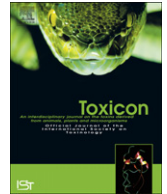




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## Review

## Snakebite envenoming from a global perspective: Towards an integrated approach

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## ABSTRACT

Snakebite envenoming is a neglected public health challenge of compelling importance in many regions of the world, particularly sub-Saharan Africa, Asia, Latin America and Papua-New Guinea. Addressing the problem of snakebite effectively demands an integrated multifocal approach, targeting complex problems and involving many participants. It must comprise:

- (a) Acquisition of reliable information on the incidence and mortality attributable to snakebite envenoming, and the number of people left with permanent sequelae.
- (b) Improvements in production of effective and safe antivenoms, through strategies aimed at strengthening the technological capacity of antivenom manufacturing laboratories.
- (c) Increasing the capacity of low-income countries to produce specific immunogens (snake venoms) locally, and to perform their own quality control of antivenoms.
- (d) Commitments from regional producers to manufacture antivenoms for countries where antivenom production is not currently feasible.
- (e) Implementation of financial initiatives guaranteeing the acquisition of adequate volumes of antivenom at affordable prices in low-income countries.
- (f) Performance of collaborative studies on the safety and effectiveness of antivenoms assessed preclinically and by properly designed clinical trials.
- (g) Development of antivenom distribution programmes tailored to the real needs and epidemiological situations of rural areas in each country.
- (h) Permanent training programmes for health staff, particularly in rural areas where snakebites are frequent.
- (i) Implementation of programmes to support those people whose snakebites resulted in chronic disabilities.
- (j) Preventive and educational programmes at the community level, with the active involvement of local organizations and employing modern methods of health promotion.

Such an integrated approach, currently being fostered by the Global Snake Bite Initiative of the International Society on Toxinology and by the World Health Organization, will help to alleviate the enormous burden of human suffering inflicted by snakebite envenoming.

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## 1. Introduction

Snakebite envenoming is a global public health problem of such size and complexity that it deserves far more attention from national and regional health authorities than it has been given up until now. This environmental and occupational disease affects mainly agricultural workers and their children in some of the most impoverished rural communities of developing countries in Africa, Asia, Latin America and Oceania (World Health Organization, 2007a). It therefore fulfills the criteria of a 'neglected tropical disease' as it affects, almost exclusively, poor and politically unempowered people living in rural parts of generally low-income, tropical countries (Kindhauser, 2003). Accordingly, the World Health Organization (WHO) recently incorporated snakebite envenoming in its list of neglected diseases ([www.who.int/neglected\\_diseases/diseases/en](http://www.who.int/neglected_diseases/diseases/en)). Like other neglected diseases, snakebite envenoming has received little attention from health authorities, pharmaceutical companies or research funding agencies in any part of the world. However, in recent years, there has been a growing awareness of the disease burden created by snakebite accidents, as reflected by the awakening interest of WHO, regional and national health authorities, non-governmental organizations, and some antivenom manufacturers and research groups, in discussing and searching for solutions to this complex health problem (World Health Organization, 2007a; Williams et al., in press).

As is the case with other health issues, addressing the problem of snakebite effectively demands an integrated approach. This should encompass: (a) research issues, (b) technology development and transfer between antivenom-producing nations and current non-producers, (c) improvements in both quantity and quality of antivenom production to ensure the provision of effective and safe antivenoms at affordable prices, (d) public health interventions at various levels to improve distribution of antivenoms, training of health staff, and care of those who have suffered permanent disabilities as a consequence of snakebites, and (e) involvement of local community organizations in the prevention and management of this problem through public education and advertising. Here, we review these issues and define a series of tasks whose completion is essential if an integrated strategy is to be launched to alleviate the burden of this devastating and neglected disease.

## 2. Assessing the actual impact of snakebite envenoming worldwide

The lack of reliable information on the true epidemiological impact of snakebite envenoming has severely hampered attempts to engage the attention and support of health authorities and other organizations. Health statistics (reporting of hospitalized cases to the authorities) relating to snakebites may be satisfactory in some cases (e.g. Ministério da Saúde in Brazil; see de Oliveira et al., 2009), but for many low-income countries the impact of this condition is little known and remains largely under-reported. This is in part due to poor health statistics and

also because a proportion of those affected do not seek medical attention and are therefore invisible to official reporting (Gutiérrez et al., 2006; World Health Organization, 2007a). The pioneering publication on global snakebite mortality by Swaroop and Grab (1954) was based mainly on hospital statistics. Chippaux (1998) and Kasturiratne et al. (2008) have presented estimates of the global impact of snakebite based on diverse methodologies. The highest burden of snakebite was identified in South and Southeast Asia, sub-Saharan Africa and Central and South America (Fig. 1). By extrapolation from point incidences obtained from studies in particular locations within the countries, Chippaux (1998) estimated global annual totals of 5,400,000 bites, over 2,500,000 envenomings and around 125,000 deaths. Kasturiratne et al. (2008) estimated that the annual global totals for envenomings ranged from 421,000 to 1,841,000, and fatalities from 20,000 to 94,000. However, when other researchers performed population surveys in some regions, by distributing questionnaires to randomly selected households, the incidence, mortality and long term disability due to snakebites was shown to be much higher than had been suggested by the official statistics (see for example Hati et al., 1992; Sharma et al., 2004; Snow et al., 1994; Trape et al., 2001). A study in Sri Lanka illustrated how snakebite deaths in rural areas could be grossly underestimated in official returns from country areas (Fox et al., 2006). Another aspect that deserves careful attention is the monitoring of the effects that ongoing environmental changes may have on the distribution of venomous snakes and, consequently, on the incidence of snakebites. Thus, field studies on the distribution of snakes *vis a vis* epidemiological data are necessary to detect changes in the patterns of snakebite incidence in specific locations.

