Reducing the impact of snakebite envenoming in Latin America and the Caribbean: achievements and challenges ahead

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Snakebite envenoming constitutes an important public health problem in Latin America and some countries of the Caribbean. The advances and pending tasks in the study and control of this neglected tropical disease in this region are reviewed in the light of a roadmap proposed in 2006. Significant progress has been achieved in the study of snake venoms, particularly regarding venom proteomics, i.e. ‘venomics’, and the analysis of the mechanism of action of toxins. Likewise, a deeper understanding has been gained in the preclinical efficacy of antivenoms produced in the region. In contrast, despite advances made in the study of clinical manifestations of envenomings and safety and efficacy of antivenoms at the clinical level, much remains to be done in this subject. Improvements have occurred in antivenom manufacturing technologies and availability, although there are still countries where there is insufficient supply of antivenoms, or where manufacture has to be improved. In spite of considerable efforts in some countries in prevention, accessibility to treatment, and training of health staff in the management of envenomings, important challenges remain for the region as a whole, with the long term goal of reducing the impact of this disease in terms of personal and social suffering.

Keywords: Antivenoms, Caribbean, Envenoming, Latin America, Snakebite, Venoms

Introduction

Snakebite envenoming is a neglected tropical disease that predominantly affects impoverished rural populations in Africa, Asia, Latin America and parts of Oceania.1-4 It inflicts a heavy load in terms of morbidity and mortality, and an unknown number of bitten persons end up with permanent physical and psychological sequelae. Studies based on hospital statistics indicate that, on a worldwide basis, between 1.2 and 5.5 million people are bitten by snakes every year, causing 25 000 to 125 000 deaths, and leaving an estimated 400 000 people with permanent sequelae.4-7 However, these figures underestimate the actual magnitude of this disease, as revealed by recent community-based surveys on incidence and mortality associated with snakebite envenomings in various countries.8,9 A growing international awareness on the magnitude of this disease has developed in the last decade, as shown by various initiatives aimed at understanding the consequences of snakebites and improving prevention and treatment.5,10,11

In Latin America and the Caribbean, hospital-based statistics indicate that at least 70 000 snakebite cases occur per year, although it is likely that the actual number of envenomings is higher owing to underreporting in many rural regions.1,12 Latin America has a long tradition in the study of snakes, venoms and envenomings, starting with the pioneer work of Vital Brazil at the dawn of the 20th century.12 In addition, advances have been made towards improving the availability and accessibility of antivenoms, through the efforts of research groups, antivenom manufacturers, ministries of health, community organizations, and the Pan American Health Organization (PAHO). However, concerted regional efforts should be strengthened, with deeper involvement and commitment of PAHO and the ministries of health. A roadmap of tasks for confronting snakebite envenomings, based on an integrated perspective of the problem and its solutions, was proposed by Gutiérrez et al.1 in 2006 (Figure 1). The present contribution analyzes the advances in Latin America and the Caribbean in fulfilling this set of tasks, and highlights the most relevant pending issues required to further reduce the impact of this neglected tropical disease in the region.

The references included in this manuscript are not exhaustive; the scientific literature on the subject is abundant and therefore representative references have been selected to illustrate the issues discussed.

Basic research and preclinical studies on antivenoms

Significant advances in toxinological research have been made in Latin America in the last decade regarding the biochemical and toxicological characterization of medically-relevant venoms and purified toxins. In particular, the field of snake venom proteomics
venomics) has flourished, with the strength provided by the methodological platform of mass spectrometry, as shown by Calvete.14 The proteomics of venoms from viperid snakes, especially from Costa Rica and Brazil but also from other countries, has provided a unique and detailed view of the predominant families of toxins in these venoms and on inter- and intraspecies (regional and ontogenetic) variations in venom composition.14–16 Likewise, the proteomes of a number of coral snake (Micrurus sp) venoms have been studied.15,17 This profuse body of information has implications in many areas of research, such as evolutionary biology, pharmacology, biochemistry and toxicology, and allows knowledge-based improvement of antivenom design.18 It is necessary to gain further insight into the composition of poorly known venoms of snakes that inflict clinically-relevant envenoming, such as those from some species of Bothrops, Bothrocophias sp. and Micrurus sp., among others.

