Target product profiles

for animal plasma-derived antivenoms

Antivenoms for treatment of snakebite envenoming in sub-Saharan Africa

World Health Organization

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TPP Development Process

These target product profiles (TPPs) were developed in line with the procedure defined in the WHO Target Product Profiles: Generic Methodology (Harmonized guidance document dated 25 January 2019).

Management of Conflicts of Interest

All TSAG members acted independently and in a personal capacity. Declarations of Interest were submitted by all members, and these were reviewed by two members of the technical unit. Potential conflicts of interest were further assessed with the technical unit team leader. Where there was a possibility of potential or perceived conflict of interest, advice was obtained from the WHO Office of Compliance, Risk Management and Ethics (CRE) and the WHO Legal Department (LEG). Nominations were approved by the Assistant Director General, Universal Health Coverage/ Communicable and Noncommunicable Diseases.

Glossary of key terms and abbreviations

This glossary provides brief definitions of terms and abbreviations used in this document; they may have different meanings in other contexts.

20WBCT	20-minute whole blood clotting test
Active pharmaceutical ingredient (API)	The specific drug substance defined by the manufacturer according to its physical and chemical composition.
Antivenom efficacy	The efficacy of an antivenom is a preclinical measure of the *in vivo* or *in vitro* neutralizing potency against a specific activity of a venom or venoms. Preclinical efficacy data is valuable for developing hypotheses that are subsequently tested in clinical trials, and for quality control of antivenom batches, where the activity of each batch lot is compared to an established minimum specification to determine the acceptability of the batch for release by the manufacturer or regulator.
CFR	case fatality rate
Clinical effectiveness	The effectiveness of an antivenom is a measure of its ability to produce a clinically effective outcome when used to treat snakebite envenoming. Antivenom effectiveness should be established through well-designed and managed clinical trials of antivenom in the treatment of real cases of envenoming.
CTD	Common Technical Document (CTD) format: a specific format for product dossier preparation recommended by WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).
DALY	disability-adjusted life year. A measure of overall disease burden, expressed as the number of years lost due to ill health, disability or early death; used to compare overall health and life expectancy in different countries. DALYs for a disease or health condition are calculated as the sum of the years of life lost due to premature mortality in the population and the years lost due to disability resulting from the health condition or its consequences.
DNDi	Drugs for Neglected Diseases *initiative*
ED_{50}	Median effective dose (or 50% effective dose): the quantity of antivenom that protects 50% of test animals injected by a particular route (e.g., subcutaneously, intravenously, or intraperitoneally), with a dose of venom (e.g., typically 5x LD_{50}) from death after an established period (usually 24–48 hours).
Envenoming	Injection of venom by an organism (e.g., a venomous snake) into another organism, leading to pathological manifestations (also called envenomation).
Fab	An antigen binding fragment of an immunoglobulin comprising a heavy chain and a light chain that each have a single constant domain and a single variable domain. Fab fragments typically result from the proteolytic digestion of IgG by papain at the amino terminal side of the disulfide bonded hinge region and have an approximate molecular weight of 50 kDa. Sometimes referred to as F(ab).
$F(ab')_2$	An antigen binding immunoglobulin fragment comprising a pair of Fab fragments connected by a protein hinge and produced by proteolytic digestion of IgG with pepsin to cleave away the Fc fragment on the carboxyl terminal side of the disulfide bonded hinge region. The approximate molecular weight is 110 kDa.

Fc	An immunoglobulin fragment without antigen binding capacity that contains paired CH_2 and CH_3 domains and the C-terminal halves of the two heavy chains connected by disulfide bonds. Approximate molecular size is 40 kDa.
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Commission on Harmonization
IgG	Immunoglobulin G: a polypeptide antibody secreted by B cells that has an approximate molecular weight of 150 kDa comprised of two heavy chains of approximately 50 kDa and two light chains of approximately 25 kDa each.
LD_{50}	Median lethal dose (or 50% lethal dose): the quantity of snake venom, injected by a particular route (e.g., subcutaneously, intravenously, or intraperitoneally), that leads to the death of 50% of the animals in a group after an established period (usually 24–48 hours).
Monovalent antivenom	Antivenoms that are raised from venom of a single species and are marketed for use in treating envenoming by that species or by closely related species (typically from the same genus). The term "monospecific" is often used and has the same meaning.
NTD	neglected tropical disease
POC	point of care
Polyvalent antivenom	Antivenoms that are raised from the venoms of multiple species and are marketed for use in treating envenoming by those species or by closely related species (typically from the same genus). The term "polyspecific" is often used and has the same meaning.
Potency [P]	Potency [P] is the amount of venom completely neutralized per millilitre of antivenom (e.g., resulting in 100% survival of test animals). Potency is a mathematically derived parameter calculated from *in vivo* antivenom ED_{50} and corresponding venom LD_{50} data using the equation $P = n - 1\ LD_{50}/ED_{50}$ where n = number of LD_{50} in the challenge dose.
QALY	quality-adjusted life year. A measure of quality of life and length of life health outcomes related to overall disease burden that assesses the value of health interventions. QALYs for a disease or health condition are calculated as the extra years lived multiplied by the weighting for quality of life.
RCT	randomized controlled trial
Total Protein	The mass of all the protein material in an antivenom solution, including but not limited to intact or fragmented immunoglobulins, non-immunoglobulin donor animal proteins, and extraneous protein material, determined by any conventional protein-specific quantification assay (e.g., colorimetric, fluorometric, spectrophotometric, chemical) and expressed in terms of mg protein per millilitre of reconstituted antivenom solution, or mg protein per gram of lyophilized antivenom solids.
TPP	target product profile
TSAG	Technical and Scientific Advisory Group on TPPs for Snake Antivenoms and Other Treatments
WFI	water for injection
WHO	World Health Organization