The true impact of snakebite envenoming can be discovered only by concerted efforts at regional, national and local levels. This involves, among other tasks:

- (a) Introducing the compulsory notification of snakebite envenoming.
- (b) Implementing the use in death certification of the specific classifier T 63.0 snake venom listed in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (World Health Organization, 2007b).
- (c) Supporting well-designed and performed epidemiological research, including hospital statistics and community surveys.
- (d) Strengthening record keeping of snakebites in health centres.
- (e) Training medical and other health staff in the appropriate procedures to keep and maintain epidemiological records of snakebites.
- (f) Promoting collaborative projects between university research groups and governmental health departments on this subject.

Undoubtedly, any global initiative aimed at effectively confronting this neglected disease depends on a robust estimate of its actual burden in every region and country. These data cannot reliably be inferred indirectly from the

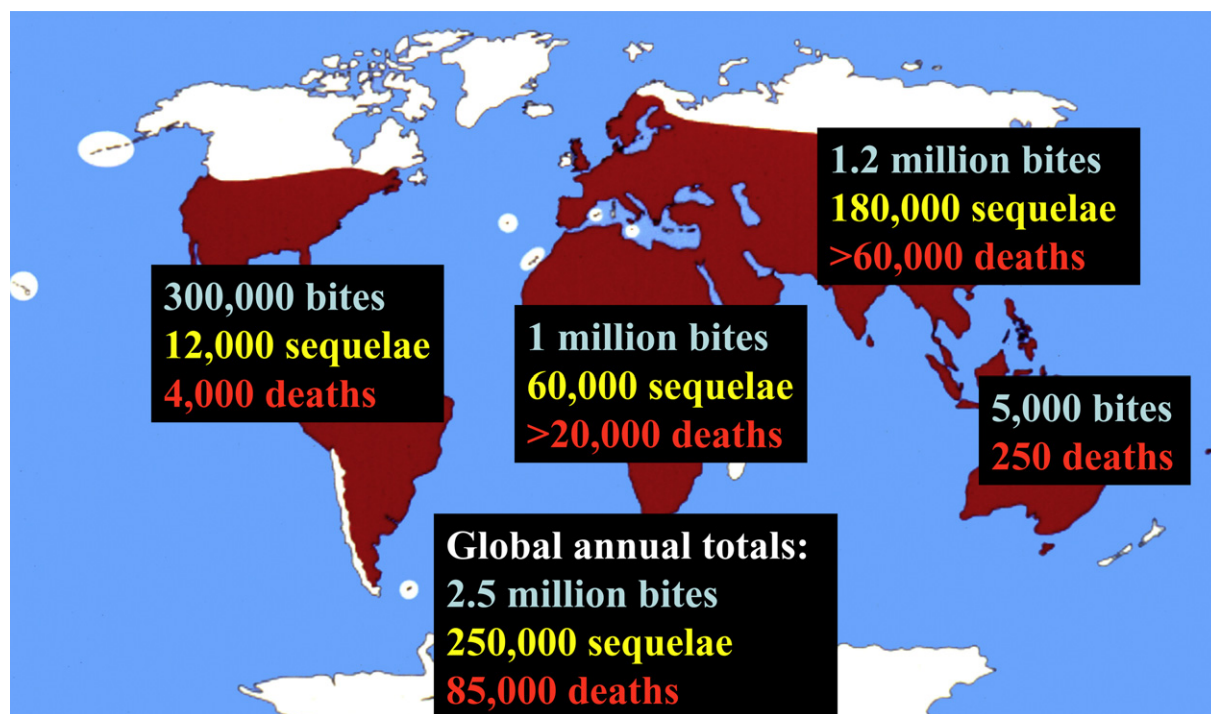


Fig. 1. Estimated regional and global morbidity and mortality from snakebite.

incidences in adjacent countries. What is required are actual country-specific estimates based on a standardized protocol that combines both hospital admissions data and broad community-based population surveys. Such a protocol could be developed by panels of experts and deployed using modern web-based database server technology and other resources, depending on the local circumstances in low-income countries.

### 3. The need to increase the production of effective and safe antivenoms

Since the end of the 19th century, animal-derived antivenoms have provided the only scientifically-validated treatment for snakebite envenoming (Bon, 1996). There are laboratories spread across all the continents that manufacture antivenoms (Meier, 1995), which consist of whole IgG molecules or products of their enzymatic digestion, bivalent F(ab')<sub>2</sub> or monovalent Fab (Laloo and Theakston, 2003; Theakston et al., 2003; Gutiérrez and León, 2009). The global community of antivenom manufacturers is a complex *collage* that includes public and private laboratories of diverse sizes and strengths (World Health Organization, 2007a). Some of them are small facilities, mostly located in public institutions, which manufacture for the needs of specific countries. Others are larger laboratories that manufacture and distribute antivenoms throughout various countries or regions. The technological resources of these heterogeneous manufacturers vary greatly. While some laboratories have adequate, up-to-date facilities and procedures which comply with good manufacturing practices (GMPs), there

are laboratories which lack well-trained personnel, have inadequate facilities, and need to improve their systems and their products. Although some countries or regions manufacture enough antivenom production for their national and regional needs (e.g. Europe, USA, Brazil, Central America, Mexico, Australia, Thailand, Japan and possibly India), in other regions of the world, especially sub-Saharan Africa, there are very few antivenom producers. Some manufacturers from other regions which used to supply antivenoms to Africa in the past have halted their production, mostly due to economic constraints and pressure by share holders when these companies move into the private sector (Theakston and Warrell, 2000; Chippaux, 2002; World Health Organization, 2007a). For these needy countries, it is necessary to implement a strategy for increasing the production of safe and effective antivenoms based on the following essential components.

