but should not be more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.
<i>Comments</i>	Current pharmacopeia and WHO guidelines recommend upper limits for total protein but make no provision for minimum quantities. Monovalent antivenoms must be capable of neutralizing the average adult venom yields of the species against which they are raised. In designing the products manufacturers need to take into consideration the possible mass of venom that could be injected during a bite from these species and ensure that sufficient protein, including API, is present to neutralize these quantities of venom. For species such as <i>Dispholidus typus</i> or <i>Echis</i> spp., the amount of total protein (and API) required to neutralize an average adult venom yield may be small. For species with large venom yields (e.g., spitting cobras) WHO has found that products with very low total protein content simply cannot contain adequate API at the minimum specifications to effectively neutralize these types of venom volumes.

PERFORMANCE

CHARACTERISTIC	OPTIMAL	MINIMAL
30. Clinical effectiveness (Including selected outcome measures)	<p>When administered within 6-8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <1% • amputations to <1%; • persistence of coagulopathy at 24 hours post-antivenom to <3%; • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <5%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for 	<p>When administered within 4-6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <2% • amputations to <2%; • persistence of coagulopathy at 24 hours post-antivenom to <6%; • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <10%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after

	renal or hormonal replacement therapy) to <2%.	lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <5%.
<i>Comments</i>	<p>The clinical effectiveness of an antivenom can only be assessed under the following conditions:</p> <ol style="list-style-type: none"> 1. It is used for treatment of envenoming by a snake species whose venom was used in its production (i.e., it is specific for that species) 2. It is given in an appropriate initial dose, that is optimally based on findings of clinical trials, or at a minimum, the results of independent pre-clinical testing by a competent laboratory and has been accepted and is recommended by national regulators, or in national/regional guidelines. 3. It is given within an acceptable time frame after the bite (i.e.: optimally within not more than 4-6 hrs; minimally within not more than 6-8 hrs). <p>Characteristics for minimal parameters were defined based on published reports of the performance of past and present antivenoms such as FAV-Afrique, IPSER-Africa, EchiTAb-G, EchiTAb-Plus-ICP, Schlangengift Immunserum and SAIMR polyvalent antivenom.</p> <p>Characteristics for optimal performance aim for an improvement over and above what is currently best-in-market performance of at least 50%, based on adoption of TPPs into manufacturing on new or improved products</p> <p>Refer to Appendix 1 for additional information.</p>	

Specific Characteristics of Target Product Profiles

3. PAN-AFRICAN POLYVALENT ANTIVENOMS FOR NEUROTOXIC ENVENOMING

SCOPE

CHARACTERISTIC	OPTIMAL	MINIMAL
31. Indication	For the treatment of snakebite envenoming by an unidentified species of WHO Category 1 or 2 Sub-Saharan African snake that produces a clinical syndrome of envenoming dominated by neurotoxic effects (namely a neurotoxic species of cobra (<i>Naja</i> spp.) or mamba (<i>Dendroaspis</i> spp.); to be used in conjunction with other treatment support interventions to address disease manifestations.	
<i>Comments</i>	Producing Pan-African polyvalent antivenoms for use in the syndromic treatment of neurotoxic snakebites aims to encourage the development of a new group of products that specifically target species from the cobra (<i>Naja</i> spp.) and mamba (<i>Dendroaspis</i> spp.) genera that produce predominantly neurotoxic clinical effects and can potentially cause rapid death through paralysis of airway and breathing muscles.	
32. Contraindication	Patients with snakebite envenoming who have evidence of coagulopathy, haemorrhagic effects, tissue necrosis and other cytotoxic venom effects without any clinical evidence of neurotoxic envenoming.	
<i>Comments</i>	A Pan-African product for non-neurotoxic snakebite envenoming is envisaged for treatment of bites that present with these other types of clinical syndrome.	