Executive summary

We describe the first WHO public-benefit Target Product Profiles (TPPs) for snakebite antivenoms. We have focused initially on sub-Saharan Africa as there is a widespread perception that the need for more and better antivenom products is even greater here than in other parts of the world. Four TPPs are described. The first is for products that are intended for widespread utility throughout sub-Saharan Africa, for treatment of envenomation irrespective of the species of snake causing a bite. The second is for products where the snakebite causes predominantly neurotoxic effects. The third is for snakebites where the effects are largely haemorrhagic or procoagulant. The fourth is for treatment of envenoming for a single species (or genus) of snake. These TPPs are intended to provide guidance to manufacturers, regulators, procurement agencies, clinicians, and researchers, to improve antivenoms and thus treatment of snakebite envenomation.

Introduction

Snakebites are responsible for considerable mortality and morbidity throughout much of the world. The World Health Organization (WHO) has convened a Technical and Scientific Advisory Group (TSAG) to generate public-sector Target Product Profiles (TPPs) for treatment of snakebite envenoming. 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 years *(1)* and are the most effective drugs currently available for treatment of snakebite envenoming. They are typically produced by immunizing 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 *(1)*.

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 2023 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 annum *(2)*. 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 deaths *(3)*. Victims are from some of the least-empowered, poorest, and most-marginalized 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 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.

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 are 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 region *(1)*. These are the venomous snakes that are most encountered and pose the greatest potential threat to human life and wellbeing. A further 24 species are 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 syndromes *(5)* 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 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 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 can 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 coupled to deeper understanding of the proteomic and pharmacological profiles of each venom used can lead to products of greater specificity and potency that are highly effective, safe, and more affordable.

Monovalent products are appropriate where one species or genus causes either most of the 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 larger quantities 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

Scope of TPPs

For every characteristic of these TPPs, we define both ideal and minimal criteria; the former as targets to which all should aspire and the latter as currently acceptable criteria, based on knowledge of products currently available.

Almost all the people living in the countries within the sub-Saharan African region are potentially at risk of snakebite envenoming because indigenous populations of venomous terrestrial snakes are so widespread. Antivenoms are used to treat snakebites in men, women (including pregnant women), and children of all ages. While patients will ultimately be the recipients of antivenoms, procurement agencies and health care professionals are the major “end-users” rather than patients themselves.

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 be encouraged as the optimal case for expanding accessibility to safe, effective antivenoms for most of the population. Minimal clinical skills for health workers administering antivenoms should include the ability to detect criteria for antivenom treatment (e.g., 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.

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 scepticism and concern over the usefulness of animal plasma-derived antivenoms in general *(6,7)*. 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% *(8,9)*. 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.

Indications and contraindications

Current Pan-Africa polyvalent products are designed for treating bites by WHO Category 1 species from the genera *Bitis*, *Dendroaspis*, *Echis* and *Naja*. The TPP for a Pan-African polyvalent antivenom slightly broadens this to include the possibility of also including immunizing venoms from Category 2 species such as *Dispholidus typus*.

Monovalent antivenoms are most appropriate for species that fulfil one or more of the following conditions:

- 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

Current monovalent African products are designed for treating bites by WHO Category 1 or 2 species such as *Echis romani/E. ocellatus* and *Dispholidus typus*. Interest in raising monovalent antivenoms for some other species such as *Naja nigricincta*, *N. ashei* or *N. mossambica* has been expressed.