#### 3.1. The development of guidelines for antivenom manufacture and quality control

In 2007 the WHO started a worldwide-consultation process aimed at preparing guidelines for the manufacture and quality control of antivenoms. As a result, the *WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins* were approved by the Expert Committee of Biological Standardization of WHO in October 2008 and will be published soon. These Guidelines represent a significant step forward in the global efforts to increase the quantity and quality of antivenoms, since they provide detailed information on the recommended steps

for antivenom manufacture and control, including antivenom design based on prioritization of medically important species within the area of intended use, snake collection and maintenance, venom preparation and storage, animal immunization, hyperimmune plasma fractionation, reduction in the risk of microbial contamination, quality control, preclinical and clinical assessments of antivenom efficacy and safety, and post-marketing surveillance.

### 3.2. Implementation of technology transfer and capacity-building programmes

Many antivenom producers operate in low-income countries of Africa, Asia and Latin America and urgently need to improve their technological capacity. Challenges faced by these institutions include inadequate training of personnel, outdated systems and processes, poor quality control and an overarching lack of capital that greatly hampers their ability to cope with innovation and to finance upgrading of their facilities and technology. It is therefore necessary to establish programmes that can foster technology transfer partnerships between well-developed research and manufacturing laboratories and less-developed production facilities. Such partnerships would first need to recognize that antivenoms are essential life-saving drugs, and as such, the need to ensure a safe, efficacious and affordable supply transcends traditional commercial expectations. These programmes should first diagnose the specific needs of each production centre, in order that the assistance provided may meet the real requirements of the particular group. Collaborative interventions may be as diverse as:

- (a) Development of higher quality facilities where snakes can be kept for venom collection and storage.
- (b) Improvement of facilities for keeping the animals that are immunized and maintaining veterinary surveillance of them.
- (c) Setting up workshops on theoretical and practical aspects of GMPs.
- (d) Implementation of quality assurance systems.
- (e) Introduction of in-process quality control tests.
- (f) On site improvement of manufacturing procedures through visits by national or international experts.
- (g) Permanent training programmes for technicians and professionals, including visits to well-developed laboratories that comply with the requirements established for antivenom production.

These training and technology transfer activities can be organized at national and regional levels, under the auspices of Ministries of Health, regional WHO offices and local universities. The participation of international non-governmental organizations (NGOs) and agencies that promote technology transfer and capacity-building on a wider scale should be promoted. An example of such a programme is the network of public laboratories for antivenom production and quality control in Latin America, which has been supported by the programme CYTED

(‘*Ciencia y Tecnología para el Desarrollo*’). Through this network, a dynamic exchange of personnel in training, workshops and research activities has contributed to the improvement of the regional capacity for antivenom manufacture and quality control (Gutiérrez et al., 2007a, 2009a).

### 3.3. Encouragement of an era of innovation in antivenom design

The antivenom field has been characterized by little innovation in the basic manufacturing methodologies. Thus, there is a need to actively promote technological development projects on various aspects of antivenom production, from the design of venom mixtures for immunization and the immunization schemes to the fractionation protocols and the improvement of antivenom formulations. Encouragement must be given to technological innovation by producers, in association with research laboratories, in order to improve existing methodologies. A better characterization of venom mixtures used in antivenom production is needed (Gutiérrez et al., 2009b) (see Section 3.4). In addition, novel immunization schemes (e.g. Chotwiwatthanakun et al., 2001), using selected native or recombinant antigens, DNA immunization or novel adjuvants and immune potentiators, are needed (Wagstaff et al., 2006). Research for the development of liquid antivenom formulations that are stable at tropical room temperatures (e.g. Segura et al., 2009a), obviating the need for a cold chain and production of the more expensive freeze-dried antivenoms, is one example of the future direction of antivenom design. Another area of relevance is the assessment of the viral-inactivating potential of several of the methods used in plasma fractionation (Grandgeorge et al., 1996; Burnouf et al., 2007; Segura et al., 2009b).

### 3.4. The design of adequate venom mixtures for antivenom production: where toxinological research and antivenom production meet

Antivenoms differ from other immunotherapeutics in that the nature of the antigen used for antibody generation varies depending on the species of snake, in contrast to tetanus antitoxin, or diphtheria antitoxin, which use a single specific immunogen. It is increasingly recognized that geographical intraspecies variation in venom composition and immunogenicity may be sufficiently great to affect clinical efficacy of antivenoms (Chippaux et al., 1991; Warrell, 1997; Saravia et al., 2002). The correct composition of venom mixtures to be used in animal immunization for antivenom production is crucial and demands meticulous attention. Antivenom producers should consider a number of issues in the design of their products:

- (a) The reliable identification of the snake species responsible for most fatalities and snakebite morbidity in the country or region.
- (b) Analysis of geographical, seasonal and ontogenetic intraspecies venom variability in order to prepare representative venom pools.