MANUFACTURING CONSIDERATIONS

CHARACTERISTIC	OPTIMAL	MINIMAL
33. Immunizing venoms	Immunizing venoms should meet the specifications of corresponding WHO reference venoms ¹⁶ 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.
<i>Comments</i>	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 at least two different <i>Dendroaspis</i> species and four species of neurotoxic <i>Naja</i> species (e.g.: non-spitting cobras such as <i>Naja haje</i>). Additional neurotoxic venoms could be used by a manufacturer at their discretion. Where no reference	

¹⁶ WHO has proposed the initial development of venom reference standards for *Bitis arietans*, *Dendroaspis polylepis*, *Echis ocellatus*/*E. romani*, *Naja haje* and *Naja nigricollis*. A process for developing these materials will be established in 2022.

standard exists then the minimal criteria for immunizing venoms shown above should be met.

The venoms used should be a pool from specimens 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.

At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.

Examples of species to be used:

- *Dendroaspis*: *D. polylepis* and at least one of the following: *D. angusticeps*, *D. jamesoni*, *D. viridis*
- Neurotoxic *Naja*: *N. haje* or *N. senegalensis*, *N. nivea*, *N. annulifera* and at least one species from the forest cobra clade (e.g., *N. melanoleuca*, *N. subfulva*, *N. savannula*, *N. guineensis* or *N. peroescobari*)

34. Total Protein content	Not less than 7.5% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	Not less than 5.0% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.
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Comments

Current pharmacopeia and WHO guidelines recommend upper limits for total protein but make no provision for minimum quantities. Polyvalent antivenoms for neurotoxic species must be capable of neutralizing large quantities of extremely potent venom from several species. The average adult venom yields from large neurotoxic cobras (*Naja* spp.) can exceed 600 mg, and average adult yields from mambas (*Dendroaspis* spp.) can exceed 120 mg. WHO has found that products with very low total protein content simply cannot contain adequate API at the minimum specifications to effectively neutralize these types of venom volumes.

PERFORMANCE

CHARACTERISTIC	OPTIMAL	MINIMAL
35. Clinical effectiveness (Including selected outcome measures)	<p>When administered within 6-8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <1% • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <5%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability 	<p>When administered within 4-6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <2% • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <10%; and, • residual disability at 6 months post-bite (e.g., contracture,

	to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <2%.	arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <5%.
<i>Comments</i>	<p>The clinical effectiveness of an antivenom can only be assessed under the following conditions:</p> <ol style="list-style-type: none"> 1. It is used for treatment of envenoming by a snake species whose venom was used in its production (i.e., it is specific for that species) 2. It is given in an appropriate initial dose, that is optimally based on findings of clinical trials, or at a minimum, the results of independent pre-clinical testing by a competent laboratory and has been accepted and is recommended by national regulators, or in national/regional guidelines. 3. It is given within an acceptable time frame after the bite (i.e.: optimally within not more than 4-6 hrs; minimally within not more than 6-8 hrs). <p>Characteristics for minimal parameters were defined based on published reports of the performance of past and present antivenoms such as FAV-Afrique, IPSER-Africa, EchiTAB-G, EchiTAB-Plus-ICP, Schlangengift Immunserum and SAIMR polyvalent antivenom.</p> <p>Characteristics for optimal performance aim for an improvement over and above what is currently best-in-market performance of at least 50%, based on adoption of TPPs into manufacturing on new or improved products</p> <p>Refer to Appendix 1 for additional information.</p>	