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 (*Naja* spp.) and mamba (*Dendroaspis* spp.) genera that produce predominantly neurotoxic clinical effects and can potentially cause rapid death through paralysis of airway and breathing muscles. Equivalent products 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 (*Naja* spp.), African adder (*Bitis* spp.), boomslang (*Dispholidus typus*) and carpet viper (*Echis* 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.

There are no absolute contraindications to treatment of snakebite envenoming with antivenom. The choice as to which type of antivenom should be used – polyvalent, monovalent, or syndrome-specific– will be guided by availability of products and clinical judgement.

Manufacturing considerations

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 types 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 immunizing venoms from snakes and the immunization and collection of hyperimmune plasma from host animals[1].

[1] https://www.who.int/activities/ensuring-fair-prices-for-medicines

Active pharmaceutical ingredient

Antivenoms are currently available as intact (whole) immunoglobulins (IgG), or as $F(ab')_2$ (or more rarely Fab) fragments. Antivenom manufacturers broadly define the active pharmaceutical ingredient (API) in animal plasma-derived antivenoms as the specific antibody component that is produced through their production process. This definition typically describes the type of antibody (e.g., IgG or a fragment that has been derived from it), the molecular weight range, physical characteristics, and tertiary structure. It refers to all the antibodies present that meet this description, not just the specific neutralizing antibodies, which typically comprise only 3–30% of the total antibodies present. Hence the definition of API adopted by the TSAG for these TPPs refers to the specific drug substance defined by the manufacturer according to its physical and chemical composition.

Antivenom preparations of $F(ab')_2$ or Fab are considered minimally acceptable whilst preparations of intact immunoglobulins (IgG) are optimal because they are:

- Higher in yield compared to $F(ab')_2$ or Fab fragments *(1)*.
- Consistently of higher purity and with lower non-API content compared to $F(ab')_2$ products *(1)*.
- Benefit from the robust contribution of caprylic acid treatment to the inactivation of lipid-enveloped viruses *(10, 11)*.
- Have favourable pharmacokinetic profiles including longer half-lives *(12)*.
- Demonstrate comparable safety and tolerability profiles with evidence that retention of the Fc region does not induce increased adverse drug reactions *(13)*.
- Clinical studies have provided evidence that intact immunoglobulins produced under GMP are safe, well tolerated, effective in neutralizing various types of venoms and with good clinical effectiveness *(8)*.

Finished product form

Both lyophilized and liquid preparations have advantages and limitations. 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). Lyophilized 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 operated to maintain the quality of the product. Faulty lyophilization can result in denatured protein that is difficult to solubilize. The TSAG also recognized that a thermal tolerance upper limit of 25°C potentially limits the use of lyophilized antivenoms since daily ambient temperatures in many parts of sub-Saharan Africa exceed this throughout the year. Many countries in sub-Saharan Africa have climates that range from ICH climatic zone III (>22°C and ⩽15 hPa) to IVb (>22°C and >27 hPa) where ambient temperature frequently exceeds 25°C. For this reason, specifications related to lyophilized product characteristics were aligned to ICH climatic zone IVb thermal tolerance range and manufacturers should demonstrate that their products comply with this specification.

Protein and immunoglobulin content

Current pharmacopeia and WHO guidelines recommend upper limits for total protein but make no provision for minimum quantities. Broad-spectrum and syndrome-directed 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 yields from large adult spitting cobras (*Naja* spp.) can exceed 1200 mg, average yields from adult mambas (*Dendroaspis* spp.) can exceed 120 mg and average yields from adult African adders (*Bitis* 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 large amounts of venom. Considering that only 3–30% of API contains venom-binding antibodies the TSAG recommended that specifications of at least 5.0 % w/v (minimal model) and 7.5 % w/v (optimal model) be introduced for the lower limits of acceptable protein content. Maximum protein content should be in accordance with requirements of regulatory agencies and the relevant pharmacopeia.

Regarding immunoglobulin content, 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. Most manufacturers currently specify that products contain not less than 85% API (e.g., whole IgG or $F(ab')_2$ molecules). Several products assessed by WHO fell short of this specification in independent laboratory assessments. For this reason, 85% was considered by the TSAG 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 FV should not be included in the measurement of this

specification. Optimally, higher purity is desirable with 90% being recommended. 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.