- (c) Establishing the optimal combinations of venoms necessary to prepare monospecific or polyspecific antivenoms. This is closely related to the difficult issues of cross-neutralization of venoms and antivenoms and the possible synergistic effects of immunizing an animal with venoms of related taxa whose antigens share common epitopes.
- (d) The possible immunological suppression provoked by some venoms on the response to others.
- (e) The need to have a good traceability system for the venoms to be used in the immunizing mixtures, including the correct taxonomic identification of the snake species.

These issues demand a close collaboration between toxinology research laboratories and antivenom-producing laboratories. Unfortunately, cooperation between academic experts and manufacturers is often weak or non-existent. The technological tools for biochemical analysis of snake venoms, especially the use of modern proteomic methodologies, allow for a detailed characterization of venom composition and variability, a subject that has been called 'venomics' (Calvete et al., 2007; Gutiérrez et al., 2009b). This technological platform allows for the identification of venom components that react with antivenoms, a subject named 'antivenomics' (Lomonte et al., 2008; Gutiérrez et al., 2009b; Calvete et al., 2009). Together with the analysis of the cross-neutralization of specific toxic effects of venoms by antivenoms (Theakston and Reid, 1983; Theakston, 1986; Gutiérrez et al., 1996) and with the epidemiological information about the medically most relevant snake species, these techniques allow for the detailed analysis of cross-reactivity of venoms and antivenoms and for the selection of the most adequate mixtures of venoms for immunization. Tools such as these may enable more rational design of antivenom products that target specific envenoming syndromes caused by locally and regionally distributed snake species. Antivenom producers also need to be mindful of advances in the taxonomy of venomous snakes, as changes in this area may be very relevant to the appropriateness of particular antivenoms to specific markets and geographical ranges. Changes in the taxonomy of a species may affect the identity of venoms from different locations, and venom producers, researchers and antivenom manufacturers must be meticulous in ensuring that the proper names are given to the species from which venom is collected (Quijada-Mascareñas and Wüster, 2009).

### 3.5. The need for preclinical and clinical assessment of antivenom efficacy and safety

Because of the great heterogeneity of available antivenoms, in their specificity, neutralizing profile and physicochemical composition, preclinical and clinical assessments of antivenoms are obligatory before their introduction into large scale clinical use. In addition to the routine quality control tests aimed to ensure the safety of antivenoms (i.e. safety test, sterility, pyrogenicity), a preclinical assessment of antivenom efficacy should be

performed against the medically relevant snake venoms from the country or region for which the antivenom is intended. In addition to the traditional assay of neutralization of lethal effect (median effective dose – ED<sub>50</sub>) in mice (World Health Organization, 1981), a series of specific tests should be included, depending on the profile of pathophysiological alterations induced by each venom. For instance, in the case of most viperid venoms, tests have been developed to assess the neutralization of haemorrhagic, myotoxic, dermonecrotic, coagulant and defibrinogenating effects (Theakston, 1986; Gutiérrez et al., 1996; Instituto Clodomiro Picado, 2008). In the case of many elapid snake venoms, neutralization of lethal effects is usually sufficient, as neurotoxicity is the main clinical manifestation, with the exception of the venoms of some species of *Naja* that induce local necrosis in humans (Warrell, 1995) and various elapids, such as sea snakes and Australasian elapids that can cause rhabdomyolysis (Reid, 1961). In Australia and Papua-New Guinea, envenoming by elapid snakes may cause profound coagulopathy and myotoxicity as well as neurotoxicity, and antivenoms for these species should be assessed for their ability to neutralize all of these effects. However, most of these WHO-approved standard tests use venom-antivenom mixtures that have been pre-incubated. Reversibility of neurotoxic effects by antivenoms cannot therefore be predicted from the ED<sub>50</sub> as the tests ignore the delay between the envenoming bite and subsequent antivenom treatment and the pharmacokinetic factors determining the tissue distribution of venom components and antivenom.

Once an antivenom has proved effective and safe on preclinical tests, it should be evaluated in well-designed clinical trials. Conventional Phase I safety studies of antivenoms in healthy human volunteers are not ethical because these equine/ovine proteins carry a risk of causing early anaphylactic and late serum sickness reactions that is too high to be justifiable in healthy subjects for whom antivenom offers no mitigating benefit. Another risk is hypersensitisation by foreign proteins. In the clinical testing of antivenoms, there is an urgent need for an alternative to conventional Phase I studies but, so far, no satisfactory solution has been offered that is practicable and affordable by manufacturers, licensing authorities or clinicians treating snakebite victims. It has been proposed that, in order to establish an effective dose of a candidate antivenom with an acceptable safety profile ("minimum effective safe dose"), the "3 + 3" dose escalation design (Rosenberg and Haines, 2002) might be used (Abubakar et al., 2009). This approach has been used to limit toxicity in trials of cytotoxic agents in oncology. In assessment of antivenoms, it is adapted to allow the determination of efficacy as well as the risk of antivenom reactions. The numbers of patients involved are the same as is recommended for classic Phase I studies (Gehan, 1961). The ultimate test of efficacy and safety is a large scale type III clinical trial, which should, ideally, be randomized, blinded and controlled, comparing a new antivenom with an antivenom whose efficacy has been established through formal trials or clinical use (see for example Cardoso et al., 1993; Otero-Patiño et al., 1998; Smalligan et al., 2004).