Specific Characteristics of Target Product Profiles

4. PAN-AFRICAN POLYVALENT ANTIVENOMS FOR NON-NEUROTOXIC ENVENOMING

SCOPE

CHARACTERISTIC	OPTIMAL	MINIMAL
36. Indication	For the treatment of snakebite envenoming by an unidentified species of WHO Category 1 or 2 Sub-Saharan African snake that produces a clinical syndrome of envenoming dominated by haemorrhagic, cytotoxic or procoagulant effects (namely cytotoxic species of cobra (<i>Naja</i> spp.), African adder/viper (<i>Bitis</i> spp.), boomslang (<i>Dispholidus typus</i>) or carpet viper (<i>Echis</i> spp.); to be used in conjunction with other treatment support interventions to address disease manifestations.	
<i>Comments</i>	Producing Pan-African polyvalent antivenoms for use in the syndromic treatment of non-neurotoxic snakebites that aims to encourage the development of a new group of products that specifically target species from the cobra (<i>Naja</i> spp.), African adders (<i>Bitis</i> spp.), boomslang (<i>Dispholidus typus</i>) and carpet viper (<i>Echis</i> spp.) genera that produce predominantly cytotoxic, procoagulant or haemorrhagic clinical effects resulting in spontaneous bleeding and haemorrhage, tissue necrosis and other non-neurotoxic clinical effects.	
37. Contraindication	Patients with snakebite envenoming who have evidence of neurotoxic envenoming (with or without tissue necrosis, and without coagulopathy or haemorrhagic effects).	
<i>Comments</i>	A Pan-African product for neurotoxic snakebite envenoming is envisaged for treatment of bites that present with a clinical syndrome dominated by neuro-paralysis.	

MANUFACTURING CONSIDERATIONS

CHARACTERISTIC	OPTIMAL	MINIMAL
38. Immunizing venoms	Immunizing venoms should meet the specifications of corresponding WHO reference venoms ¹⁷ 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.
<i>Comments</i>	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 at least two different <i>Bitis</i> species, two different	

¹⁷ WHO has proposed the initial development of venom reference standards for *Bitis arietans*, *Dendroaspis polylepis*, *Echis ocellatus*/*E. romani*, *Naja haje* and *Naja nigricollis*. A process for developing these materials will be established in 2022.

Echis species and two species of non-neurotoxic *Naja* species (e.g.: cytotoxic spitting cobras). Additional venoms from other haemotoxic or cytotoxic species could be used by a manufacturer at their discretion. Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met.

The venoms used should be a pool from specimens 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.

An ideal immunizing venom pool should exhibit minimal compositional redundancy. Also ideally, all the toxins present in the pool should have similar "opportunity" to elicit an immune response. The immunogenic surface area presented by a toxin depends on the molecular mass of the toxin. Thus, ideally pooled venoms should contain compositionally similar toxins, and when possible, also LD₅₀. Manufacturers tend to immunize different horses with different venom pools (e.g., viperid venom pool, elapid venom pool) and then combine the different hyperimmune plasma into a single product.

At a minimum, internal working reference standards for each population selected, and for the common pool used in immunization (and/or quality control) should be established to ensure batch-to-batch consistency.

Examples of species to be used:

- *Bitis*: *B. arietans*, *B. gabonica* or *B. rhinoceros*
- *Echis*: *E. romani/ocellatus*, *E. leucogaster*, *E. pyramidum*
- *Cytotoxic Naja*: *N. ashei*, *N. nigricollis*, *N. mossambica*, *N. katiensis*, *N. pallida*, *N. nigricincta*.

39. Total Protein content	Not less than 7.5% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.	Not less than 5.0% w/v, and not more than the maximum recommended by relevant national pharmacopeia and regulatory guidelines. Total protein content to be included in vial labelling.
<i>Comments</i>	Current pharmacopeia and WHO guidelines recommend upper limits for total protein but make no provision for minimum quantities. Polyvalent antivenoms for non-neurotoxic species have to be capable of neutralizing large quantities of venom from several species, and while the average adult venom yield of some species (e.g.: carpet vipers, <i>Echis</i> spp.) may be as little as 10-30 mg, the average adult yields from large spitting cobras (<i>Naja</i> spp.) can exceed 1200 mg, and average adult yields from African adders (<i>Bitis</i> spp.) can exceed 500 mg. WHO has found that products with very low total protein content simply cannot contain adequate API at the minimum specifications to effectively neutralize these types of venom volumes.	

PERFORMANCE

CHARACTERISTIC	OPTIMAL	MINIMAL
40. Clinical effectiveness (Including selected outcome measures)	<p>When administered within 6-8 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <1% • amputations to <1%; • persistence of coagulopathy at 24 hours post-antivenom to <3%; • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <5%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <2%. 	<p>When administered within 4-6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces:</p> <ul style="list-style-type: none"> • case fatality rate (CFR) to <2% • amputations to <2%; • persistence of coagulopathy at 24 hours post-antivenom to <6%; • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofting of blisters) to <10%; and, • residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) to <5%.