Preclinical efficacy studies

Antivenom should be comprehensively evaluated in a preclinical laboratory environment prior to marketing authorization or licensing. WHO Guidelines set out a suite of quality control, viral safety, stability, and efficacy tests that should be used to evaluate products *(1)*. Establishing preclinical efficacy using biologically relevant toxin activity neutralization bioassays is fundamentally important for ensuring products that do not meet specifications are not marketed. At a minimum, the assessment of an antivenoms ability to neutralize venom-induced lethality is required. This establishes the exact volume of antivenom that is required to neutralize venom lethality as determined by the antivenom median effective dose (ED_{50}) bioassay in laboratory animals. ED_{50} data should be converted to Potency (P), to estimate efficacy based on the amount of antivenom required to provide complete neutralization of a given quantity of venom *(14)*. This is more relevant the ED_{50}, since P 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. In addition to estimating the dose required to prevent lethality, antivenoms that meet the optimal TPP specifications will also be robustly evaluated for their ability to neutralize specific toxin activities (e.g., necrotic, haemorrhagic, myotoxic, defibrinogenating or coagulant activities) through various toxin-specific activity bioassays *(1)*.

It is also important that preclinical efficacy data should demonstrate the potential of the antivenom to neutralize *in vivo* a biologically relevant amount of venom. Many products currently express efficacy in terms of the ability of antivenom to neutralize a specified number of murine median lethal doses (LD_{50}). This is disingenuous because depending on the LD_{50} of the species concerned the mass of venom neutralized using this metric can vary substantially *(14)*. In the absence of empirical data on the mass of venom injected by various species during defensive strikes, TSAG considered that the approach adopted elsewhere (e.g., Seqirus antivenoms in Australia), using neutralization of the average adult venom yield for each immunizing species by the recommended dose of antivenom, should be applied to preclinical efficacy testing of antivenoms in sub-Saharan Africa.

Antivenoms should not be marketed based on preclinical efficacy studies alone, however the use of robust preclinical data in the development of hypotheses that are subsequently tested through well-designed and managed clinical trials is appropriate. All antivenoms should be subject to clinical evaluation to validate the proposed dosage and its safety profile before the product is marketed. WHO Guidelines recommend that national regulatory authorities should expect antivenom manufacturers to either provide data confirming the clinical effectiveness and safety of products against envenoming by local snake species, or to support in-country clinical testing of the products to validate the preclinical efficacy and proposed dosages *(1)*. Such studies must incorporate robust methodologies for reliable identification of the biting species as an essential component of all clinical trials and other clinical studies of antivenoms.

Clinical considerations

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 routinely. Hence all patients, irrespective of body size, need to receive the same, standardized initial dose of antivenom, one which is adequate to neutralize the potential mass of injected venom.

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 *(1)*.

Well-designed, pragmatic and transparently managed clinical trials of antivenom are essential, and these TPPs recommend that antivenoms be carefully evaluated in both preclinical 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. The International Council for Harmonization (ICH) GCP 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.

To define minimal parameters for clinical effectiveness the TSAG considered available data from 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 antivenoms. Characteristics for optimal performance were then defined with the aim of aspiring to a 50% improvement over and above what is currently best-in-market performance, based on adoption of these TPPs in the design and manufacturing of new or improved products. In both cases the effectiveness parameters assume that patients will receive treatment 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), and that antivenom will be given in an appropriate initial dose, optimally based on results of independent pre-clinical testing by a competent laboratory and preliminary dose-finding clinical trials, and which has been accepted and is recommended by national regulators, or in national/regional guidelines. Prima facie evidence of effectiveness should first be established for treatment of envenoming by a snake species whose venom was used in its production (i.e., it is specific for that species). Clinical effectiveness against other species for which there is preclinical data supporting a hypothesis of paraspecific neutralization should also be established based on the same assumptions. Additional information about clinical effectiveness parameters is included elsewhere in this document.

Frequency and route of administration

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 can neutralize all 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 plans to coordinate collection of data on average adult venom yields and include these data in its Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins.

Intravenous infusion and intravenous injection are the two available methods for delivery of antivenom. Each has advantages and disadvantages. Infusion of antivenom diluted in isotonic fluid is safe, easy, and convenient, but equipment and consumables add additional cost in resource-poor settings. One advantage is that venous access can be maintained for administration of other drugs or for ongoing fluid management. Potential risks include (1) that patients may be left unattended during administration at a time when there is a risk of evolution of adverse drug reactions, (2) unobserved and uncontrolled infusion rate may lead to fluid overload, and (3) that antivenom will be incorrectly diluted in a large quantity of intravenous fluid (e.g., 1 L) and wrongly given over a protracted time at a maintenance rate.

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.

Stability, storage, presentation and packaging

As previously mentioned, much of sub-Saharan Africa is classified as falling between ICH climatic zones III, IVa or IVb. Temperature tolerance of at least 30°C ± 2°C, and relative humidity of up to 75% ± 5% is required for long term stability of products deployed in these environments. Longer shelf lives are preferred. Both real-time and accelerated stability studies should be considered to establish the thermal tolerances of antivenoms.

