



Stability, distribution and use of antivenoms for snakebite envenomation in Latin America: Report of a workshop

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ABSTRACT

The issues of antivenom stability and distribution, and the training of health staff in the correct use of antivenoms in Latin America were discussed in a workshop held at Instituto Clodomiro Picado, Costa Rica, in September 16–19, 2008, under the auspices of the program CYTED. Participants from public antivenom production laboratories of the region, together with representatives of the Ministries of Health, from Argentina, Paraguay, Brazil, Bolivia, Perú, Ecuador, Colombia, Venezuela, Panamá, Costa Rica and Nicaragua participated in the event. Technical advances in the study of antivenom stability and in the design of novel formulations aimed at generating products of higher stability were presented. In addition, antivenom acquisition and distribution systems in every country were presented and discussed, together with novel tools that could be useful for improving antivenom distribution, such as the software SIGEpi, developed by the Pan American Health Organization. The issue of the cold chain, as well as the most frequent causes of misuse of antivenoms in the region, were also analyzed. Finally, the experiences of training programs for health staff on the correct use of antivenoms in snakebite envenomation treatment in Latin America were presented. It was concluded that, in addition to the fostering of antivenom production and quality control, renewed efforts should be implemented at improving the stability, distribution and correct use of antivenoms in the region.

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1. Introduction

Snakebite envenomations constitute a significant public health problem in Latin America (Fan and Cardoso, 1995; Gutiérrez, 1995; Chippaux, 1998; Warrell, 2004; Kasturiratne et al., 2008). Antivenoms, the only validated treatment for these envenomations, are produced in the region by a heterogeneous universe of manufacturers which includes laboratories predominantly belonging to public institutions and others located in the private realm (Gutiérrez et al., 2007). Some countries and subregions in Latin America are

self-sufficient in terms of antivenom supply, whereas others are not. A regional project, supported by the organization CYTED ('Ciencia y Tecnología para el Desarrollo'), started in 2006 with the aim of strengthening the endogenous capacity of public institutions in the region to produce and control antivenoms. This network, which includes laboratories and groups from 10 countries, has a research component, as well as a capacity-building component based on training exchange activities and organization of annual workshops. Technical workshops on antivenom production and quality control were organized in 2006 and 2007 at Instituto Butantan (Brazil) and Instituto Clodomiro Picado (Costa Rica), respectively (Gutiérrez et al., 2007).

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The success of the use of antivenom in the treatment of snakebite envenomations involves other issues in addition to the production and quality control of these immunobiologicals. These issues, often neglected in the analyses of this subject, include the stability and distribution of antivenoms to the regions where they are going to be used, as well as the training of the health staff in the correct use of these drugs. This report presents the discussions and conclusions of a workshop on the stability, distribution and training in the use of antivenoms in Latin America, which was held at Instituto Clodomiro Picado, Costa Rica in September 16–19, 2008.

2. Stability of antivenoms and the cold chain

Stability studies of liquid antivenoms manufactured in Costa Rica, Brazil, Peru and Colombia were presented. These studies confirmed the stability of various liquid preparations stored for three years at $5 \pm 3^\circ\text{C}$. Since different types of antivenoms, i.e. whole IgG and F(ab')_2 antivenoms, are manufactured by different laboratories, the need to have stability studies by each manufacturer and product formulation was emphasized. Two issues that remain open for investigation are (a) what is the actual shelf-life for liquid antivenom preparations?, and (b) what is the effect on antivenom stability of short-term interruptions in the cold chain during the storage of these products?. Preliminary evidence was presented supporting the contention that the shelf-life of liquid preparations stored at $5 \pm 3^\circ\text{C}$ may be higher than three years, an issue that requires further investigation. This is particularly important in the case of antivenoms for envenomations that occur infrequently, such as those induced by *Lachesis* sp. and *Micrurus* sp. In these cases, it is common that antivenoms are not used at the time of expiry; since these antivenoms are precious medicines, difficult to produce and scarce, the possibility of extending their shelf-life is very important and needs to be documented. A similar situation occurs with freeze-dried antivenoms, whose shelf-life has been estimated as being five years (Theakston et al., 2003). There is circumstantial evidence indicating that their shelf-life is likely to be more prolonged.