Alternatively, two different doses of the same antivenom can be compared (Jorge et al., 1995). The use of a placebo control group in snake antivenom studies would be hard to justify on ethical grounds. In addition, prospective observational studies are useful when existing antivenoms are going to be used in a new geographical setting. Such clinical trials also provide valuable information on the clinical manifestations of snakebite envenoming by different species in various regions. Although the clinical picture of envenoming is well known for some species, in the case of other snakes that provoke bites less frequently, the clinical features are poorly known and demand investigation (e.g. Ariaratnam et al., 2008). Moreover, post-marketing surveillance studies should be also promoted in the evaluation of safety and efficacy of antivenoms. Clinical trials should use robust, objective clinical and laboratory endpoints both for efficacy and safety. In addition to clinical trials on antivenom efficacy and safety, renewed efforts should be carried out in the search for novel therapeutic alternatives, such as enzyme and toxin inhibitors that may ameliorate the extent of local tissue damage characteristic of envenomings by many viperid and elapid species (Gutiérrez et al., 2007b).

### 3.6. Commitment of regional producers to manufacture antivenoms for regions where local antivenom production is not currently feasible

There are countries, and regions, where local production of antivenoms is not feasible at the present time. Examples are several sub-Saharan and south Asian countries and Papua-New Guinea (Theakston and Warrell, 2000; Cheng and Winkel, 2001; World Health Organization, 2007a). Cooperative international programmes could lead a commitment by established antivenom manufacturers to the production of antivenoms for these deprived regions. In the case of sub-Saharan Africa, several laboratories are now manufacturing antivenoms which have been tested in clinical trials in Cameroon, Benin, and Nigeria (Chippaux et al., 1998, 2007; Meyer et al., 1997; Gutiérrez et al., 2005; Stock et al., 2007; Abubakar et al., 2009). However, these initiatives will fail in the longer term unless they are complemented by recognition and strong commitment by national governments, sound commercial planning, financial incentives from donors and the necessary international coordination to ensure that the resulting antivenoms will be deployed to snakebite stricken countries continuously and at affordable prices, thus breaking the vicious cycle that has hampered the supply of antivenoms to various regions of the world (Chippaux, 2002). Local capacity-building should be carried out in parallel. For example, in countries where no manufacturing laboratories exist, it might be a relevant and realistic objective to establish facilities for the collection, identification and captive maintenance of medically important species so that their venoms can be extracted and stored under appropriate conditions. The production of high-quality venom pools in snakebite-affected countries is crucial to overcome current deficiencies in antivenom supply. Locally produced venoms that meet recommended production standards could be sent to the collaborating antivenom production laboratories, through institutional

agreements, to enable production of antivenoms that will target venoms of the medically relevant local species. Locally produced venoms can also be used for the quality control of the antivenoms being purchased by health authorities. This would strengthen the capacity of local regulatory agencies, enabling them to directly assess the suitability of products offered in their jurisdictions. The serious problem resulting from the marketing in Africa, Cambodia, Papua-New Guinea and elsewhere of geographically inappropriate antivenoms (Visser et al., 2008; Warrell, 2008; Warrell and Williams, 2009) could be prevented by the development of national quality control laboratories that use expertly-identified pools of locally-collected snake venoms in their analyses. Thus, international cooperative programmes aimed at building local capacity for venom preparation and quality control in low-income countries should be actively promoted.

## 4. Ensuring access to antivenoms where they are most needed

Increased antivenom production, and improvements in the technological capacity of laboratories in low-income countries to produce safe and effective antivenoms, will not necessarily ensure that these essential drugs will reach the affected patients in time to be useful. An intractable problem in this area is the inadequate supply of antivenoms to the peripheral health posts close to areas where the most snakebites occur, i.e. in remote, rural communities in Africa, Asia, Latin America and Papua-New Guinea (World Health Organization, 2007a) (Fig. 2 shows the case of a boy who took 48 h to reach the nearest place where antivenom was available). This problem involves complex political, social, administrative and logistical considerations that typically extend to many other areas of health service delivery, in addition to the challenge of drug distribution. Solving these complicated dilemmas will in many cases involve finding answers to system-wide failures that may have different root causes in different settings (see Section 4.2). Where markets are open to corruption, bribery, and unstable governance, real solutions will only be brought about by lasting, sustainable changes in the parameters that define the underlying problems. Antivenom producers must work with agencies and organizations involved in stabilizing, strengthening and restructuring political, institutional and service delivery frameworks if effective and functional change is to be achieved.

### 4.1. The provision of antivenoms at affordable prices

Many antivenoms are produced in low volumes using costly processes, sometimes in costly regulatory environments, leading to high prices. The result is that even when an adequate volume of a particular antivenom is available, the price of the product may be too high for the public health systems of low-income countries. The cost of antivenoms ex-manufacturer may range from US\$10 to values as high as US\$1500 (McGain et al., 2004; Gutiérrez and León, 2009), with these prices often pushed higher by wholesalers and distributors. For example, the price for Indian-made polyvalent antivenom that sold for US\$10 in



**Fig. 2.** Consequences of snakebite. This 12-year-old boy was bitten by a *Bothrops atrox* “jergón” 1.5 m in total length in a remote area of Ucayali, Perú. The local health post had no antivenom and so he travelled with his mother by boat for 24 h to a second post, which also lacked antivenom. He finally reached a hospital 48 h after the bite but, despite continuing haemorrhage, he was refused antivenom on the grounds that it was too late. He was finally transferred to the regional hospital 13 days after the bite where his gangrenous arm was amputated (Photo: D.A. Warrell).