Comments

The clinical effectiveness of an antivenom can only be assessed under the following conditions:

4. It is used for treatment of envenoming by a snake species whose venom was used in its production (i.e., it is specific for that species)
5. It is given in an appropriate initial dose, that is optimally based on findings of clinical trials, or at a minimum, the results of independent pre-clinical testing by a competent laboratory and has been accepted and is recommended by national regulators, or in national/regional guidelines.
6. It is given within an acceptable time frame after the bite (i.e.: optimally within not more than 4-6 hrs; minimally within not more than 6-8 hrs).

Characteristics for minimal parameters were defined based on published reports of the performance of past and present antivenoms such as FAV-Afrique, IPSEr-Africa, EchiTAb-G, EchiTAb-Plus-ICP, Schlangengift Immunserum and SAIMR polyvalent antivenom.

Characteristics for optimal performance aim for an improvement over and above what is currently best-in-market performance of at least 50%, based on adoption of TPPs into manufacturing on new or improved products

Refer to Appendix 1 for additional information.

Appendix 1

ADDITIONAL COMMENTS IN RELATION TO CLINICAL EFFECTIVENESS OF ANTIVENOMS FOR SUB-SAHARAN AFRICA

Well-designed and well-manufactured antivenoms are very effective treatments for snakebite envenoming even in resource-poor settings where there are a myriad challenges and potential barriers to optimal outcomes. If the right combination of venoms is used as immunogens, manufacturing and quality control processes are well-designed and conducted in compliance with Good Manufacturing Practice (GMP), and efficacy of the product is robustly evaluated in the laboratory and in clinical trials, the outcomes of antivenom treatment at an appropriate initial dose should be very good in almost all patients who receive the product within the first 4-6 hours after a bite by a snake specifically covered by that product (see above).

Much of the current distrust of antivenom arises from the use of poorly designed, low-quality products, some having been marketed despite a complete absence of any preclinical efficacy or clinical effectiveness data. Many products currently marketed in sub-Saharan Africa without prior pre-clinical or clinical testing carry dose recommendations that are inadequate and result in systematic under-dosing of patients, with consequential poor results. These antivenoms are often marketed aggressively at low prices and with financial incentives, with the aim of capturing market share at the expense of better products that cost more. The poor clinical outcomes that result from their use undermine confidence in antivenom as the frontline treatment for snakebite envenoming and this in turn has contributed to market failures and chronic shortages of safe, effective antivenoms^{18,19,20}.

Amid considerable negative reporting around the lack of effectiveness of poor quality antivenoms in sub-Saharan Africa and allowing that there is considerable poor reporting of data, positive information on outcomes is often missing or incomplete. Relatively few papers have been written reporting on the outcomes of antivenom use in general, but there is sound data available that demonstrates the effectiveness of good quality antivenoms. In Ghana for example, the use of the Aventis (now Sanofi) Pasteur FAV-Afrique antivenom at a remote hospital in Yeji (Central Ghana) was associated with a low case fatality rate (CFR) of 1.8%, compared to 12.1% for ASNA-C (Bharat Serums)²¹. The average administered dose of FAV-Afrique was also less than half that of ASNA-C. FAV-Afrique was manufactured in France under strict European GMP standards and had been clinically evaluated in Africa during development; ASNA-C was manufactured in India and was marketed without any prior clinical testing. One prospective study of IPSEAF-Africa (precursor to FAV-Afrique also made by Pasteur) in Cameroon reported a CFR of 1.3%, with a good safety profile (0.4% anaphylaxis, 6.3% total early adverse reactions)²². In a wider prospective study in Cameroon the average CFR for this product was 0.8% (fatality range: 0-4.3%), compared to 4.9% (fatality range 0-23.9%) retrospectively²³. In both cases the highest rates are from the same health facility and suggest that factors other than antivenom effectiveness also contribute to observed mortality. In a remote mission hospital in south-western Chad, the CFR associated with use of IPSEAF-Africa and later, FAV-Afrique, were 2.3% and 6.7% respectively, compared to 15% for a central African polyvalent antivenom marketed there without prior clinical trials by the Serum Institute of India²⁴. In an early randomized comparative trial of a new monovalent antivenom (EchiTab) for treating bites

¹⁸ Theakston RD, Warrell DA. Crisis in snake antivenom supply for Africa. *Lancet*. 2000 356(9247): 2104.