The results of preliminary studies with liquid antivenoms in which the cold chain was interrupted for short time intervals also evidenced that stability was not significantly affected in these circumstances. This is a relevant finding since failures in power supply often result in such temporary interruptions in the cold chain. Moreover, the effects of temporary freezing of antivenoms have to be also considered and investigated, since this might occur during storage and transportation. Alvaro Segura and María Herrera, from Instituto Clodomiro Picado, presented the results of investigations aimed at developing new formulations for liquid and lyophilized antivenoms, in order to improve their stability. Promising results have been obtained with the use of sorbitol in the stabilization of liquid preparations, in order to store them at temperatures of around 25°C . Overall, the results presented reinforce the need to perform more detailed studies on the stability of antivenoms in the region. The subject of cold chain was presented by Carmen Silvera, from Brazil, who discussed all aspects related with

the correct storage and transportation of antivenoms and the most common problems found in the region concerning the maintenance of a cold chain. Due to a number of difficulties for keeping a cold chain, especially in some rural regions of Latin America, the need for a quality control of the cold chain, including the regular monitoring of temperature, was stressed.

3. Distribution of antivenoms

The situation of antivenom distribution to the hospitals and other health facilities in the various countries in the region was analyzed in detail.

3.1. Brazil

The situation of acquisition and distribution of antivenoms in Brazil was presented by Hui Wen Fan and Carmen Silvera. This country, which has a long tradition of antivenom manufacture, created a National Program for Self-Sufficiency in Immunobiologicals, which includes antivenoms, in 1985. In addition, a National Program for the Control of Accidents by Venomous Animals was established in 1986. This program includes: (a) epidemiological surveillance; (b) modernization of technology and infrastructure for antivenom production; (c) standardization of diagnostic and therapeutic parameters; (d) analysis of the geographical distribution of venomous animals in the country; and (e) introduction of permanent training programs for health personnel. A total of 29,121 snakebite cases were reported in Brazil in 2006. There are four public laboratories that manufacture antivenoms, i.e. Instituto Butantan, Fundação Ezequiel Dias (FUNED), Instituto Vital Brazil, and Centro de Produção e Pesquisa de Immunobiológicos (CPPI). Antivenom production by these laboratories is coordinated with the needs of the Ministry of Health and the annual production is organized accordingly. A total of 424,763 antivenom ampoules were produced in 2007. The acquisition process is centralized and antivenoms are received by the National Center for the Distribution and Storage of Immunobiologicals (CENADI). After the quality control is performed by the National Institute for the Quality Control in Health (INCQS), the distribution of antivenoms is authorized. Such distribution process is a decentralized one, and is based on the antivenom needs of the various regions; antivenoms are distributed to the State Secretaries of Health, then to the Regional Offices of Health, then to the Municipal Secretaries and finally to the Health Services.

The planning of antivenom distribution is based on the following equation:

$$N = [(x \cdot y) + (\alpha + \beta)] - \delta$$

where:

N = number of vials to be distributed.

x = number of snakebite cases.

y = mean number of antivenom vials used per patient.

α = estimated underregistration of snakebite cases.

β = technical losses of antivenom (expired and/or incorrectly stored or transported).

δ = vials of antivenoms in stock in that region.

When antivenom is distributed for the first time to a region or a health center, this formula is modified as follows, in order to ensure an adequate antivenom stock:

$$N = [(x \cdot y) + (\alpha + \beta)] \cdot 2$$

Evidently, an adequate epidemiological information is a key element for the correct application of this equation and, consequently, for a correct distribution strategy.