The mechanisms of the actions of venoms and toxins have received attention from researchers in Latin America. The complexity of the local tissue damage characteristic of viperid envenomings has been partially understood, especially regarding phospholipase A\textsubscript{2}-induced muscle necrosis and metalloproteinase-induced hemorrhage and skin damage,19 and the inflammation promoted by the action of these toxins has been investigated. Likewise, the pathophysiology of the systemic effects of envenomings, such as the mechanisms involved in hemostatic alterations in viperid envenomings have been understood.20,21 In addition, the severe systemic manifestations, especially neurotoxicity and rhabdomyolysis, associated with envenomings by rattlesnakes (Crotalus durissus) in South America have been thoroughly studied.22 There are, however, important effects induced by viperid venoms at the clinical level whose mechanisms of action remain poorly investigated, like the autonomic effects characteristic of Lachesis sp. envenomings,23 and the severe thrombosis associated with envenomings by the Caribbean species Bothrops lanceolatus and B. caribbaeus.24 Furthermore, the pathogenesis of acute kidney damage induced by Bothrops sp. venoms has been only partially studied.

Another area in which significant advances have been made is the preclinical assessment of antivenom efficacy. The clinical use of antivenoms has to be preceded by a rigorous preclinical testing of efficacy. In the past, this was performed solely on the basis of the neutralization of lethality. However, toxinological research has shown that, especially for viperid venoms, a proper preclinical assessment has to be based on the study of neutralization of other clinically-relevant effects, in addition to lethality, such as hemorrhagic, myotoxic, edema-forming, coagulant and defibrinogenating activities.25 In the case of Latin America and the Caribbean this is particularly relevant because antivenoms manufactured in some countries are used in other countries. Due to the well-known phenomenon of geographic venom variation, it is necessary to study in detail the paraspecific protection of antivenoms.

In the case of Bothrops sp. venoms and antivenoms, an extensive cross-reactivity between antivenoms and venoms has been described in Latin America and the Caribbean.26 In addition to neutralization assays, the methodology of antivenomics
constitutes a significant advance in the preclinical testing of antivenoms, as it allows the identification of venom components which are recognized, or not recognized, by antivenom antibodies. This analytical platform complements the information generated by neutralization studies and provides valuable information for the improvement of antivenom design. The studies on the preclinical efficacy of a polyspecific viperid antivenom manufactured in Costa Rica have been recently reviewed. Taken together, these studies support, at the preclinical level, the use of some antivenoms in various countries, especially for the treatment of envenomings by Bothrops sp., hence contributing to the availability of antivenoms even in circumstances where local manufacture is reduced. In contrast, lack of cross-neutralization has been described for antivenoms against Crotalus sp. and Micrurus sp. Further research is needed on the preclinical efficacy of poorly studied antivenoms, and to assess which antivenoms are effective in the neutralization of the venoms of viperid species not classified within the genus Bothrops. This demands cooperative and coordinated regional efforts, along the line of a study performed under the auspices of a multinational project supported by CYTED (Ciencia y Tecnología para el Desarrollo) in which bothropic antivenoms manufactured in various countries were assessed against the venoms of medically-relevant species.

Research efforts have been also focused to the search for natural and synthetic inhibitors of venom components, with the rationale that some toxic activities, especially those associated with local tissue pathology induced by metalloproteinases and phospholipases A2, could be confronted by the local application of specific inhibitors. For example, the rapid application of the metalloproteinase peptidomimetic hydroxamate inhibitor Batimastat abrogates local hemorrhage and dermonecrosis induced by Bothrops asper venom. Likewise components derived from plant extracts and the blood of vertebrates have proven effective in the experimental neutralization of venom toxicity. It is expected that these and ongoing studies will identify lead compounds that can be developed into effective toxin inhibitors, and that the future of snakebite envenomation therapy might be based on the rapid administration of venom inhibitors in the field, followed by antivenom administration in health centers.