¹⁹ Warrell DA. Unscrupulous marketing of snake bite antivenoms in Africa and Papua New Guinea: choosing the right product--'what's in a name?'. *Trans R Soc Trop Med Hyg*. 2008 102(5): 397-9.

²⁰ Williams DJ, Gutiérrez JM, Calvete JJ, Wüster W, Ratanabangkoon K, Paiva O, Brown NI, Casewell NR, Harrison RA, Rowley PD, O'Shea M, Jensen SD, Winkel KD, Warrell DA. Ending the drought: new strategies for improving the flow of affordable, effective antivenoms in Asia and Africa. *J Proteomics*. 2011 74(9): 1735-67.

²¹ Visser LE, Kyei-Faried S, Belcher DW, Geelhoed DW, van Leeuwen JS, van Roosmalen J. Failure of a new antivenom to treat *Echis ocellatus* snake bite in rural Ghana: the importance of quality surveillance. *Trans R Soc Trop Med Hyg*. 2008 102(5): 445-50.

²² Chippaux JP, Lang J, Eddine SA, Fagot P, Rage V, Peyrieux JC, Le Mener V. Clinical safety of a polyvalent F(ab')₂ equine antivenom in 223 African snake envenomations: a field trial in Cameroon. VAO (Venin Afrique de l'Ouest) Investigators. *Trans R Soc Trop Med Hyg*. 1998 92(6): 657-62.

²³ Chippaux JP, Rage-Andrieux V, Le Mener-Delore V, Charrondière M, Sagot P, Lang J. [Epidemiology of snake envenomations in northern Cameroon]. *Bull Soc Pathol Exot*. 2002 95(3): 184-7.

²⁴ Bregani ER, Cantoni F, Tantardini F. Snake bites in South Chad. Comparison between three different polyvalent anti-snake venom immunotherapies. *Giorn. Ital. di Med. Trop*. 2006 11(1-2): 25-28.

by carpet vipers (*Echis* spp.) in Nigeria, used the French IPSE Africa antivenom as the gold standard comparator, no deaths were recorded following use of either product even though the doses given were subsequently found to have been too low to halt coagulopathy within 24 hrs in most patients²⁵. An improved formulation of this monovalent product (EchiTabG) was compared to a new trivalent antivenom (EchiTab-plus-ICP) in a subsequent double-blinded randomized controlled trial in Nigeria. No deaths were recorded among the 400 patients enrolled and randomized to receive one or the other of these products. Both products were shown to be highly effective in permanently restoring blood coagulability within 24 hrs (93.2% and 94.8% respectively) and had low rates of post-antivenom necrosis (7.3% and 3.6% respectively)²⁶.

It should be noted that clinical environments in which prospective studies and comparative trials of antivenom can take place potentially skew outcomes towards the positive because of inherent additional patient care and safety provisions written into trial protocols. Real-world data is vitally important to understand the effectiveness of products under normal day to day clinical practice conditions. For sub-Saharan Africa, this data is relatively rare at large scale, although data from small case series are available. One such study in two hospitals in Mali found that the use of French IPSE Africa, FAV-Afrique or German Schlangengift Immuneserum (Behringwerke) in 137 patients was associated with a CFR of 1.5% compared to a rate of 4.0% among 177 patients who received either the Indian ASNA-C or SII polyvalent antivenoms²⁷. The authors of this report also noted that CFR increased significantly ($p=0.03$) with time to presentation (post-bite). For patients who presented within 24 hrs the CFR was 3.7 times lower than for those who presented late (e.g., >72 hrs post-bite). None of the patients treated with SAIMR polyvalent antivenom (SAVP) in a small cohort treated at Ngwelezana Hospital in KwaZulu Natal, South Africa died, but 23.1% had anaphylaxis and another 15.4% had less severe allergic reactions²⁸. In a large study of the real-world outcomes of antivenom use in Nigeria, 82 deaths were reported in a cohort of 5,367 snakebite patients (CFR: 1.53%) treated at the Kaltungo Hospital in Gombe State over a 2-year period with the British EchiTabG monovalent antivenom²⁹. The authors state that prior to the introduction of this antivenom the CFR was 35-45%, but other reports from the same hospital setting noted the historical CFR as 10-20%⁹.