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. To ensure that all patients receive an effective therapeutic dose of antivenom as early as possible, presenting the antivenom as a single effective therapeutic dose (e.g., in single 50–100 ml vials or sterile infusion bags) is needed. Another alternative is to package several smaller vials (e.g., 10–20 ml) together in a single outer container or carton that clearly indicates that all the contents should be administered to deliver an effective initial dose. All outer packaging should clearly indicate that the product is intended for 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.

Vial labels and packaging should also include the amount of total protein (e.g., mg protein/vial), the proportion (e.g., NLT 85%) that is comprised by the API, and indicate the presence of other potential vial contents (e.g., aggregates, non-API immunoglobulins, other proteins, preservatives, stabilizers).

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 lower-cost products of limited effectiveness and safety. Whilst it is tempting to indicate an acceptable unit price for an antivenom, the TSAG 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. It is apparent to WHO through its risk-benefit assessment of antivenoms for the sub-Saharan African market that some manufacturers may base dose recommendations on marketing considerations rather than preclinical or clinical performance. Procurement agencies should adopt policies that support the selection of antivenom products based on clinical effectiveness (e.g., cost per effective treatment), rather than cost per unit (e.g., vial, ampoule). This has implications for cost-effectiveness evaluation of antivenoms since it shifts the criteria to base pricing on cost of an effective treatment, rather than a single arbitrarily formulated unit of product. Performance and cost-effectiveness data are not currently available across all 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. 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[2]. Further information is given elsewhere in this document.

Supportive/adjunctive therapy

The WHO guidelines on Prevention and Clinical Management of Snakebite in Africa should be followed. The items listed in those guidelines should be available for potential use with all patients who present with a suspected snakebite. They represent 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.

Training and education

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.

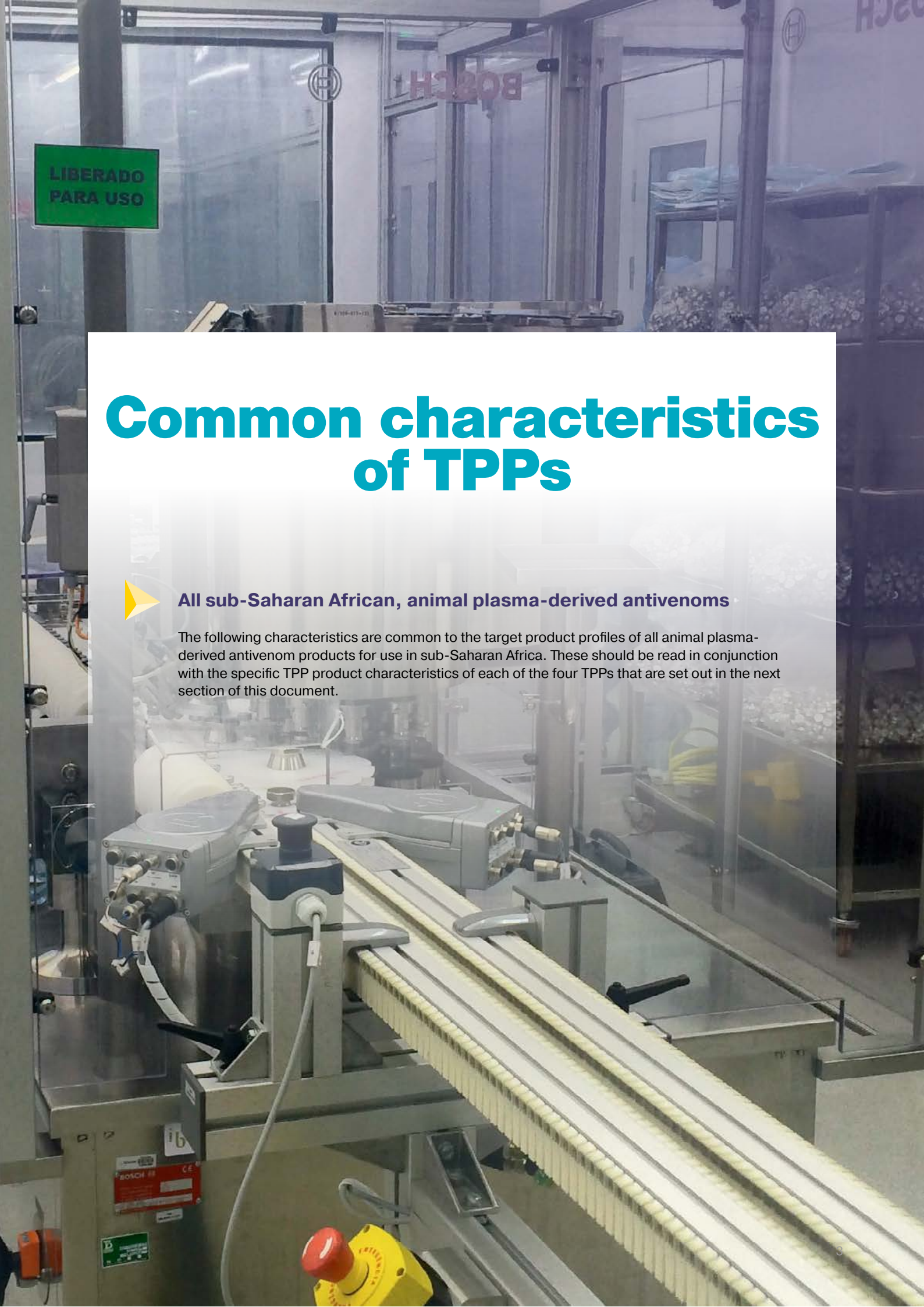
[2] https://www.who.int/activities/ensuring-fair-prices-for-medicines