The information available allows the analysis of the percentage of distributed antivenom ampoules which are not used. This percentage is low in the case of *Bothrops* sp. antivenom, but is higher for *Lachesis* sp. and *Micrurus* sp. antivenoms; this is due to the higher incidence of cases by *Bothrops* sp. In the case of the other two antivenoms, despite the low incidence of these envenomations, antivenoms have to be distributed to all health posts where these cases might occur and, consequently, the percentage of antivenom ampoules not used by the time of expiry is higher. The decision on which regions should receive antivenoms is therefore based on the following parameters: (a) epidemiological risk of envenomations; (b) conditions for adequate storage and administration of antivenoms; (c) existence of health posts and health staff; (d) access to health centers in a relatively short time interval; and (e) feasibility to perform medical references. There are still regions in Brazil where the access to antivenoms is limited and where patients have to travel long distances to receive antivenom treatment.

3.2. Argentina

The situation of antivenom acquisition and distribution by the Ministry of Health in Argentina was presented by Christian Hertlein. The following number of snakebite cases were reported between 2004 and 2007 in the various regions of the country: Northeast region: 624; Northwest region: 275; Central region: 146; Cuyo region: 25; and Southern region: 8. The Ministry of Health receives the antivenoms produced by the public manufacturer, the National Institute for the Production of Immunobiologicals – ANLIS, which produces antivenoms against viperid and elapid venoms. During the last years, this laboratory has provided the Ministry of Health with between 5000 and 8000 vials of antivenom per year, an amount that covers the total needs of the country for the treatment of snakebite envenomations. Antivenoms are provided to the section of Zoonoses of the Ministry of Health (central level), which then distributes them to the jurisdictional referents (intermediate level), and from there to the health centers in the provinces (local level).

3.3. Paraguay

The situation of antivenom acquisition and distribution in Paraguay was presented by Arnaldo Vera. Compulsory notification of snakebite envenomations was introduced in 2005; this information is forwarded to the Coordination of Snakebite Accidents of the Ministry of Health and Social Welfare. A total number of 470 cases were reported in 2007, although it is likely that this pathology is underreported. There is no local production of antivenoms; therefore they have to be

imported either by direct purchase processes or by donation. In 2008 a total of 1071 antivenom vials were distributed in Paraguay; however, the total number of vials used is higher, since there are decentralized acquisition processes at the local levels. There is concern with the quality control of the antivenoms being imported, since there is no local quality control laboratory and no information has been gathered on the preclinical efficacy of imported antivenoms. There is a need to prepare national reference venoms, to develop endogenous capacity for quality control, and to establish partnerships with laboratories in neighboring countries to perform preclinical assessment of antivenoms.

3.4. Bolivia

The situation of antivenom acquisition and distribution in Bolivia was presented by Williams Velasco. An estimated total number of 1000 snakebite cases occur per year, although there is an evident underreport. There is a local public laboratory that manufactures antivenoms, the National Institute of Health Laboratories (INLASA), which produced 1000 vials in 2007 and has produced 1300 vials in 2008. The country does not have a coordinated national program for snakebite envenomations, and antivenom distribution is deficient, since it does not reach the health centers in the regions where most snakebite cases occur.

3.5. Ecuador

The situation of antivenom acquisition and distribution in Ecuador was presented by Leonor Suárez. Epidemiological surveys by the Ministry of Health indicate that, during 2007, a total number of 1470 snakebite cases occurred in this country: 210 in the Sierra region, 765 in the Coast region, and 495 in the Western region. A total number of 2673 vials of antivenom were used in 2007. There is a national public manufacturing laboratory, the National Institute of Health 'Leopoldo Izquieta Pérez'. Antivenoms are acquired by the Ministry of Health for distribution in the country. This institute also harbors the laboratory of the National Control for Biologicals, in charge of the quality control of all antivenoms used in the country. In addition to the locally manufactured products, antivenoms imported from Brazil, Mexico, Colombia and Costa Rica have been used in emergency situations. Donations of antivenoms are sometimes received. After the process of quality control, antivenoms are sent to the National Bank of Vaccines, in Quito, for storage. Distribution is organized on the basis of the needs of each region, through the Regional Subsecretaries, which distribute antivenoms to the provinces, areas and operative units.