How clinical effectiveness is measured needs to be carefully considered. Any metric selected is only as good as the ability of health workers at the lowest levels of a health system to recognize the criteria and report the outcomes against them easily and reliably. For this to happen, the criteria need to be unambiguous and universally relevant from one setting to another, and from country to country, or region to region. The following criteria and markers of antivenom effectiveness are pragmatically based on timely administration of antivenom within 4-6 hours of snakebite.

Death

Death of a patient despite the timely administration of an appropriate dose of a specific antivenom is a simple metric that can easily be recognized and recorded. The actual cause of death however may not always be snakebite envenoming and attempting to distribute deaths to specific cause would likely pose challenges at some levels of health systems. Deaths may be due to other causes including anaphylaxis to antivenom, comorbidities, complications of bite wound infection, treatment errors (e.g., inadequate, or incorrect dosing with antivenom) or, rarely, anaphylaxis to antivenom; some health workers will be unable to differentiate between these causes. Nevertheless, accurate recording of deaths at facility level would greatly increase the available data and comparison of rates between facilities serves as a potential audit trigger to identify health centres where other factors may be

²⁵ Meyer WP, Habib AG, Onayade AA, Yakubu A, Smith DC, Nasidi A, Daudu IJ, Warrell DA, Theakston RD. First clinical experiences with a new ovine *Fab Echis ocellatus* snake bite antivenom in Nigeria: randomized comparative trial with Institute Pasteur Serum (Ipser) Africa antivenom. *Am J Trop Med Hyg.* 1997 56(3): 291-300.

²⁶ Abubakar IS, Abubakar SB, Habib AG, Nasidi A, Durfa N, Yusuf PO, Larnyang S, Garnvwa J, Sokomba E, Salako L, Theakston RD, Juszcak E, Alder N, Warrell DA; Nigeria-UK EchiTab Study Group. Randomised controlled double-blind non-inferiority trial of two antivenoms for saw-scaled or carpet viper (*Echis ocellatus*) envenoming in Nigeria. *PLoS Negl Trop Dis.* 2010 4(7): e767

²⁷ Dramé BS, Diarra A, Diani N, Dabo A. [Epidemiological, clinical and therapeutics aspects of snakebites in the Gabriel-Touré and Kati national hospitals of Mali: a ten-year retrospective study]. *Bull Soc Pathol Exot.* 2012 105(3): 184-8.

²⁸ Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: treatment modalities and outcomes. *S Afr Med J.* 2009 99(11): 814-8.

²⁹ Ademola-Majekodunmi FO, Oyediran FO, Abubakar SB. Incidence of snakebites in Kaltungo, Gombe State and the efficacy of a new highly purified monovalent antivenom in treating snakebite patients from January 2009 to December 2010. *Bull Soc Pathol Exot.* 2012 105(3): 175-8

contributing to higher-than-average mortality. Based on the limited evidence, it is reasonable to expect that antivenoms that are more robustly designed and comprehensively tested (preclinically and clinically) may meet the characteristics of the proposed TPPs, resulting optimally in CFR lower than 1% and minimally lower than 2% as has been observed for some of the products already in the market that are discussed above.

Restoration of blood coagulability

The immediate outcome measures will vary depending on whether coagulopathy is established (and detectable) prior to the administration of antivenom.

1. For patients who present with no evidence of spontaneous systemic bleeding or incoagulable blood, the appearance of spontaneous systemic bleeding or incoagulable blood at any time greater than 3-hour post-antivenom administration would indicate that the dose of antivenom chosen and administered was inadequate (and therefore ineffective).
2. Likewise, for patients who present with evidence of spontaneous systemic bleeding or incoagulable blood, the failure to stop spontaneous systemic bleeding, prevent new spontaneous bleeding within 6 hours also indicates that the dose of antivenom was inadequate and ineffective.