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 TPPs

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.
2. Geographic working range	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, United 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. *There are no venomous snakes of category 1 or 2 importance: Cabo Verde, Comoros, Madagascar, Mauritius, Seychelles*.	
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 in accordance to recognized standards and existing national regulatory requirements.	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 in accordance to recognized standards and existing national regulatory requirements.
4. Intended end-users	End users include procurement agencies and health care professionals	
MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
5. Immunizing venoms	In addition to minimal requirements, immunizing venoms should meet the specifications of corresponding WHO reference venoms[3] for each species of snake included in the immunizing mixture for the product.	Immunizing venoms should be selected based on a detailed analysis of the composition of venoms from specimens across the geographic range of each species, to ensure that all medically important toxin groups are represented in the immunizing venom pool for the product. Pooled venoms should be designed to have minimal compositional overlap and broad geographic representation of venom variants.
6. Active Pharmaceutical Ingredient (API)	Intact (whole) IgG immunoglobulin molecules obtained through appropriate technology	Either intact (whole) IgG immunoglobulin molecules or $F(ab')_2$ immunoglobulin molecule fragments obtained through appropriate technology.
7. Finished Product Form	Lyophilized final product forms are optimally acceptable.	Either liquid or lyophilized final product forms are minimally acceptable.
8. Specific Immunoglobulin Content (Active Pharmaceutical Ingredient [API] content)	Not less than 90% of the total protein content must consist of intact active pharmaceutical ingredient [e.g., intact (whole) IgG that have been defined by the manufacturer as the Drug Substance in the Product Dossier/Master File]. Total API content to be included in vial labelling.	Not less than 85% of the total protein content must consist of intact active pharmaceutical ingredient [e.g., whole IgG or $F(ab')_2$ fragments of IgG that have been defined by the manufacturer as the Drug Substance in the Product Dossier/Master File]. Total API content to be included in vial labelling.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
9. Preclinical efficacy (Including potency of the antivenom)	Preclinical determination of median effective dose (ED_{50}), potency (P) and toxin-specific activity bioassays *(1)* demonstrates the potential of the antivenom to neutralize *in vivo* at least the average adult venom yield of each species by the proposed initial dose of the product.	Preclinical determination of median effective dose (ED_{50}) and potency (P) demonstrates the potential of the antivenom to neutralize *in vivo* at least the average adult venom yield of each species by the proposed initial dose of the product.
10. Safety and tolerability[4]	Incidence of anaphylaxis[5] <2.0%. Incidence of other early adverse drug reactions or late-presenting serum sickness of <10%.	Incidence of anaphylaxis <5.0%. Incidence of other early adverse drug reactions or late-presenting serum sickness of <20%.
11. 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.
12. 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 clinical picture and considering the natural time course for reversal of functional and physiological disturbances.	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 administered based on the observed clinical picture and considering the natural time course for reversal of functional and physiological disturbances.
13. 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.	
14. 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.
15. Product stability	**For lyophilized products**: 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 2 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 2 years in conditions up to and including ICH refrigerated zone (temperature of 5°C ± 3°C).

16. Storage	**For lyophilized products**: Room temperatures up to ICH climatic zone IVb (30˚C ± 2˚C and relative humidity of up to 75% ± 5%).	**For lyophilized products**: Room temperatures up to ICH climatic zone IVb (30˚C ± 2˚C and relative humidity of up to 75% ± 5%). **For liquid products**: ICH refrigerated zone (temperature of 5˚C ± 3˚C).
17. 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) or a carton/box that is clearly labelled as containing vials that must be given together in order to constitute a clinically effective initial dose comprising sufficient active pharmaceutical ingredient to neutralize 100% of the average adult venom yields of each of the snake species for which it is intended.
18. 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 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.	