India, was inflated to US\$149 in Cambodia (Williams et al., 2009); similarly, when the same US\$10 antivenom was placed on sale in Papua-New Guinea in 2007, the local price of this product soared to US\$940 per vial (Warrell, 2008). Where prohibitively priced antivenoms are offered to low-income countries one of the outcomes is that the purchase of sufficient doses to guarantee clinical cure for all patients is precluded. The privatization of some former public laboratories (Theakston and Warrell, 2000; Gutiérrez et al., 2006) has complicated supply and cost issues in some countries. The sole drive of free market forces cannot ensure an adequate provision of antivenoms, particularly in low-income countries. A coordinated programme of action is necessary if the price of antivenoms is to be better matched to the purchasing capacity of consumers (governments, NGO's and individuals), and should include:

- (a) Incentives to participation by antivenom producers in programmes which can open doors to donor-funded sales of approved antivenoms, both securing and growing market share, while at the same time introducing positive quality improvements.
- (b) Encouragement through taxation relief or other instruments for established antivenom producers in high-income countries to use surplus production capacity to produce standardized antivenom preparations at low cost for low-income countries which lack local capacity. Such schemes could be incorporated into national programmes of overseas aid and development funding.
- (c) Investigation of direct price reduction strategies such as:
  - i Pooled purchasing schemes where countries that share the same snake fauna and antivenom requirements ‘pool’ their purchasing to obtain antivenom from a single supplier at a lower unit price in return for secure, medium-long term purchasing contracts.
  - ii Differential pricing models (World Health Organization, 2006), in which the price of a product is tiered according to an independent measure of a country buying capacity, such as gross domestic product (GDP) or the average annual income of persons at risk.
  - iii Third party negotiated price ceiling agreements between manufacturers and governments, similar to those used by the Clinton Foundation HIV/AIDS initiative (CHAI), whereby real cost price + negotiated returns are negotiated with the antivenom producer, incentives to further cost reduction such as technical improvements or technology transfer are agreed on, and participating governments then enter purchasing agreements. It is noteworthy however that a recent study of these strategies as they are applied to containment of antiretroviral (ARV) drug costs (Waning et al., 2009) found little evidence to support downstream benefits from price pooling of ARVs. Desktop modeling and/or limited trials would need to be conducted to establish clear benefits in the case of antivenoms.
- (d) The strengthening of public laboratories that have the capacity to produce antivenoms at affordable prices, as occurs in many low-income regions of the world.

1. Acquisition of reliable information on incidence and mortality
2. Improvements in the production and quality control of antivenoms
3. Increase in the capacity of low-income countries to develop quality control of antivenoms
4. Commitment of manufacturers to produce antivenoms for regions devoid of local production
5. Accessibility of antivenoms at affordable prices in low-income countries
6. Preclinical and clinical assessment of antivenom efficacy and safety
7. Development of effective antivenom distribution programmes
8. Permanent training programmes for health staff on snakebite envenomings and their treatment
9. Development of programmes to support people suffering sequelae of snakebites
10. Preventive and educational programmes at the community level

**Fig. 3.** A Decalogue that summarizes some of the most important tasks proposed for the design of an integrated strategy to confront the global problem of snakebite envenoming. These actions should be developed as a concerted and integrated strategy and should involve multiple actors and synergies. These tasks demand a widened and renewed research agenda, the integration between research, development, production and public health policies, and a human rights-based approach in the search of solutions.

- (e) The development of other public-private partnerships involving the design of innovative purchase arrangements and the participation of donor groups that could fund purchase of antivenoms to be distributed to low-income countries at affordable prices, as has been achieved in the case of drugs for other neglected diseases (Hotez et al., 2006). The recent creation of the Global SnakeBite Initiative ([www.snakebiteinitiative.org](http://www.snakebiteinitiative.org)) is a promising initiative to foster this approach (Williams et al., *in press*) and to coordinate actions with similar groups.
- (f) Engagement with the governments of low-income countries to increase recognition of the need to address snakebite. The status of snakebite as a neglected tropical disease, and of antivenoms as WHO-mandated essential medicines should be emphasized. Governments should be further encouraged to provide resources for dealing with snakebite under the umbrella of the UN Millennium Development Goals (MDGs), particularly MDG 8.4 “In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries”, but also taking into account the goals of other MDG themes which emphasize child health, maternal health, alleviation of poverty, and benefits of new technologies (<http://www.un.org/millenniumgoals/global.shtml>).

In addition to political and administrative tasks, this aspect of the problem demands renewed research efforts in the areas of health economics, which has been largely absent in the past. The involvement of social science research is badly needed to understand the social, political

and economic hurdles that prevent the adequate production, marketing and distribution of antivenoms.

#### 4.2. The need of rational and well-designed antivenom distribution policies

The purchase of a suitable volume of antivenom by governmental procurement offices does not ensure that this antivenom will be deployed efficiently to the public health posts of the rural areas where it is most needed. Governments and collaborating regional health organizations should be encouraged to develop novel knowledge-based programmes and strategies for the efficient distribution of antivenoms. Given that antivenoms are essential, life-saving medicines for an acute illness, there is a strong argument for developing distribution strategies independently of systems and processes relevant to routinely dispensed medicines, or drugs for the treatment of non-acute illnesses. A number of issues are relevant:

- (a) An adequate epidemiological surveillance system is essential in order to identify high risk areas for rational antivenom deployment. Surveillance systems should where possible take advantage of Geographical Information System (GIS) tools for data analysis, such as the free-access programme SIGEpi, developed by the Pan-American Health Organization (Leynaud and Reati, 2009).
- (b) It is necessary to have updated information on the status of the health facilities of the rural areas where antivenom has to be sent, including the reliability of the cold chain system.