Epidemiological and clinical research

The epidemiology of snakebite envenomings in Latin America and the Caribbean has been studied only to a partial extent. The majority of studies have been based on hospital statistics, and for some countries there is no published information at all. Hence, there is an urgent need to undertake regional efforts on at least three levels: improving the collection of data on snakebites by the ministries of health; this involves the introduction of compulsory notification of envenomings in the public health systems of all countries; performing systematic nation-based epidemiological surveys using statistics emanating from the ministries of health; and introducing the methodology of community- and household-based surveys, especially in rural communities where health services are deficient, in order to gain a more realistic view of the magnitude of this problem, as has been recently performed in parts of Asia. This includes the use of ‘verbal autopsies’ at the household level, to assess the number of under-reported deaths occurring outside medical facilities. The application of geographical information systems (GIS) methodologies in the study of snakebites is of utmost relevance and has great potential for identifying regions at risk and to guide public health interventions.

Of special relevance is the assessment of the magnitude of this problem in vulnerable communities with poor health services, such as indigenous communities in various countries; preliminary evidence suggests that the impact of snakebite in these settings is very high. Additional aspects that have been largely neglected are the physical and psychological sequelae developing as a consequence of envenomings. The implementation of community-based and household-based surveys, including qualitative research based on in-depth interviews to affected people, would provide a better understanding of this aspect of the problem. Likewise, a biosocial perspective of envenomings has to be introduced in order to document the ‘social suffering’ associated with this disease, i.e., the effects that these accidents have not only on the bitten person, but also on his/her family and the community as a whole.

Important advances have been made in the characterization of the clinical profiles of envenomings in Latin America and the Caribbean. Studies in which the identification of the offending snake is performed with confidence are highly valuable, hence allowing the description of clinical patterns associated with different species. Such types of studies have been performed on envenomings by several species in Latin America and the Caribbean. These studies have highlighted common clinical manifestations in envenomings by vipers, as well as unique patterns associated with some species. In spite of these advances, much remains to be done in the study of clinical characteristics of envenomings by other medically-relevant species. For instance, the conventional view that coral snake (Micrurus sp.) accidents are associated only with neurotoxic manifestations needs to be revised. Likewise, envenomings by viperid species of the genera Cerrophidiun, Porthidium, Atropoides, Bothrophophis, and Bothriopsis have not been characterized from the clinical standpoint. The analysis of specific aspects of snakebite envenomings, such as secondary infection, acute kidney injury, myonecrosis, cerebrovascular accidents and others should be better understood, in order to design more effective therapeutic interventions.

The study of the clinical efficacy and safety of antivenoms is another area that requires renewed cooperative research in the region. The plethora of preclinical data concerning antivenom efficacy contrasts with the relative scarcity of clinical validation of antivenoms. Randomized, controlled, double blind trials have been performed in Brazil, Colombia and Ecuador, and other clinical studies with antivenoms have been carried out in various countries. The experience gained by these investigations should be extended to other countries in the region through collaborative projects. In addition, research is required on aspects such as adequate antivenom dosage and ancillary treatments for complications of these envenomings.

Antivenom availability: technological development and regional cooperation

Latin America has a long tradition in antivenom production since the pioneer work of Vital-Brazil at Instituto Butantan at the
beginning of the 20th century. Currently, antivenoms are manufactured in Argentina, Brazil, Peru, Bolivia, Ecuador, Colombia, Venezuela, Costa Rica and Mexico. Most laboratories belong to public institutions, i.e., ministries of health or universities, although there are private manufacturers in various countries as well (see http://apps.who.int/bloodproducts/snakeantivenoms/database/). Despite the achievements of Latin America in terms of antivenom production, as compared to other regions of the world, important gaps remain in our continent in terms of antivenom availability. Antivenom manufacturing is heterogeneous in terms of technological platforms, volumes of production, quality of the products, qualification of staff and technological innovation. In some cases, local production fulfills all the needs of a country, whereas in others it does not guarantee self-sufficiency, and antivenoms have to be imported. Therefore, there is a need to improve antivenom availability on a regional level; to achieve this goal it is necessary to promote and consolidate regional cooperative efforts, with the auspices of PAHO and other entities. These efforts should be focused on technology transfer programs between laboratories, organization of workshops, upgrading of infrastructure and technological platforms, and investment in technology and training of personnel. The Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins, issued by WHO, constitutes a useful tool for manufacturers and regulators in the region.