OPERATIONAL CHARACTERISTICS		
CHARACTERISTIC	OPTIMAL	MINIMAL
19. 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.
20. Supportive and adjunctive therapy	Information is available in the WHO Guidelines on Prevention and Clinical Management of Snakebite in Africa.	
21. Training and 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 (positioning), iv access, iv cannula placement, management of iv infusion, criteria for use of/administration of adrenaline/epinephrine and other ancillary drugs.	

[3] 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 2023.

[4] Expected characteristics in naïve populations. There is heightened risk in specific groups of people (e.g., snake handlers) who may be hypersensitized through previous exposure to equine or ovine (exogenous) immunoglobulin products.

[5] 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.

A. Chadian carpet viper (*Echis romani*)
B. Puff adder (*Bitis arietans*)
C. Brown forest cobra (*Naja subfulva*)
D. Mozambique spitting cobra (*Naja mossambica*)
E. Black mamba (*Dendroaspis polyepis*)
F. Western green mamba (*Dendroaspis viridis*)
G. Boomslang (*Dispholidus typus*)

Specific characteristics of TPPs

Broad-spectrum pan-African polyvalent antivenoms

Products that are intended for all the major genera of WHO Category 1 medically important venomous snakes throughout all sub-Saharan Africa.

Venoms should be representative of each of the WHO Category 1 genera. Minimally this would involve the use of at least two different *Bitis*, *Echis* and *Dendroaspis* species, two species of cytotoxic *Naja* and two species of neurotoxic *Naja* species (e.g., proposed WHO reference standard venoms).

Examples of species that could be used:

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

Other combinations, or additional venoms, including those from Category 2 (e.g., *Dispholidus typus*) could be used by a manufacturer at their discretion. The goal should be to select venoms from species that will induce the broadest possible immune response in plasma donor animals, resulting in polyvalent antivenom with the ability to neutralize as wide a range of venoms across as large a geographical area as possible. In line with recommendations in the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins[1] *(1)* the venoms used should be a pool from across the geographic range of each species, including male and female juveniles, sub-adults, and adults. Venom from each individual geographic population should be characterized and selected to ensure that the broad range of intraspecific variation likely in that species is incorporated into the final immunizing venom pool.

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, in part, on the molecular mass of the toxin. Thus, optimally pooled venoms should contain compositionally similar toxins, and when possible, those with similar LD_{50}. 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 more effective approach is to immunize groups of horses with different venom pools *(1)*. The different hyperimmune plasma pools should be fractionated and purified separately, and the specific immunoglobulins combined proportionally to yield the final formulation.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. 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.

Naja pallida (Kenya) © David J. Williams

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
22. 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.
23. Contraindication	None	None

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
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.

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: • 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 deroofing of blisters) to <5%.	When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces: • 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 deroofing of blisters) to <10%.

Sub-Saharan African monovalent antivenoms

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

Examples of species for which monovalent antivenoms might be raised:

- Species specific: *Dispholidus typus*
- Genus specific: *Echis*: *E. romani/E. ocellatus*, *E. leucogaster*, *E. jogeri*, *E. pyramidum*
- Locally important species: *Naja*: *N. nigricincta*, *N. ashei*, *N. mossambica*

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

In line with recommendations in the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins *(1)* 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.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. 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.

Green *Dispholidus typus* (Kenya) © David J. Williams

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.	
27. Contraindication	None	None

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
28. 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.	

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
29. 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: • 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 deroofing of blisters) to <5%.	When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces: • 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 deroofing of blisters) to <10%.

Pan-African polyvalent antivenoms for neurotoxic envenoming

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

Venoms should be representative of each of the WHO Category 1 or 2 genera that have neurotoxicity as the dominant action of the venom. Minimally this would involve the use of at least two *Dendroaspis* species and three species of neurotoxic *Naja* species (e.g., non-spitting cobras such as Naja haje).

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*)

Other combinations, or additional neurotoxic venoms could be used by a manufacturer at their discretion. In line with recommendations in the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins *(1)* 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.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. 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.

Naja haje (Kenya) © David J. Williams

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
30. 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 (*Naja* spp.) or mamba (*Dendroaspis* spp.); to be used in conjunction with other treatment support interventions to address disease manifestations.	
31. 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.	

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
32. 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.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
33. 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: • case fatality rate (CFR) to <1%. • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofing of blisters) to <5%.	When administered within 4-6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces: • case fatality rate (CFR) to <2% • need for debridement of dead tissue and/or skin grafting (excluding decompression or deroofing of blisters) to <10%.