- (c) The identification of vulnerable regions, where snakebites are common and where health posts are absent, should be a priority in snakebite-affected countries, and used to guide political actions aimed at strengthening public health infrastructure and human resources in these regions.
- (d) Resources for the design of training programmes for health and administrative staff relating to the correct storage and use of antivenoms should be sought.
- (e) As previously mentioned, research that further improves the stability, safety and shelf life of antivenoms should be a high priority, particularly for addressing the needs of low-income countries.
- (f) Finally, an active programme to follow up the use of antivenom is mandatory, in order to have a feed-back on the possible wastage of this product that would allow the introduction of corrective measures to ensure its efficient use (Gutiérrez et al., 2009a).

All these interventions demand concerted actions between a wide range of organizations, interested groups and related parties. Governments, WHO, antivenom producers, toxinology researchers, herpetologists, public health economists, social scientists, non-governmental aid donors, philanthropists and the general medical profession, all have roles to play, and should all be engaged in order to derive solutions.

#### 4.3. *The need for improvement of regulatory control, especially where regulatory frameworks are weak*

Antivenoms should be subject to a process of regulatory control by appropriate national regulatory bodies, and regulators should be assisted wherever possible to develop efficient, well-designed and practical systems for the licensing of antivenoms. The *WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins* provide an excellent starting point for improving the capacity of regulators, although in circumstances where production of antivenom takes place in another country, it may be difficult for some regulators to adhere to well-established conventional processes, such as manufacturing site inspections, and individual batch release. Many regulatory bodies, particularly in developing countries, will also lack the resources and personnel to undertake detailed licensing investigations. Therefore, it is necessary to confront this issue by cooperative regional and national efforts aimed at strengthening the regulatory capacity of health authorities in low-income countries through a variety of training programs, workshops and support from international experts and well-developed laboratories. In situations where local regulatory bodies are weak, regional health authorities may rely on well-qualified external laboratories to assess the quality of antivenoms being offered to a particular country or region. This approach has been successfully implemented in Latin America by the Pan-American Health Organization. In sub-Saharan Africa, where an antivenom crisis currently exists, an efficient way to approach the problem of poor or non-existent regulatory control may be for WHO to establish an independent panel

of experts and reference laboratories which could evaluate all of the current products and make licensing recommendations to regulators, donors and national health authorities. This could be an effective way to ensure quality control analysis and sustainable access to the necessary range of safe, efficacious products needed throughout the region.

#### 5. **The correct use of antivenom: training programmes for the health staff**

No amount of antivenom is of any value if the medical staff who must administer it do not have the relevant skills and training to correctly treat bitten patients. Even where governments purchase sufficient volumes of appropriate, effective antivenom and have efficient distribution strategies to allocate these products to the rural locations where they are needed, it is necessary to ensure that health staff has the skills needed to ensure appropriate, safe and efficient use of these immunotherapeutics. This is a critical issue in view of the widespread ignorance about the correct diagnosis and treatment of snakebite envenomings (Simpson, 2008; Gutiérrez et al., 2009a). The causes of this problem are multiple, and include:

- (a) Poor coverage of the subject in the curricula of university medical, nursing and pharmacy schools.
- (b) Lack of permanent educational programmes for health professionals.
- (c) The concentration of educational activities in the main cities, far from the physicians and nurses who actually deal with the majority of cases in rural health centres.
- (d) Lack of adequate teaching materials (situational relevant textbooks or manuals, access to scientific literature, videos, etc.).

As a consequence, serious deficiencies exist among health workers in many countries in the correct diagnosis of snakebites, clinical assessment and the use of simple tests that are the basis of the decision on whether or not antivenom should be administered, the selection of the proper antivenom to be used, as well as an appropriate initial dose, the protocol for repeated antivenom administration, the monitoring of early antivenom reactions, knowledge of the most common complications of envenoming and their management, and other vital aspects of the treatment of this pathology. Certain technical skills and basic equipment may be needed to save the lives of snakebite victims. One of the most important in areas where neurotoxic snakes abound is support of the patient with respiratory paralysis who needs an artificial airway and assisted ventilation, sometimes for several days. As a consequence of failures in medical staff training, irreparable and easily avoided mistakes have been described in snakebite treatment. This situation demands concerted efforts at various levels, including:

- (a) Research to assess the status of the qualification of health workers for managing these envenomings in places of highest incidence.
- (b) The introduction and evaluation of this subject in medical, nursing and pharmacy university schools, as

well as on the programmes of public health technicians who may also attend these cases.

- (c) The elaboration of national and regional guidelines for the diagnosis and treatment of snakebite envenomings, involving the participation of national and international experts.
- (d) The preparation of manuals, textbooks, videos, posters, CDs and other teaching materials to be used in permanent educational programmes, especially in rural health centres, and taking into account that it is very important that these materials be specific for each country or region.
- (e) The assessment of the content and efficacy of permanent educational programmes through validated evaluation tools, in order to continuously improve these training activities.

## 6. Documenting and attending the snakebite victims and their families' needs

As with other neglected diseases, the victims of snakebite envenoming are often abandoned by the institutions responsible for their care, not only by not receiving the correct treatment, but also through a lack of the necessary support required after these tragedies. Although the precise numbers of people left with permanent sequelae and disability following snakebites are unknown, it is estimated that they are more numerous than the fatalities (World Health Organization, 2007a). For the real impact of this disease to be properly assessed, snakebite envenoming needs to be analyzed in terms of DALYs (*disability adjusted life years*) lost, but at present there is not a single study in print which looks at the problem using this widely accepted system of impact measurement. The impact may even be more wide-reaching, since it is often not only the victim who suffers, but given that many of them play a key role in the income of a rural family, their death or disability has economic, social and psychological consequences that extend to the whole family, and often the wider community. The impact of chronic snakebite disability, with its associated stigma and trauma, is in urgent need of investigation. An integrated strategy to confront snakebite envenoming on a global basis has to consider not just incidence and mortality, but the long term morbidity that afflicts many thousands of people each year. There is a pressing need to define the magnitude of the sequelae and disabilities that are secondary to snakebite envenoming through adequate epidemiological, socio-economic and psychological assessments carried out at community level. Only when armed with this information will it be possible to engage with governments and non-governmental organizations to develop intervention programmes aimed at identifying the incapacitated survivors of snakebite and provide them with appropriate access to support and rehabilitation services. Such efforts should involve integration with some of the different kinds of existing national and regional programmes for people suffering from chronic ailments secondary to other pathologies, such as land mine disabilities.

## 7. Community programmes: incorporating local organizations in the prevention and recognition of snakebite envenoming

Prevention programmes should be actively promoted through a wide variety of community programs, particularly in regions of high incidence of snakebites, such as rural areas devoted to agricultural activities. The involvement of the community is of paramount importance in combating the problem of snakebite. Any intervention programme must be based on the local cultural, socio-economic and political conditions. Ignoring this necessity can ultimately lead to the failure of programmes and projects, especially if it leads to the intervention being wrongly perceived by the community. Particular attention has to be given to vulnerable and marginalized groups, such as indigenous and native peoples, who are often the most impoverished and the most exposed to snakebite, due to their hunter-gatherer and subsistence agriculture modes of living, and yet who often do not benefit from official public health programmes. Local leaders and communal organizations must be directly involved in the design and performance of educational campaigns (health promotion) aimed at the prevention and management of snakebites. Local organizations of different sorts, i.e. health committees, local political groups, youth organizations, minority associations, school-based groups, etc., should be encouraged to take interest in the issue. This implies the need to know and understand, through well-designed research programmes, the way in which individual communities or populations perceive the problem and the most effective strategies with which to confront it. Particular attention has to be given to the interaction and communication with local traditional healers, in order to develop partnerships aimed at reducing the use of harmful interventions and to avoid delays in getting effective medical treatment. Thus, the unidirectional, paternalistic and culturally-biased approach that sometimes characterizes health intervention programmes in rural communities must be changed to become more interactive and participatory, creating a climate in which the affected population is actively engaged in the design and implementation of preventive and educational activities associated with primary health care.

## 8. Concluding remarks: an integrated approach is required

Snakebite envenoming, like many other neglected diseases, is a complex phenomenon demanding concerted intervention and participation by many actors at various levels. Public awareness of the magnitude of this problem on a global basis must be created through a variety of complementary mechanisms. This is an objective of the recently created Global Snake Bite Initiative (Williams et al., *in press*). The research agenda for studying this problem has to be broadened by amalgamating basic science, technological development and social science. Traditionally, the concepts of 'innovation' and 'entrepreneurship' have been used to promote technological innovation to increase economic profits, but they must now be used on

a more philanthropic and communal basis to incorporate the goals of social innovation and social entrepreneurship, i.e. directing ingenuity and creativity towards the solution of problems, such as snakebite envenoming, that afflict the poorest people in the poorest rural settings. Our attention to snakebite envenoming, and to other neglected diseases, is a matter of social conscience and human rights. States have obligations to ensure the right of access to health facilities, goods and services on a non-discriminatory basis, especially for vulnerable and marginalized groups, to provide essential drugs such as antivenoms (World Health Organization, 2007c) and to bring education and access to information about the main health problems in the community, including, particularly, methods for their control and prevention (Hunt, 2007).

An integrated strategy to confront this problem, at global, regional and national levels, must be based on a better knowledge on the real impact of snakebite envenoming and its resultant chronic disability worldwide. Efforts should also be directed towards better understanding of the biochemistry and toxicology of relevant medically important snake venoms, as well as the geographical variation of venoms and its implications for the design of optimal immunization mixtures for antivenom production. Research should be also directed towards the discovery of new ancillary treatments, especially targeting those venom effects that are less susceptible to antivenom therapy such as the severe local pathological manifestations of snakebites (Gutiérrez et al., 2006, 2007b). There is an urgent need to improve the quality and volume of antivenom production and to strengthen the technological capacity of antivenom-producing laboratories in low-income countries, through effective technology transfer programmes based on North–South and South–South collaboration. Capacity-building efforts should be also directed towards improving the capacity of low-income countries to both produce their own snake venoms for antivenom production, and to assess the preclinical and clinical efficacy and safety of the antivenoms offered by commercial manufacturers for distribution to these countries. Efforts aimed at facilitating the purchase of antivenoms at affordable prices to low-income countries, through a number of mechanisms involving public–private partnership initiatives, together with the mobilization of donor agencies, should be complemented by efforts to build effective distribution strategies for deployment of antivenoms to the rural health posts where they are most needed. Long term educational programmes for health staff on the correct diagnosis and treatment of envenomed patients, together with effective prevention strategies involving the participation of community organizations, should complement a wide agenda of multiple tasks and participants working at many levels (Fig 3). Such integrated global efforts will undoubtedly help to reduce the burden of human suffering caused by snakebite envenoming.

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The authors declare that there are no conflicts of interest.

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