3.6. Colombia

The situation of antivenom acquisition and distribution in Colombia was presented by Teresa Sarmiento. Compulsory notification of snakebite envenomation was introduced in 2004; a total number of 2737 snakebite cases were reported in 2007. A public institution, the National Institute of Health (INS), and a private laboratory manufacture antivenoms in Colombia. A regulatory entity, the National Institute for the Surveillance of Medicines and Food (INVIMA), authorizes the

registration of antivenoms and performs the quality control of antivenoms on a regular basis. Antivenom distribution occurs by two main mechanisms: (a) the health insurance companies, responsible of guaranteeing the provision of antivenoms to their clients according to the epidemiological profile of the various regions in the country, and (b) the Ministry of Social Protection, which has antivenom stocks to satisfy antivenom needs in situations of emergency and natural disasters. Likewise, the Ministry purchases antivenoms that are not produced in the country, such as anti-*Micrurus* antivenoms.

3.7. Panama

The situation of antivenom acquisition and distribution in Panama was presented by Nereida Quintero, from Caja del Seguro Social, and Diógenes Castillo, from the Ministry of Health. These two institutions have hospitals where snakebite envenomations are treated. Panama presents the highest incidence of snakebite cases in the Americas (40–65 cases per 100,000 population per year), with an estimated total number of 1300–1800 cases per year. Compulsory notification of snakebite envenomation was established in 2001. Polyvalent (Crotaline) and anti-coral (Elapid) antivenoms are regularly purchased, according to the needs of the health system, through well-established acquisition protocols. In the last decade, all antivenoms required in the country have been provided by Instituto Clodomiro Picado (Costa Rica). During 2007 the Caja del Seguro Social acquired 9600 vials of polyvalent antivenom and 125 vials of anti-coral antivenom, whereas in 2008 the Ministry of Health acquired 12,000 vials of polyvalent antivenom and 400 vials of anti-coral antivenom. Once purchased, antivenoms are received by the institution main stockroom and, after quality control is performed, the products are distributed to hospitals and health centers of the various regions in the country through a well-controlled cold chain. A system of pharmacological surveillance of antivenoms is being organized in Panama.

3.8. Costa Rica

The situation of antivenom acquisition and distribution in Costa Rica was presented by Desirée Sáenz and Iliana Chavarría. Compulsory notification of snakebite envenomations was introduced in Costa Rica in 1997. The number of snakebite cases in this country is around 600 per year, all of which are attended in hospitals, clinics and other health centers of Caja Costarricense del Seguro Social (CCSS). Antivenoms are included in the official list of medicines of CCSS. A public laboratory, Instituto Clodomiro Picado (University of Costa Rica) provides all the antivenoms needed in the country, which amount approximately to 15,000 vials of polyvalent (Crotaline) and 2500 vials of anti-coral (Elapid) antivenom. After the purchase of antivenoms, the quality control laboratory of CCSS certifies antivenom quality. Antivenoms are then distributed, on the basis of regional needs, to three different levels: (a) National hospitals (level III); (b) major clinics and peripheral hospitals (level II); and (c) primary health care units (EBAIS) (level I). An institutional protocol for the use of antivenom and the

treatment of snakebite cases was recently approved and distributed (Caja Costarricense del Seguro Social, 2008).

3.9. Nicaragua

The situation of antivenom acquisition and distribution in Nicaragua was presented by Luz Marina Lozano. A total of 636 snakebite cases were reported in this country in 2007. This pathology is of compulsory notification. Antivenoms are imported and acquired by the Ministry of Health and are included in the Basic List of Medicines in Nicaragua. During the last decade, all antivenoms used in this country have been provided by Instituto Clodomiro Picado (Costa Rica). The Ministry of Health acquired 9000 vials of polyvalent (Crotaline) and 2000 vials of anti-coral (Elapid) antivenoms in 2008. According to the epidemiological patterns and the needs of each region, antivenoms are distributed to three basic types of health units: (a) National reference hospitals and regional hospitals; (b) health centers with beds; (c) primary health care units at local levels that have physicians. There are problems with the accessibility of antivenoms in regions where the cold chain is deficient or where the health units are located far from the sites where snakebites occur.