There has been a surge of technological innovation in antivenom manufacture in some countries, with the introduction of caprylic acid fractionation, chromatographic steps, procedures for ensuring viral safety, and efforts to increase the thermal stability of liquid antivenoms. Likewise, some laboratories produce both liquid and freeze-dried antivenoms, in order to guarantee the deployment of these products to settings where the cold chain is deficient. Efforts in technological innovation should also focus on the generation of recombinant antigens for immunization, particularly in the cases of venoms difficult to obtain, such as those of Micrurus sp., as well as on generating recombinant antibody fragments (such as scFv fragments) that could neutralize key toxins in medically-relevant venoms.

A highly productive regional training program was developed in Latin America for over a decade through a series of courses organized at Instituto Butantan, in Brazil, with the support of the Japanese agency JICA. Moreover, another significant step forward was achieved through a regional program, supported by the organization CYTED, developed between 2006 and 2009, in which antivenom production and quality control laboratories from nine countries were involved. This project generated a number of cooperative efforts and synergies that contributed to the strengthening of antivenom availability on a regional level. This initiative has continued with a new project supported by the program FEMCIDI of the Organization of American States (OAS). It is expected that this continuous networking in Latin America will upgrade the region’s ability to produce the volume of high quality antivenoms required for the region as a whole.

The issue of quality control and regulation of antivenoms deserves consideration. Although quality control laboratories that analyze antivenoms, either locally produced or imported, exist in various countries (an example is the Instituto Nacional de Controle de Qualidade em Saude [INCQS] in Brazil), there are nations where antivenoms are imported without performing local quality control. This brings the risk that some imported antivenoms might not be effective in the neutralization of the most relevant snake venoms in the country. This situation should be addressed by strengthening local regulatory entities in each country, enabling them to carry out quality control of antivenoms. Again, regional cooperative workshops and training activities should be promoted, supported by the political will of local health authorities. Guidelines and technical manuals describing the tests used for the preclinical testing of antivenoms are available.

The promotion of public health initiatives

A great challenge for reducing the burden of snakebite envenomings worldwide has to do with broad public health goals such as improving the prevention of snakebites, the appropriate management and transportation of those bitten, the accessibility to effective medical treatment, including the provision of primary health care and the follow-up of people and social groups suffering the consequences of envenomings. The design and implementation of effective public health interventions should be based on a biosocial approach that goes beyond the traditional biomedical perspective. Key issues required for success in these efforts are: the adaptation of interventions to the local contexts; the design of ‘diagonal’ interventions instead of the more traditional vertical, top-down approaches; leveraging shared delivery infrastructure; and the understanding that interventions to reduce the impact of snakebite envenoming should be viewed within the frame of strengthening public health systems as a whole, instead of promoting the focalization on a single health issue.

In the landscape of prevention, significant efforts have been achieved in various countries in Latin America and the Caribbean, based on public information campaigns of various types involving public and private stakeholders. These include, among others, the publication of printed and electronic materials and the organization of activities in communities and groups presenting a high incidence of envenomings. In Costa Rica, for example, attention has been given to various indigenous groups by organizing prevention campaigns in schools and communities, based on the distribution of printed material in their own languages and other strategies encompassing synergic efforts with local organizations and with public health and education institutions. Nevertheless, snakebite prevention campaigns are scarce and discontinuous in several Latin American countries, and should be implemented by means of diverse communication strategies, in which the local community organizations should play a key role. In addition to the involvement of public institutions and organizations, prevention campaigns must incorporate public–private partnerships and other types of initiatives originating in the civil society. Much remains to be done in this aspect.