Pan-African polyvalent antivenoms for non-neurotoxic envenoming

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

Venoms should be representative of each of the WHO Category 1 or 2 genera that lack neurotoxic activity and instead have haemotoxicity or cytotoxicity as the dominant actions of their venoms. Minimally this would involve the use of at least two *Bitis* species, two *Echis* species and two species of non-neurotoxic *Naja* species (e.g., cytotoxic spitting cobras).

Examples of species to be used:

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

Other combinations, or additional venoms from other haemotoxic or cytotoxic species could be used by a manufacturer at their discretion. In line with recommendations in the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins *(1)* 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.

Where no reference standard exists then the minimal criteria for immunizing venoms shown above should be met. 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.

Bitis nasicornis (Uganda) © David J. Williams

SCOPE		
CHARACTERISTIC	OPTIMAL	MINIMAL
34. 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 (*Naja* spp.), African adder/viper (*Bitis* spp.), boomslang (*Dispholidus typus*) or carpet viper (*Echis* spp.); to be used in conjunction with other treatment support interventions to address disease manifestations.	
35. Contraindication	Patients with snakebite envenoming who have evidence of neurotoxic envenoming (with or without tissue necrosis, and without coagulopathy or haemorrhagic effects).	

MANUFACTURING CONSIDERATIONS		
CHARACTERISTIC	OPTIMAL	MINIMAL
36. 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.

PERFORMANCE		
CHARACTERISTIC	OPTIMAL	MINIMAL
37. 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: • 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 deroofing of blisters) to <5%.	When administered within 4–6 hours of a snakebite by one of the immunizing venom species, the antivenom reduces: • 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 deroofing of blisters) to <10%.

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 good in most 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 *(15, 16)*. 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 may 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 *(17, 18, 19)*.

Young woman bitten by a carpet viper in Nigeria © David A. Warrell

Clinical Outcomes

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) *(15)*. 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 *(15)*. One prospective study of IPSER-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) *(20)*. 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%) retrospectively *(21)*. In both cases the highest rates were from the same health facility and suggest that local factors other than antivenom effectiveness also contributed to observed mortality. In a remote mission hospital in south-western Chad, the CFR associated with use of IPSER-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 India *(22)*. In an early randomized comparative trial of a new monovalent antivenom (EchiTAb) for treating bites by carpet vipers (*Echis* spp.) in Nigeria, used the French IPSER 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 patients *(23)*. 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) *(24)*.

It should be noted that clinical environments in which prospective studies and comparative trials of antivenom 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 IPSER Africa, FAV-Afrique or German Schlangengift Immunserum (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 antivenoms *(25)*. 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 reactions *(26)*. 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 antivenom *(27)*. 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 but attempting to attribute deaths to specific underlying causes 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 contributing to higher-than-average mortality.

Based on the limited evidence, including examples discussed above, 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.

Restoration of blood coagulability

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

- 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).
- 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 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 some clotting factors (e.g., of fibrinogen to about 0.5 g/L or about 25% the lower limit of normal), the complete restoration of normal levels of these factors may take more than 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:

- 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.
- 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 reduce 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 in reversing the paralysis.

Amputation and other functional loss

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 organ failure (e.g., a kidney) post-antivenom also indicate that antivenom did not 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%. Use of effective antivenom should reduce the likelihood of 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) but other factors that influence long-terms outcomes.

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 cm^2) 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:

- 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 >3-hour post-antivenom indicates antivenom effectiveness.
- 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.

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 efficacy (measured in terms of DALYs averted or QALYs gained) 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 most snakebite victims can afford. As the cost per treatment often exceeds several months of income *(28)* if patient out of pocket payments remain the main source of antivenom funding in SSA, then there will be continued low demand for effective antivenoms, and utilisation will be tied 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 procurement and supply in SSA should transition to government funding and/or donor funding particularly as product quality and safety improve and are supported by prequalification *(29)*.

It is currently not possible to define optimal absolute cost targets for antivenoms intended for use in sub-Saharan Africa due to highly variable clinical effectiveness. 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-African neurotoxic antivenom than a Pan-African non-neurotoxic antivenom. The acceptable and optimal antivenom costs must be tailored to the use case scenario of the antivenom.

Nevertheless, it remains desirable to minimize the cost of effective antivenoms. Antivenom manufacturers could be incentivized to adopt a pricing that is fair to both buyers and sellers, even if the manufacturer is in a monopolistic situation. A fair price would be higher than manufacturing and distribution costs, and includes a reasonable profit or return on investment, while being 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. 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.

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.

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Department of Control of Neglected Tropical Diseases
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

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