4. The use of Geographic Information System (GIS) in antivenom distribution

The need to have tools to develop more rigorous and effective national policies of antivenom distribution was emphasized. Gerardo Leynaud presented the experience at the province of Córdoba, Argentina, with the use of a free access GIS software, developed by the Pan American Health Organization (PAHO) for research in epidemiology and public health, named SIGEpi (<http://ais.paho.org/sigepi/index.asp?xml=sigepi/index.htm>), which can be used for the determination of high-risk areas of snakebite envenomation. These areas are selected on the basis of an integrated analysis that includes distribution of venomous snakes, epidemiology of envenomations, access to health centers, quality of the road systems and coverage of the cold chain. The applications of this software were discussed, and the need to undertake cooperative efforts between health authorities and research groups of the various countries to implement its use was stressed.

5. The correct use of antivenoms: experiences with the training of health staff in snakebite envenomation treatment

The correct use of antivenoms constitutes, together with an adequate distribution system, an essential component in the overall control of snakebite envenomations (WHO, 2007). The training of medical, pharmacy and nursing staff in the basic aspects of diagnosis, prescription, and administration of antivenoms, together with the management of adverse reactions to these immunobiologicals, is of utmost importance. This training has to be performed through a variety of activities at the university level, as well as by permanent educational programs at the health centers, particularly in regions with high incidence of these

envenomations. The experiences in the training of health professionals carried out in Brazil, Paraguay, Costa Rica and Panama were presented by Hui Wen Fan, Arnaldo Vera, Alexandra Rucavado and Hildauro Acosta, respectively. Diverse training methodologies have been used, such as the introduction of this subject in university courses, the development of permanent programs taught in health centers, the publication of national guidelines for treatment of envenomations, the publication of papers in scientific journals, and the development of materials in posters, CDs and other media (see for example *Ministério de Saúde de Brasil, 1998; Ministerio de Salud Pública y Bienestar Social de Paraguay, 2008; Caja Costarricense del Seguro Social, 2008*).

Despite the successes achieved by many of these programs, a critical appraisal of these activities was performed on the basis of the mistakes occurring in the treatment of these envenomations. These include a frequent lack of knowledge on the clinical presentation of these envenomations, on the selection of the type of antivenom to be used, on the decision on whether a patient requires antivenom or not, on the volume of antivenom required according to the severity of the case, and on the prompt treatment of the most common complications in these envenomations. This situation demands renewed efforts at improving the training programs, both in terms of preparing new teaching materials, the basic structure and methodology of the activities, and the design of strategies to reach the health staff of the regions of highest incidence of snakebites, often located in remote rural areas. The need to develop national and regional guidelines for the diagnosis and treatment of snakebite envenomations was emphasized. In addition, the participants discussed the urgent need to develop methodologies aimed at the evaluation of the effectiveness of the various types of training activities.

6. Conclusions and recommendations

- (1) There is a large heterogeneity in Latin America in the consolidation of strategies aimed at confronting the problem of snakebite envenomation. It is necessary to strengthen the cooperative links between countries in order to improve the regional production, quality control and distribution of antivenoms, as well as the training programs to health staff in the region.
- (2) Antivenom manufacturers should undertake the study of the stability of their antivenoms and the development of novel formulations aimed at improving this stability.
- (3) It is recommended that all countries develop their endogenous capacity to prepare national references of the most important venoms and to perform quality control of antivenoms being produced in the country or being imported. The development of these capacities demands regional cooperation and training programs. The meticulous preclinical assessment of the efficacy of antivenoms produced and used in the region is an important task.
- (4) Due to problems of antivenom acquisition in various countries, it is recommended that rapid and effective procurement processes should be developed in the

region. The active participation of PAHO in these processes in situations of emergency is very important.