It should however be noted that although spontaneous bleeding may stop within less than 3 hours of administering an effective dose of antivenom, and the 20-minute whole blood clotting test (20WBCT) may become negative, as a result of synthesis in the liver of clotting factors (e.g. of fibrinogen to about 0.5g/L or about ¼ the lower limit of normal), the complete restoration of normal levels of these factors may take up to 24 hours. During this time a patient remains at risk of death from coagulopathy due to cerebral, or massive gastro-intestinal haemorrhage and must be closely monitored. Considering data from the well-designed RCT of antivenoms in Nigeria, the optimal clinical effectiveness of antivenom against venoms affecting haemostasis could be a rate of persistence of coagulopathy at 24 hours (evidenced by spontaneous bleeding, positive 20WBCT or INR >1.3) post-antivenom that is less than 3%, and the minimally acceptable level would be less than 6%.

Neurotoxicity

While the death of the patient is the ultimate indicator of failure of antivenom to either prevent development, or reverse the course of postsynaptic neurotoxicity, such as is caused by African terrestrial elapid snakes, there are intermediate criteria indicating effectiveness at the dose administered (e.g., lack of necessity for administration of additional doses, or other inventions, to prevent death) which should also be considered. For example:

1. For patients who have a patent airway at time of antivenom administration and who can maintain adequate ventilation on room air (assessed by oximeter) without intervention, an effective antivenom should optimally prevent the loss of airway patency (e.g., by aspirated vomitus or bulbar muscle paralysis) or appearance of Type 2 (hypoventilation, hypercapnic) respiratory failure from respiratory muscle paralysis and/or the need to protect the airway and breathing.
2. For patients who do not have a patent airway at time of antivenom administration (other than from prolapsed tongue), require some form of airway protection, or who are undergoing manual or mechanical ventilation, an effective antivenom should optimally prevent the need to maintain these measures beyond 6 hours following an adequate dose of antivenom without ancillary use of anticholinesterase drugs such as neostigmine.

In both cases recognition of these events provides the opportunity to continue or instigate other potentially life-saving interventions and a recognition that the dose of antivenom given has been ineffective.

Amputation and other functional loss

Aside from death itself, the loss of a limb or digit due to amputation arising from the locally destructive effects of some snake venoms, particularly where severe tissue damage arises after the administration of the antivenom (rather than being already evident pre-antivenom) is a clear indication that the activity of the venom was not adequately neutralized by the antivenom. Other post-antivenom functional losses, such as use of an organ (e.g., a kidney) post-antivenom also indicate a failure of antivenom to prevent severe sequelae.

Optimally the rate of amputation and other functional loss following treatment with an effective dose of antivenom should be less than 1%, and at a minimum it should be less than 2%.

Tissue necrosis

Optimally the need for debridement of dead tissue and/or skin grafting (excluding any deroofing of blisters) should be less than 5% and minimally less than 10%. In addition, residual disability at 6 months post-bite (e.g., contracture, arthrodesis, weakness, inability to walk unaided after lower-limb bites, or the requirement for renal or hormonal replacement therapy) would be limited to less than 2% and at a minimum to less than 5%.

More immediately, if there is no evidence of necrosis present at the time antivenom is administered, the appearance of any obvious tissue necrosis more than 3-hours post-antivenom indicates that treatment with antivenom was ineffective, or inadequate, against necrotic toxins. Where antivenom is administered to patients who already have tissue necrosis on presentation, any subsequent expansion (of the area of dermonecrosis greater than 100 cm²) post-antivenom would indicate treatment failure at the dose administered. Other surgical interventions, such as fasciotomy, are too controversial to be acceptable as criteria of antivenom failure.