One issue that should receive higher attention, and which also demands education and community-based work, is the improvement of the early management of snakebite cases. This includes a reduction in harmful interventions that also delay the transportation of people to health facilities. Studies in Colombia, for instance, have shown that a relatively high percentage of bitten people receive initial attention based on traditional medicine, hence delaying access to antivenom treatment; similar observations have been made in other countries in Latin America. It is necessary to generate research to understand the most common
traditional practices used to attend people bitten by snakes in different countries and settings. Likewise, a dialogical approach must be promoted in the interaction of health authorities with traditional healers in such a way that harmful interventions are avoided and rapid transportation to health facilities is guaranteed. Along this line, a project developed by the Ministry of Health of Nicaragua in the southern region of this country, supported by PAHO, yielded excellent results in terms of forging alliances between traditional healers and local health authorities (Luz Marina Lozano, Ministry of Health of Nicaragua, personal communication). The experiences gained in other parts of the world, such as the use of motorcycle transportation of people bitten by snakes in Nepal, should be analyzed to consider the feasibility of introducing these and similar practices in Latin America.

**Box 1.** Summary of some of the achievements and pending tasks in the struggle against snakebite envenoming in Latin America and the Caribbean

<table>
<thead>
<tr>
<th>Domain of activity</th>
<th>Achievements</th>
<th>Pending tasks</th>
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<tbody>
<tr>
<td>Basic and preclinical research</td>
<td>• Proteomics of medically-relevant venoms.</td>
<td>• Biochemistry and toxicology of some poorly studied, medically-relevant venoms.</td>
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<td></td>
<td>• Mechanisms of action of most important toxin types.</td>
<td>• Identification of toxins responsible for clinical manifestations not yet understood.</td>
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<td></td>
<td>• Preclinical evaluation of many antivenoms, especially anti-Bothrops sp.</td>
<td>• Immunological relationships of Micrurus sp. venoms.</td>
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<tr>
<td></td>
<td>• Natural and synthetic inhibitors of snake venoms.</td>
<td>• Preclinical analysis of poorly studied antivenoms.</td>
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<td></td>
<td>• Cooperative research efforts between groups of various countries.</td>
<td>• Search for novel natural and synthetic inhibitors, especially of PLA2s and metalloproteinases.</td>
</tr>
<tr>
<td>Epidemiological and clinical</td>
<td>• Hospital-based epidemiological studies in some countries.</td>
<td>• Community-based epidemiological studies.</td>
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<tr>
<td>research</td>
<td>• Characterization of clinical manifestations of envenomings by some species.</td>
<td>• Identification of social and ethnic groups with high incidence of snakebites.</td>
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<td></td>
<td>• Clinical evaluation of antivenoms made in Brazil, Colombia, Costa Rica and Mexico.</td>
<td>• Analysis of the sequelae resulting from envenomings.</td>
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<tr>
<td>Antivenom availability, technological development and transfer of technology</td>
<td>• Production of antivenoms in many countries.</td>
<td>• Clinical manifestations of envenomings by some medically-relevant species.</td>
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<tr>
<td></td>
<td>• Innovation in some aspects of antivenom manufacture.</td>
<td>• Clinical evaluation of safety and efficacy of antivenoms not studied yet.</td>
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<td></td>
<td>• Effective regulatory bodies in some countries.</td>
<td>• Re-evaluation of the most appropriate immunizing venom mixtures for antivenom manufacture.</td>
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<td></td>
<td>• Technological cooperation networks in some countries.</td>
<td>• Improvement of technological platforms, including GMPs.</td>
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<tr>
<td>Public health policies</td>
<td>• Implementation of preventive programs in some countries.</td>
<td>• Improvement of quality control of antivenoms and consolidation of regulatory agencies in all countries.</td>
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<tr>
<td></td>
<td>• Improvements in antivenom accessibility and distribution in some countries.</td>
<td>• More extensive cooperation between manufacturers, developers and basic researchers in the region.</td>
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<td></td>
<td>• Training of health staff and elaboration of Guidelines for treatment in some countries.</td>
<td>• Improving prevention at the community level, especially in regions of high incidence of snakebites.</td>
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<td></td>
<td>• Isolated efforts to enhance the awareness of the relevance of the problem through advocacy.</td>
<td>• Improving treatment of envenomings and preparation of regional guidelines.</td>
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<td>• Improving antivenom access in remote rural places in the context of strengthening of public health programs.</td>
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<td></td>
<td>• Actions in support of people suffering of sequelae due to envenomings.</td>
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<td></td>
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<td>• Advocacy campaigns directed to authorities and the civil society on the relevance of snakebites.</td>
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A significant hurdle that impacts on the magnitude of this problem in Latin America is the lack of provision of health services, including attention to people bitten by snakes, in remote rural regions in many countries. In these settings, the lack of local services forces people bitten by snakes to travel long distances to reach health facilities, with consequent delay in antivenom administration and medical attention. In this regard, there are particularly vulnerable populations, such as those of indigenous communities or regions affected by warfare or natural disasters. An effective attention of people bitten by snakes should be based on the rapid access to health facilities where antivenom and other health interventions are provided. This demands, in many regions, an overall improvement in the provision of primary health care and the design of knowledge-based strategies for antivenom distribution. In addition, the presence of health staff with adequate training in antivenom administration and in the basic clinical management of envenomings is mandatory. As an example, a proposal was presented for the organization of health services in Colombia, particularly at the primary health care level. It is necessary to generate similar schemes in other countries which should adapt to local settings and to the overall organization of the health systems; this is an area that demands renewed efforts in Latin America and the Caribbean in the realms of research, design, teaching and implementation.

The training of medical and nursing staff in the management of snakebite envenomings is another issue that deserves close attention in this region. In some countries the subject is regularly taught in medical and nursing schools, and permanent education programs for health professionals include the diagnosis and treatment of snakebite envenomings. However, in other countries this subject is largely excluded from university schools and permanent education programs. It is necessary to generate research on this aspect, in order to identify its main gaps, to evaluate existing programs and to design permanent education activities tailored to the needs of professionals and other health staff working in rural areas of high snakebite incidence. Likewise, the preparation of national and regional guidelines for the diagnosis and treatment of these envenomings is of paramount importance. Guidelines have been developed in Brazil, Colombia, Paraguay, Argentina, Venezuela, Ecuador, Costa Rica, and Panama, and other countries. A pending task is the preparation of PAHO-sponsored regional guidelines for Latin America and the Caribbean, such as the ones generated by the WHO for Africa and southeast Asia. Moreover, the use of information and communication technologies in the training of health staff on snakebite envenomings should be actively pursued. The platform Elluminate (http://www.campusvirtualsp.org/?q=es/elluminate-live), used by PAHO for videoconferences, is an example of a tool with a potentially high impact for reaching health facilities in urban and rural settings.

For a variety of reasons, the advocacy for raising awareness of the impact of snakebite envenomning among politicians, health authorities, philanthropic organizations and other sectors of society has been weak. This has contributed to the low profile of this disease in the scientific, political and public health agendas in Latin America and the Caribbean; the Ministries of Health in the region rarely include snakebite envenomning in their list of public health priorities. There is an urgent need to promote awareness of the importance of this pathology and of its social, psychological and economic impacts in the region. The advocacy strategies successfully used for other diseases, involving a diverse array of stakeholders, should be studied, and lessons should be brought to the field of snakebite envenoming. Without an increase in the relevance that politicians, health authorities and citizens in general give to this disease it would be difficult to reach significant advances in its control.

**Final remarks**

Important progress has been made in Latin America and the Caribbean towards generating a better understanding of snakes, snake venoms, snakebite envenomings and their treatment. Such body of knowledge and experiences should be harnessed to design interventions at various levels (scientific research, technological development and production of antivenoms, clinical management of envenomings, organization of public health services for effective attention to envenomed patients, and others). Box 1 summarizes the main accomplishments and pending tasks in the struggle to reduce the impact of snakebite envenomning in Latin America. The interaction and the forging of synergies between scientists, technologists, health authorities, health workers, community organizations, and the general population should be stimulated in order to generate effective public policies aimed at reducing the impact of this neglected tropical disease.

Efforts in research, antivenom availability and accessibility, teaching and delivery of health services should be based on an holistic, biosocial approach whereby the interventions to reduce the burden of snakebite envenomings must be viewed within the general strategy of strengthening the public health system as a whole, and should include not only the biomedical aspects associated with this pathology, but also the social, economic, cultural, and political contexts in which the disease occurs. The advances made in Latin America and the Caribbean hereby described should stimulate renewed efforts to circumvent the limitations that still cause much human suffering as a consequence of snakebite envenomings.

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