- (5) There is an urgent need to perform research in the antivenom distribution systems in Latin America, in order to gain a precise understanding on the main problems associated with this issue and, consequently, to develop more effective distribution strategies.
- (6) It is necessary to improve the information systems on the epidemiology of snakebite envenomations in the region. This information is essential for the design of effective distribution policies and training programs.
- (7) The use of GIS methods in the study of snakebite envenomation should be encouraged, as a tool to gain more precise and objective information of the most vulnerable areas.
- (8) There is a need to develop methods for the qualitative and quantitative assessment of antivenom usage in the region. The quality of the medical attention provided to snakebitten patients has to be properly evaluated in order to detect deficiencies and to design more effective training programs.
- (9) The development and strengthening of permanent training programs to health staff is an essential component in an integrated strategy to confront snakebite envenomation in the region. It is necessary to develop tools to assess the efficacy of the training activities developed.
- (10) The preparation of national and regional guidelines for the diagnosis and treatment of snakebite envenomations, including the correct use of antivenoms, should be actively encouraged in the region.
- (11) Training programs, aimed at health and administrative staff, on the correct storage, distribution and use of antivenoms, including the maintenance of an adequate cold chain, should be developed.
- (12) It is necessary to organize national pharmacological surveillance programs to monitor the therapeutic performance of antivenoms, both in terms of efficacy and safety.

7. Participants in the workshop

Argentina

- Gerardo Leynaud, Universidad de Córdoba.
- Christian Hertlein, área de Zoonosis, Ministerio de Salud.
- Patricia Geoghegan, Administración Nacional de Laboratorios e Institutos de Salud "Dr Carlos G. Malbrán".

Bolivia

- Gil Patrick Fernández, Instituto Nacional de Laboratorios de Salud (INLASA).
- Williams Velasco, Instituto Nacional de Laboratorios de Salud (INLASA).

Brazil

- Hui Wen Fan, Instituto Butantan.
- Isolete Pauli, Centro de Produção e Pesquisa de Imunobiológicos (CPPI).
- Joseane Zaja Almada, Instituto Vital Brazil.
- Carmen Lucia Miranda Silvera.

Colombia

- Teresa Sarmiento, Ministerio de Protección Social.
- Adriana Gómez, Instituto Nacional de Salud (INS).

Costa Rica

- Desirée Sáenz, Caja Costarricense del Seguro Social y Universidad de Costa Rica.
- Iliana Chavarría, Caja Costarricense del Seguro Social.
- Yamileth Angulo, Instituto Clodomiro Picado, Universidad de Costa Rica.
- Alberto Alape, Instituto Clodomiro Picado, Universidad de Costa Rica.
- Fabián Bonilla, Instituto Clodomiro Picado, Universidad de Costa Rica.
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- Álvaro Segura, Instituto Clodomiro Picado, Universidad de Costa Rica.
- Eduardo Segura, Instituto Clodomiro Picado, Universidad de Costa Rica.
- Gabriela Solano, Instituto Clodomiro Picado, Universidad de Costa Rica.
- Cristian Vargas, Instituto Clodomiro Picado, Universidad de Costa Rica.

- María de los Ángeles Villalobos, Instituto Clodomiro Picado, Universidad de Costa Rica.

Ecuador

- Leonor Suárez, Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez".

Nicaragua

- Luz Marina Lozano, Ministerio de Salud.

Panamá

- Hilda Acosta, Universidad de Panamá.
- Nereida Quintero de Velasco, Caja del Seguro Social.
- Diógenes Castillo, Ministerio de Salud.

Paraguay

- Arnaldo Vera, Ministerio de Salud Pública y Bienestar Social.

Perú

- Percy Torres, Instituto Nacional de Salud (INS).

Venezuela

- Dora Manzini, QUIMBIOTEC.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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