Rhabdomyolysis

Some snake venoms destroy muscle tissue through either direct or indirect myotoxicity, and this may lead to elevation of urine myoglobin and blood creatine kinase, lactate dehydrogenase, and other muscle enzyme levels. Severe myotoxicity can contribute to acute kidney injury (AKI), and this has been reported after bites by sub-Saharan African snakes. Data to estimate optimal or minimal rates of rhabdomyolysis or AKI are not available in the current literature. Recognizing the appearance of rhabdomyolysis and any failure of antivenom to prevent or reduce its severity is important to improving patient outcomes, and thus the following criteria for recognition of antivenom effectiveness in patients with rhabdomyolysis should be considered:

1. In patients with no biochemical (e.g., elevated creatine kinase or lactate dehydrogenase) or physical evidence (e.g.: muscle weakness with pain or swelling; dark urine and/or myoglobinuria) of rhabdomyolysis at the time of antivenom administration, prevention of the subsequent appearance of any of these signs more than 3-hour post-antivenom indicates antivenom effectiveness.
2. Where there is evidence of rhabdomyolysis prior to antivenom administration if there is no further increase in elevation of biochemical markers and no deterioration of renal function 6 hours post-antivenom this indicates antivenom effectiveness.

In both cases these criteria would make it possible to make an informed and correct decision to administer further antivenom and/or take other steps to protect renal function and manage AKI.

Appendix 2

ADDITIONAL COMMENTS ON COST-EFFECTIVENESS OF ANTIVENOMS FOR SUB-SAHARAN AFRICA

Cost-effectiveness is a function of both antivenom clinical effectiveness and procurement cost. The most cost-effective antivenoms will have maximal effectiveness and minimal costs; however, a product that is more expensive than another product may still be more cost-effective if the potency or effectiveness (measured in terms of DALYs averted) is commensurately higher. Thus, cost-effectiveness provides a way of measuring the value of financial investment for procurement agencies.

The price of an effective antivenom will almost certainly be higher than several months of income for most snakebite victims. If out of pocket expenses remain the main source of antivenom funding in SSA, then there will be continued low demand for effective antivenoms and antivenom use will be associated to catastrophic health expenditure. Out-of-pocket expenses should no longer be the main source of antivenom funding in SSA in the future. Predominant sources of antivenom funding in SSA should transition to government funding and/or donor funding particularly as product quality and safety improve and are supported by prequalification.

It is currently not possible to define desired absolute cost targets for antivenoms intended for use in sub-Saharan Africa. Based on what is known about manufacturing costs and effectiveness of existing products, the costs of effective antivenoms will primarily differ according to the list of snake species that they target and to the breadth of their spectrum. For example, it may be more costly to manufacture an effective antivenom for puff adders than for carpet vipers, and it may be more costly to manufacture a pan-neurotoxic antivenom than a pan-non-neurotoxic antivenom. The acceptable and optimal antivenom costs must be tailored to the use case scenario of the antivenom.

Antivenom manufacturers could be incentivized to adopt a price that is fair to both buyers and sellers, even if the manufacturer is in a monopolistic situation. A fair price is higher than manufacturing and distribution costs, as it also includes a reasonable profit or return on investment; it is lower than the buyer's affordability threshold. Transparency on manufacturing costs is critical to evaluate whether the price for a given antivenom product is fair or not.

Local production of antivenom in SSA should be encouraged to enhance supply security but quality assurance, quality control and cost-effectiveness should not be compromised.

Manufacturers should take advantage of economies of scale to reduce unit costs and contribute to the reshaping of the market, and increased sustainability of supply.

Appendix 3

ADDITIONAL RESOURCES

The following documents referred to in the TPPs are available here:

World Health Organization. *Guidelines for the production, control and regulation of snake antivenom immunoglobulins*. Expert Committee on Biological Standardization. Technical Report Series no. 1004. Appendix 5. 2018.

https://www.who.int/bloodproducts/AntivenomGLrevWHO_TRS_1004_web_Annex_5.pdf

World Health Organization. *Snakebite envenoming: A strategy for prevention and control*. 2019.

<https://apps.who.int/iris/rest/bitstreams/1230920/retrieve>

World Health Organization. Regional Office for Africa. (2010). *Guidelines for the prevention and clinical management of snakebite in Africa*. World Health Organization. Regional Office for Africa.

<https://apps.who.int/iris/handle/10665/204458>

ICH Harmonised Guideline. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Current Step 4*, 9 November 2016.

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf