

**SNAKEBITES IN THE GLOBAL HEALTH AGENDA OF THE TWENTY FIRST CENTURY:
A SOUTH-TO-SOUTH COLLABORATIVE EFFORT**

by

Francesca Schiaffino Salazar

A thesis submitted to the Johns Hopkins University in conformity with the requirements for the
degree of Master in Arts

Baltimore, Maryland

March 2021

© 2021 Francesca Schiaffino

All Rights Reserved

Abstract

Snakebite envenomation constitutes to be a major public health problem in the most resource poor, tropical areas of the world, resulting in death or severe sequelae. Snakebites were officially included in the Neglected Tropical Disease portfolio of the World Health Organization in 2018, after the World Health Assembly acknowledged it as a Global Health problem. This study details the journey of snakebites from obscurity to its inclusion in Global Health agenda over the course of the twentieth and twenty first century and argues that the main thrust of the movement came from South-to-South partnerships between academic and public-private research institutions. It explores how Latin American countries, such as Costa Rica and Brazil, played crucial roles in promoting the international movement of snakebites, challenging the paradigm that scientific and pharmacological knowledge and objects only emerge from the Global North and flow to the Global South, and provides evidence of scientific excellence at the periphery.

Advisor

Dr. Randall Packard

Professor

Department of the History of Medicine

Johns Hopkins School of Medicine

“Few subjects have stimulated the minds and imagination of man more than the study of snakes and snake venoms. No animal has been more worshipped yet more cast out, more loved yet more despised, more envied yet more caged, and more collected yet more trampled upon than the snake.”

Findlay E. Russell; J. Toxicology,7(1); 1-82; 1988

Table of Contents

Abstract.....	ii
Introduction.....	1
Background: Global Burden and Key Challenges in Snakebite Control.....	3
Brief Overview of the History of Neglected Tropical Diseases.....	5
Snakebite Antivenin Production in Latin America: Key players	8
Instituto Clodomiro Picado, Costa Rica	9
Instituto Butantan, Sao Paulo, Brasil	14
Antivenin Institute of America, United States	18
Late Twentieth Century Stagnation	20
South to South Cooperation in the Twenty First Century.....	24
From Costa Rica to the World.....	26
The Final Step: Global Advocacy for Snakebites.....	30
Snakebite Research in Latin America: Excellence in <i>Science at the Periphery</i>	35
Upcoming Challenges	38
Conclusion.....	40
References	41

Introduction

Snakebite envenoming is a life-threatening condition that is prevalent in the most resource poor settings of the world. Approximately 412,000 to 1.2 million cases of snakebites and 81,000 to 138,000 associated deaths a year are estimated to occur, according to estimates from the World Health Organization(1, 2). This is a disease that has been prevalent for millennia, yet only in the second decade of the 21st century did it entered the Global Health agenda as a result of its inclusion as a Neglected Tropical Diseases during the tenth World Health Organization strategic and technical advisory group (STAG) for Neglected Tropical Diseases (NTDs) meeting that took place on March 29-30 2017, and the subsequent resolution (WHA71.5) of the of the 71st World Health Assembly that took place on May 24, 2018 (3, 4).

Resolution WHA71.5 acknowledge the worldwide neglect of snakebites as an important public health issue, and made access to effective, affordable, and safe antivenin a priority. The resolution also recommended the creation of partnerships and international cooperation that would enable the attainment of these goals, through the efficient evaluation of the burden of snakebites in low- and middle-income countries, as well as the technological transfer of antivenin production technologies to areas of the world were the burden is greatest (4).

Snakebites was one of the latest additions to the NTD portfolio, which currently holds 20 diseases, most of which are caused by parasitic pathogens that disproportionately affect people living in the poorest nations of the world. Strikingly, snakebites are differentiated from the rest of the NTD portfolio because envenomation is not a disease caused by a pathogen, but by the toxicological and physio pathological effect of venom introduced to the body by the bite of a venomous snake. Additionally, there is no one single universal solution for snakebite envenomation. On the contrary, antivenom is specific to the snake genus. As a result, antivenom production needs to be tailored towards the territorial distribution of venomous snakes and incidence of envenomation cases. The lack of resemblance of snakebites with other

NTDs was highlighted in the report of the tenth meeting of the WHO STAG for NTDs held in Geneva in 2017. The STAG agreed that WHO should address the issue but it was “*unsure that the programmatic aspects of this would be best handled by the NTD Department*” (3).

How did snakebites become a Neglected Tropical Disease? In this essay, we will explore the main forces, actors and events that led to the transition of snakebites from obscurity to its inclusion in the NTD portfolio of the World Health Organization. We argue that the main efforts that led to this crucial step was driven by multiple South-to-South international coalitions and partnerships, with South American countries playing key roles in this quest. This study will challenge the traditional view that scientific advances in Global Health emerge from the scientific and technological hubs of the Global North, and unidirectionally flow to the receptive peripheries of the Global South. To explore this argument, this study will provide a detailed view of the process by which the public health problem of snakebites became recognized as a Global Health problem. Specifically, we will examine the first steps in snakebite research, antivenom production and inter-institutional collaboration among four key countries in the early twentieth century: Costa Rica, Brazil, and the United States. This review will enable us to understand the social, political, and economic factors that led to the emergence of early snakebite research and that helped foster later international collaborations. Next, it will examine how key South American countries, serving as champions of snakebite research and advocacy, created South to South public-private partnerships that helped catapult the problem of snakebites into the NTD portfolio of WHO. Finally, it will explore the current challenges facing efforts to keep snakebites in the NTD portfolio. We will contextualize and seek to explain these developments through a framework that focuses on the history of science in Latin America. In doing so, the paper will utilize the concept of “*peripheral science*” and “*science at the periphery*”, concepts that has been employed by historians studying the science in Latin America and elsewhere(5, 6).

Background: Global Burden and Key Challenges in Snakebite Control

In 1954, the World Health organization requested a study to evaluate the importance snakebite mortality worldwide. S. Swaroop, as chief of the Statistical Studies Section of WHO, was commissioned to conduct this study (7). In Swaroop's report it was estimated that at least 30,000 to 40,000 deaths occurred per year. Yet The New England Journal of Medicine acknowledged that same year that the recording and reporting of snakebite deaths was "*obviously handicapped by the fact that registration of deaths in general is inadequate*"(8). Unfortunately, this is still the case in the 21st century, as set forth both by J.P. Chippaux's appraisal of the global situation of snakebites, and a modelling effort by a group of researchers from the University of Kelaniya in Sri Lanka, the WHO department of Control of NTDs and the Liverpool School of Tropical Medicine in the United Kingdom(2). In the latter, researchers performed a meta-analysis for which they were able to extract reliable data from only 160 publications from 68 countries (1). The majority of cases were estimated to occur in South East Asia (18.82-84.65 cases per 100,000 people year), followed by Central Sub Saharan Africa (20.28 – 53.37 cases per 100,00 people a year), and Central Latin America (12.90 -54.47 cases per 100,000 people a year) (1). Jean Phillippe Chippaux and Jose Maria Gutierrez argued that the lack of primary data on the burden of snakebites at a national level resulted from patients not reaching primary health centers or hospitals once injured or doing so with substantial delay(9, 10). The sequelae and morbidity associated with snakebites was presumed to be further underestimated because of case underreporting, low rates of attendance to the health centers, and the absence of traditional healing information(10). The delay in reaching health centers in rural areas of the world was further highlighted by modeling estimates done by Joshua Longbottom and collaborators. Longbottom estimated that 11.0% of people living with a risk of high exposure to venomous snakes lived more than 1 hour away from an urban center (and thus a health care center). Additionally, 65.3% of people with access to the lowest quality of care (as catalogued by Healthcare Access and Quality (HAQ) Index) were at risk of exposure

to venomous snakes for which there was no known antivenom, in comparison to only 29.8% of people with access to the highest quality of care. Strikingly, antivenom was not available for more than 57% of known venomous snakes (11).

The production, distribution, and access to antivenom in isolated and at-risk areas for venomous snake exposure was the most critical need to tackle this disease. This was termed the *antivenom crisis* and was the catalyst of working and analysis groups that have attempted (unsuccessfully) to resolve it (12). Several obstacles have blocked progress over the decades. The first, and perhaps the most critical one, was the lack of antivenom production at a local level, a problem which was associated with scant research and development of new production techniques that were able to go through an efficient technological transfer process (13).

The commercial production and distribution of snake antivenin in Latin America (and the world) was initiated in the early twentieth century, with Brazil as a pioneer in research, development, and technological transfer. These early Latin American collaborative efforts formed the foundation for efforts to move snakebites onto the Global Health agenda. It is important to highlight that collaborations between South American countries, or between South American, Asian and African countries were the result of scientific work produced within each nation's own history of scientific development, and that were influenced by national and regional sociopolitical, cultural, and economic developments. As a result, it is important to frame these collaborations within each country individual microcosm of scientific development, as well as within the overall global trends.

Brief Overview of the History of Neglected Tropical Diseases

Dr. Kenneth S. Warren, the head of the Rockefeller Foundation launched in 1977 the “*Great Neglected Diseases of Mankind Program*” (GND) an international effort to study parasitic diseases that were being mostly ignored by academic scientists of United States and Europe (14, 15). As a parasitologist himself, Warren and the GND program predominantly focused on the study of parasitic diseases of the tropics, such as Schistosomiasis, Filariasis, Trypanosomiasis, Onchocerciasis and Hookworm. Warren aimed to modernize the field of parasitology by bridging the gap between parasitology and the evolving field of molecular biology (14). As Conrad Keating described, over the eight years the program existed, it trained over 360 individuals (150 from the Global South) and produced over 180 scientific publication on parasitic diseases of the developing world, revolutionizing the field of parasitology, and global health research as a whole (14). Warren classified these parasitic diseases as incredibly common, globally distributed, yet largely forgotten by Western medicine. Warren conceptualized these diseases as a numerical problem, which low-cost interventions at a population scale would be able to control. In fact, Warren was critical WHO's focus on building primary health care services, following on the 1978 Alma Atta declaration, and advocated the use of more targeted health interventions that could “*maximize improvement of health and medical care in less developed countries*”(16).

A concomitant effort to tackle unattended diseases of the poorest was the creation of the Special Program for Research and Training in Tropical Diseases by the World Health Organization in 1977, financially supported by the United Nations Development Program and the World Bank(17, 18). The program aimed to improve the control of six tropical diseases (Malaria, Schistosomiasis, Filariasis, African trypanosomiasis, Chagas diseases, Leishmaniasis and Leprosy) by increasing the research capacity of countries with a high burden of disease and promoting research and the development of new tools for controlling these diseases(19).

The push for global health recognition of neglected tropical disease was accelerated by the incorporation of multinational pharmaceutical companies as major suppliers of low cost antiparasitic and antibacterial drugs. Antiparasitic drugs, like Ivermectin, albendazole, mebendazole, praziquantel and azithromycin produced by Merck, GlaxoSmithKline, MSD and Pfizer markedly changed the prospects for controlling neglected tropical disease. By agreeing to donate these drugs for mass-administration campaigns, multinational pharmaceutical corporations became important partners in the push to place neglected tropical disease onto the global health agenda. It is worth noting that many of the new drugs had little commercial value for the pharmaceuticals, yet their participation as *benefactors* of the Global South directly benefited them through tax deductions, as well as by improving their global institutional image.

In December 2003 the World Health Organization met in Berlin for the first time with the German Corporation for International Cooperation (GTZ) and established a collaborative and collective effort to combat neglected tropical diseases(20). The meeting produced the first conceptual framework by the agency in which the need to tackle these diseases using a holistic approach was emphasized. This meant that the disease should be tackled on various fronts and under a coordinated approach, through a variety of mechanisms. These could include research and development, improved health care access and delivery, health care capacity building and enactment of policies that would facilitate the implementation of programs. Additionally, these programs were supposed to undertake a horizontal approach to disease control, involving not only the academic institutions, but also health care facilities, private companies, non-governmental organizations, grass-roots organizations, and the general public at large. In addition, the link between NTDs, poverty and development was finally agreed upon and established so that controlling NTDS became viewed as an important step towards achieving the Millennium Development Goals(21).

In a second meeting in April 2005 (*Berlin II*), the World Health Organization in alliance with the German Ministry of Health, the German Ministry of Economic Cooperation, German Corporation for International Cooperation (GTZ), the Kreditanstalt für Wiederaufbau (KfW) development bank, and the WHO Special Program for Research and Training in Tropical Diseases (TDR) met again in Berlin to discuss the strategic and technical aspects of escalating the control of neglected tropical diseases(21). Three approaches were highlighted in their report: 1) *the use of rapid-impact interventions*, 2) *increased vector control to decrease transmission*, and 3) *improved surveillance and high-quality care*. The underlying intervention promoting these approaches was the population level implementation of mass drug administration programs through an integrative framework, rather than through a clinical approach. The report highlighted the need for establishing “*long-term linkages*” across programs to ensure the overall success of the strategy. A direct result of this meeting was the creation of the WHO department of Neglected Tropical Diseases in 2005 with Dr. Lorenzo Savioli as its founding director. The main goal of the department was the translation of research and advocacy into global health policy for the prevention and control of 17 NTDs. The Global Plan to Combat Neglected Tropical Diseases: 2008-2015 was published in 2007(22). However, it was not until 2013 that WHO member states endorsed the resolutions for the proposed NTDs and confirmed the political will by signing countries to their prevention and control (66.12 World Health Assembly Resolutions on Neglected Tropical Diseases: 1948-2019).

The diseases included in the First WHO report on Neglected Tropical Diseases were Dengue, Rabies, Trachoma, Buruli ulcer, Leprosy, Chagas disease, Human African trypanosomiasis, Leishmaniasis, Cysticercosis, Dracunculiasis, Echinococcosis, Foodborne trematode infections (Fascioliasis), Lymphatic filariasis, Onchocerciasis, Schistosomiasis, Soil-transmitted helminthiasis and Yaws(23).

Snakebites clearly did not fit the model of a neglected tropical disease that had been built between the 1970s and early 2000s. Antivenin could be considered a rapid-impact intervention. However, there was not a single antivenin that could be efficiently used globally, due to the specific nature and toxicological effects of snake venom. Vector control did not apply to snakebites unless one considered the reptile itself as the vector of the venom. That said, the incidence of human-snake encounters, like that of NTDs, was highest at the interphase with wildlife, such as subsistence farming and agricultural areas in the tropics.

Yet in other ways, snakebite control strategies that were used by institutions working in Latin America to help tackle this issue were compatible with the holistic framework of action required by the NTDs program. First, it called for a coordinated approach focused on treatment access and improved health care delivery at a marginal cost compared to the morbidity and overall loss of human potential associated with the disease. Secondly, like other NTDs snakebite strategies required a coordinated action and collaboration with pharmaceutical companies, which is an active area of work of the department of NTDs. Finally, snakebites required a “*multi-faceted holistic*” approach to control this complex problem at a global scale. The challenge for snakebite advocates was to make this case to the WHO.

Snakebite Antivenin Production in Latin America: Key players

Snakebites were not originally considered a neglected tropical disease. This was a result of the initial concept and framework under which NTDs were classified as such, and because of the nature of the problem of snakebites and its corresponding solution. However, a network of Latin American public reference laboratories producers of antivenin, demonstrated the World Health Organization and the Neglected Tropical Disease department that snakebites could be tackled using the comprehensive and integrated framework of disease control and prevention that the NTD department of WHO preached. Although there were multiple laboratories in this network, the role of two champion institutions needs to be described in detail: Instituto

Clodomiro Picado and Instituto Butantan. Thanks to the work and early research of these institutions we can analyze the circumstances under which a successful snakebite control program succeeded, setting a regional and global example and precedent for success. Finally, it is also important to highlight the early development of the Antivenin Institute of America because its history draws attention to other forces that helped trigger snakebite research and control strategies in North America.

Instituto Clodomiro Picado, Costa Rica

The Institute Clodomiro Picado (ICP) is one of the leading institutions in snake envenoming research and production of antivenom and technological transfer in the Americas, and perhaps the most important Latin American institution that helped shape the movement of snakebites onto the NTD portfolio and WHO global health agenda.

ICP was founded on the 13th of April of 1970 under the governance of the Ministry of Health, with Dr. Róger Bolaños as its founding director. Two years later, on June 2nd 1972, it was transferred to the jurisdiction of the Faculty of Microbiology of the University of Costa Rica and has remained under that institution until present day. However, the true intellectual origins of ICP started decades earlier, with the work of visionary scientist Dr. Clodomiro Picado Twight. Twight was the first individual who managed to align the goals of a research institution and the goals of the ministry of health and its dependencies towards the control of snakebites using an integrated approach to envenomation control. We will explore the visionary work of Picado in the control and prevention of snakebites before continuing analyzing the role of ICP in more current events.

Clodomiro Picado Twight was born in 1887 in Nicaragua. He moved with his family to Costa Rica in 1890, where he obtained his bachelors diploma (current equivalent of secondary education) at the “Liceo de Costa Rica” in 1906 (24). “Clorito”, as he is known among Costa

Rican scientists, travelled to Paris under the auspice of the congress of Costa Rica. He obtained a Diploma in advanced studies of Zoology and Botany at La Sorbonne in 1909 and 1912, respectively, and a Doctorate in Science from the University of Paris in 1913. After this, he spent some time at the Pasteur Institute and Institute of Colonial Medicine in Paris (24). Upon his return to Costa Rica, Picado was assigned as the head of the San Juan de Dios Hospital in Costa Rica, the oldest hospital of the nation. Picado brought back to Costa Rica the rigor of the scientific method, as well as new revolutionary concepts in microbiology and immunology, with strong influence from European mentors including Raymond Jacques Sabouraud and Elie Metchnikoff (13, 25).

“*Clorito*” is described by Afonso Trejos Willis, in the foreword of the first volume of Picado’s complete memoirs, as a person who has “*a particular close of love, not for science or for truth, but for the search of truth through science*”(26). He thrived on searching for scientific truth, focusing his studies on the biology of bromeliad epiphytes, the physiology of aging, thyroid physiology, mycology, and of course snakebites. Picado was an example of a group of early twentieth century scientists who were trained in European institutions, and who returned to Latin America bringing with them the European institutional model of academic science(27). Costa Rica had exited the state of oligarchy that reigned the country between 1849 and 1870 and had welcomed liberalism in all aspects of national life. These scientists aimed to modernize the state and science was a vehicle to achieve that. As historians of science in Latin America have argued, most nations in early twentieth century underwent a period in which “*European Positivism*” pushed forward the evolution of scientific knowledge. Positivism related to the notion that the progress of the nations had been stalled because of colonial rule, offering a framework under which economic, industrial and cultural development could move forward. The model of European scientific education and scientific institutionalization was the medium under which progress could be achieved. Vessuri also argues that under Latin American positivism, new

scientific knowledge, “*expeditions to the interior and inventories of native flora and fauna were seen as effective ways to gain true understanding of a new nations resources and possibilities*”(27). The work of Clodomiro Picado is a successful example of the goal of the state of Costa Rica to move scientific development forward. Picado’s early studies on the nation’s epiphytes, as well as snake taxonomy, are examples of this nationalist trend in scientific knowledge.

One of Picado’s main scientific interests was snakebite envenoming. He approached this topic from a variety of scientific perspectives, including snake taxonomy, envenoming toxicology and pathobiology, immunology, and anti-serum production. He built the first snake house (serpentarium) of the San Juan de Dios hospital to further develop his research (13). His connection with French scientists was strong, as demonstrated by his collaboration with Pierre Poutet from the Institute of Pasteur, who, in Paris, immunized horses with venom from Costa Rican snakes for research purposes. Picado described this as an “*act of generosity of French Sciences and from the Pasteur home*”. The long-term objective of this collaboration was to provide antiserum with higher specificity and efficacy, in sufficient quantities and for lower prices(28). However, the solution to supply of antivenin in Costa Rica, came from a partnership between Picado and Instituto Butantan in Sao Paul, Brazil. Thanks to Picado’s knowledge on snakes, and to his connection with Viral Brazil director of the *Instituto Butantan* in Sao Paulo, Brazil, antivenin was imported to Costa Rica and successfully used throughout the country, until national production initiated in the 1960s. Picado speculated that antivenoms produced at Butantan would work with Costa Rican viper envenoming cases because of the distribution and taxonomic similarity of snakes throughout Central and South America. This evidence of technological transfer between institutions, as well as intergovernmental collaborations between two South American governments was the first success story for the control of snakebites. It proved that antivenin could be efficiently shipped across borders.

One of the key aspects of Picado's approach to snakebite control was his view of snakebites as a complex problem. This meant that Picado understood that there was not a single cause, effect, and solution to the problem of snakebite envenomation in Costa Rica, and as a result, it required interventions on various fronts: research on venom toxicology, distribution of antivenin, health care access and management, training of health care workers to recognize and treat cases of envenomation, and a national policy that would encompass these strategies. In order to achieve a national snakebite policy of Costa Rica, Picado supported legislation that insured the use of antivenoms throughout Costa Rica. On May 24th 1916, the Costa Rica congress approved a law that mandated the distribution of antivenin to all main hospitals, police stations, railway stations, and plantations. Plantation managers and owners were required to have a stock of antivenin in case agricultural workers were bitten, and if the death of a worker resulted from the lack of antivenin, the owner was obliged to compensate the family of the victim (13, 28).

Later in 1926, Picado would publish an early version of his most famous treaty on snakebite research, "*Venomous Snakes of Costa Rica: Their Venoms and Snake Antivenin*" (*Serpientes venenosas de Costa Rica: sus venenos, y seroterapia antiofidica*), a publication he would complete in 1931. Picado's later work would focus on other matters such as the immunology of aging. His last years of productivity would be spent under the direction of the Hygiene Institute in 1940. Some accolades included his inclusion in the Paris Society of Biology in 1931 and his naming as "*Benefactor of the State*" in 1943, a year before his death in 1944.

Picado's vision and approach to snakebite control constituted one of the earliest examples of an integrated program in Latin America that aimed to tackle a public health problem, in a way that mirrored the current goals of the NTD program at WHO. However, progress stopped temporarily. Costa Rica went through several decades of political and social unrest until the end of the 1950s. The world economic crisis of 1929 and the emergence of

socialist parties helped end the thrust provided by the positivism movement. The start of World War II, and the civil war of 1948 further delayed endeavors to produce antivenin locally, even though the human resources were available. It was not until the early 1960s that snakebite research in Costa Rica re-emerged, and the Costa Rican government gained interest in locally producing snake antivenin that was specific to the snake population of the country. As a result, the “*Programa de Sueros Antiofidicos*” was created in 1965 by the University of Costa Rica, the Embassy of the United States in Costa Rica, and the Costa Rican Ministry of Health. In charge of the project was Herschel H. Flowers, a US army veterinarian and expert in snake venom toxicology and antivenom production in the US(29). According to Jose Maria Gutierrez, Roger Bolano, from the University of Costa Rica, assumed the leadership of the project in junction with Flowers, because Jesus Maria Jimenez (expert in snake venom biochemistry) and Flowers were unable to work together (30). Polyvalent and anti-coral antivenin was successfully produced in 1967. In that same year the National Commission Against Snakebite Envenoming (Comisión Nacional contra el Ofidismo) was launched to support and advise the Ministry of Public Health with all matters related to snake envenomation control. The Instituto Clodomiro Picado were created three years later in 1970, with Roger Bolanos as head(13).

The National Commission Against Snakebite Envenoming mirrored the previous legislation enacted by the government in 1916 to confront and control the problem of snakebite envenomation. This framework was also adopted by ICP. As a result, all major institutions in Costa Rica dealing with snakebites shared the same goals and horizontal approach to such a complex problem. This is relevant because it proved that complex diseases and public health problems (such as snakebite envenomation) could be tackled under this framework at a national level. The Ministry of Health, the ICP, the University of Costa Rica, the social security of Costa Rica, medical training programs, the primary health network of the country, and social extension groups all shared the same goals and philosophy of tackling snakebites under a unified

approach. It is this framework that has been working in this Central American country for decades that was subsequently mirrored in WHO approach to NTD control. As a result, the experience of Costa Rica provided an example of a success story in snakebite control that could be presented to WHO and the NTD strategic advisory group in the form of scientific publications, and epidemiologic indicators.

Instituto Butantan, Sao Paulo, Brasil

Instituto Butantan pioneered snakebite control in Latin America and the world. Butantan was the product of the Brazilian government drive to institutionalize its response against epidemic diseases. Specifically, Bubonic Plague was ravaging Sao Paulo in 1899. As a result, the Bacteriological Institute commissioned the creation of the Serum Institute (later called the Instituto Butantan) which was officially established on the 23rd of February 1901. Dr. Vital Brazil Mineiro da Campanha was assigned as its founding director by Dr. Adolpho Lutz, the director of the Bacteriological Institute. Brazil was a pioneer of snake venom research and antivenin production and the Instituto Butantan became the first Latin American institution to produce and distribute antivenin to Brazilian population and to its regional partners.

Brazil was a physician trained in the Faculty of Medicine of Rio de Janeiro, working and studying at the same time to support himself and his family. Unlike Picado in Costa Rica his early training cannot be traced to European institutions. Nonetheless, Vital was comfortable reading the scientific publications of those at the forefront of the microbiologic revolution in Europe(31) .

Vital Brazil's interest in snakebite research can be traced back to 1895, during his time as a private practitioner in rural Botucatu, near Sao Paulo. Botucatu was a largely agricultural city at the time, with coffee and cattle farming (31), and as a result of his experience there, Vital

Brazil noticed the different clinical syndromes produced by the bite of different snakes. These observations led to Vital's most prominent discovery: the specificity of snake antivenin. In other words, he proved that Calmette's snake antivenin against *Naja* venom did not work against envenomation with *Bothrops* or *Crotalus* venom. This was a turning point in snakebite research and control because it meant that the control of snakebite envenomation had to be tailored towards the distribution of venomous snakes and the specific incidence of snakebites within each country(31, 32). Ironically, this discovery made snakebites look dramatically different from other NTDs. It would take a century for modern inter-governmental organizations to recognize this as a strategy towards antivenin production and distribution, and one of the main limitations towards a successful control of snake envenomation in various countries. By 1898, Brazil had proven his theory by inoculating and treating dogs with different venoms and antivenoms. However, it was not until 1901 that he was able to formally finish this work at Butantan and publish it at the *Revista Medica de Sao Paulo* (33). Vital's observations were also noted by other researchers such as bacteriologist Joseph McFarland, in association with Munford Laboratories in the United States(34). As a result of these studies, Brazil produced the first polyvalent antivenom against *Crotalus* and *Bothrops* species. This achievement is important because using an effective antivenin against more than one snake simplified the treatment of envenomation in rural areas of the world, reducing the technical requirements for its use. This was an important hurdle that was circumvented in the path towards the inclusion of snakebites as an NTD. By having antivenin that was efficient against more than one specific snake, the production and distribution of antivenin could extend to a group of countries or areas that had a shared venomous snake diversity and distribution.

Interestingly, Vital Brazil's research and strategy for serum distribution was illustrated by a trading mechanism between farmers and the Institute of Butantan. Local farmers would deliver snakes to Butantan, and the institute would deliver antivenin in exchange(31). Brazil also made

sure that he received the epidemiological and clinical characteristics of each envenomation case associated with the snakebites that were delivered to the Institute and that were associated with a case of envenomation. It is worth noting here the intricate relationship between agricultural production in the city of Sao Paulo and snakebite research. Farmers were (and currently are) disproportionately affected by snakebite envenoming due to the nature of their work at the human-animal interphase of disease. This is a key characteristic of an NTD. This connection is not only associated with local, small-scale farming, it is also associated with industrial agricultural endeavors of large-scale corporations. As we will see in a different scenario in the United States, the economic effect of snakebite envenomation at agricultural plantations made the problem relevant at a national level. For Sao Paulo, it was not only agricultural corporations, but also the burden of snake envenomation on subsistence farmers what triggered the demand for antivenin. It was ultimately an economic and social problem that needed to be addressed. Vital Brazil retired to Rio de Janeiro and founded the Instituto Vital Brazil in 1919, but later returned to redirect Butantan between 1924 and 1927.

Marcelo De Franco and Jorge Kalil describe the history and evolution of Instituto Butantan. The first stage was characterized by the life and contributions of Vital Brazil. The second period, between 1930 and 1970 was characterized by strong efforts to institutionalize scientific research and development in Brazil. This is evidenced by the creation of National Council for Scientific and Technological Development and the Foundation of Research Support of the State of Sao Paulo (35). However, during this period, Butantan's administration was inefficient, and the institution received little federal funds. The reason for this can be explained by Vessuri's narrative of what she called "*The Development Decades*" in Latin America(27). Vessuri argues that after World War II, Latin America underwent a period of industrial growth at the urban centers, and consequentially displaced the importance of agriculture.

As a result of this displacement, envenomation by snakebites was also regarded as a second-tier problem. This does not mean that Brazilian science halted, on the contrary, it grew exponentially, while at the same time the Brazilian government aimed to link industrial and economic development with scientific development. This led to the National Immunization Program in 1973 which promoted the industrial production of vaccines and serums.

Large injections of capital into the Butantan Institute followed, facilitating the renovation of the institute's laboratories. With the implementation of the National Program for Self-Sufficiency in Immunologicals in 1985, the National Program for Snakebite Control in 1986 which its later conversion to the National Program for the Control of Accidents by Venomous Animals in 1988, the institutionalization of snakebite envenomation control was completed (36).

In the Twenty First Century, the Instituto Butantan regained its status as a worldwide leader in snakebite research and international collaboration. Along with Instituto Clodomiro Picado, the creation of the Latin American network of public laboratories producing antivenin was created. With the support of the Pan American Center for Foot and Mouth Disease (PANAFTOSA), the network (RELAPA) was created (37). In this network, Butantan was not the only Brazilian institute that produced antivenin. Other institutions included the Instituto Vital Brazil in Rio de Janeiro, the Center of Production and Research in Immunobiologicals and the Ezequiel Dias Foundation (FUNED). Of this network, those with the largest production capacity included ICP, Butantan, Instituto Vital Brazil, and Mexico's Laboratory of Biologicals and Reactives, with over 1.2 million doses produced altogether per year. (For further account of this regional network of laboratories see the section "*South to South Collaboration in the Twenty-First Century*"). The creation of this network provided a crucial example of inter-institutional collaboration and technological transfer between Latin American countries. This would help advance the case for including snakebite in WHO agenda.

The histories of Instituto Clodomiro Picado and Instituto Butantan help understand why these two institutions were key players in the movement of snakebites as a Global Health problem. It is important to explore the formation of the Antivenin Institute of America as a way of highlighting other forces particular to the North and Latin American context that helped shape the response towards snakebite control and trigger national alliances and technological transfer programs early on.

Antivenin Institute of America, United States

The production of snakebite antivenin in the United States introduced new sets of interests in snakebite treatment and played an important role in the expansion of antivenin production in Latin America. These interests included American agricultural corporations in Central America, the expansion of tourism and the increasing role of the US military in tropical regions of the globe. It also introduced new private-public partnerships in the production of antivenom.

The history of antivenin production in the United States is strongly associated with American agro-industrial endeavors in Central America. The United Fruit Company (now Chiquita) had operated in Honduras since 1899, producing bananas for exportation. Their main administration and processing buildings were in the Caribbean town of Tela, while an experimentation station, called the *Lancetilla Agricultural Experimentation Station* was located 5km away from the port. The construction of this station was completed in 1926, and, as Lily Pearl Balloffet details in her account "*Venomous Company: Snakes and Agribusiness in Honduras*", as part of this experimentation station, the company built a serpentarium (38). Herbert C. Clark, a pathologist and former director of the Gorgas Memorial Laboratory in Panama (who was also associated with the United Fruit Co), narrates how the interest in snake research resulted from a financial "*stimulus*" awarded by Dr. William Edgar Decks, the manager of the medical department of the United Fruit Co., in 1924 (39, 40). Snakebite envenomation

was a problem in the fields of the United Fruit Co, incapacitating and causing the death of plantation workers. This stimulus led to the collaboration between Dr. Afranio Pompilio Do Amaral, a researcher from Instituto Butantan who had transferred to Harvard University in 1922, Dr. Thomas Barbour of the Museum of Comparative Zoology at Harvard University, Mr. Arthur Loveridge of the British Museum and Prof. E.R. Dun of Haverford College(32, 41). The goal of the project was to complete a snake census of Central America and Colombia, and both snakes and venom were shipped to the newly established Antivenin Institute of America. The Antivenin Institute of America was established as a coalition of institutions and as subdivision of Mulford Biologicals Laboratory, the first institution to produce antivenin in the United States in 1927, at least 26 years after Instituto Butantan in Brazil. The institute was directed by Do Amaral, who facilitated technological transfers between Brazil and the United States, and cultivated the Antivenin Institute of America relationship with Butantan and other Central American countries¹ (32, 41).

Besides agribusiness one of the main drivers in snakebite research and control, was military interventions in tropical regions of the globe, including Latin America. The US – Brazilian relationship with respect to antivenin production was initiated by President Theodore Roosevelt, who visited Vital Brazil at Instituto Butantan in 1909, asking for antivenin for the troops who were after Jose Doroteo Arango Arambula, also known as “Pancho Villa”. Later in 1915, Brazil visited Carnegie Mellon University, as well as the National Zoological Park in New York (42). Snakebites were later perceived as a problem for US troops fighting in Southeast Asia during the 1960s and 70s, and in parts of Latin America during the 1980s.

Finally, the dawn of the tourism industry also played an important role in highlighting the problem of snakebites. Before the production of antivenin in North America by Mulford

¹ An interesting detail is that, according to a Times article published in August 1926, in his trip to Harvard University, where he was set to give a lecture at Harvard University, Do Amaral brought with him 40 South American snakes as a gift to herpetologist Dr. Raymond Lee Ditmars the curator of reptiles at the New York Zoological Park at the time.

Laboratories, the United States imported antivenin from Instituto Butantan and Institute Pasteur in France. However, the demand of the nation was growing and could no longer be met by its commercial partners. With the commercialization of automobiles and the work benefit of paid vacation, any middle-class member of society could afford a vacation trip. As a result internal tourism in the USA was growing exponentially. The creation of National Parks by Woodrow Wilson in 1916 expanded tourism to wilderness areas of the US, fading the line that separated human and snake habitats(39, 43). For example, visits to the Yellowstone National Park increased from 30,000 to more than 400,000 between 1916 and 1936. As a result of their explorations into the American's backyards, people were increasingly "*snake conscious*" increasing the demand for antivenom.

Late Twentieth Century Stagnation

Progress made by individual laboratories in Latin America and the world by the mid of the twentieth century helped paved the way for snakebites inclusion in the global agenda in the twenty first century. It could be argued that the road to inclusion would have been shortened if it wasn't for a period of stagnation between the 1970s and the turn of the century. During this period global progress on epidemiological research, antivenin production and snakebite control languished.

The WHO Coordination Meeting on Venoms and Antivenoms was held in Zurich Switzerland between the 24 and the 27 of September of 1979. In this meeting, it was recommended that more data should be collected on the epidemiology of snakebites as well as on effective therapy (44). A list of laboratories producing snake antivenin was provided, which included 16 laboratories in Asia, 2 in Africa, 7 in Europe, 8 in Central and South America, 3 in North America and 1 in Australia. The resources for global partnerships were there, yet the political will and technological capabilities were absent. Only 5 institutions tentatively agreed to produce international standard antivenin: Instituto Clodomiro Picado in Costa Rica, Institute of

Hygiene in Mexico, Commonwealth Serum Laboratories in Australia, Razi State Vaccine and Serum Institute in Teheran, Iran, and the Chemo-Sero-Therapeutic Research Institute in Japan. It is impressive that given the early stages of worldwide collaboration in antivenin production, two of the 5 institutes were in the Americas, with Costa and Rica (with Roger Bolanos as director of the ICP as its representative) and Mexico (with J. Fernandez de Castro from the Institute of Virology in Mexico D.F. as its representative) as early representatives of the regional efforts towards tackling the issue of snakebite envenoming. These were the two only Latin American representatives in the meeting, and the reason for the absence of Instituto Butantan needs to be further investigated. Other representatives from developing areas of the world with high incidence of snakebites included Ghana, Iran, and Thailand. The remainder were multiple representatives from the United States, England, Czechoslovakia, Germany, Japan and WHO representatives from Switzerland. It is worth noting that the University of Liverpool was also represented in this meeting. Liverpool would take a leading role in future worldwide collaboration. At this early stage, the role of Latin American institution was recognized and acknowledged by the World Health Organization and by R. David G. Theakston (now Professor at the University of Liverpool). However, there was still a lack of global consensus of the way forward.

The meeting held in 1979 was the last of the century. For almost 22 years there were no global efforts to address this issue, causing a worldwide antivenin crisis. European laboratories stopped producing antivenin altogether, South East Asian laboratories were producing for the local demand, and the African region was facing an unprecedented problem in antivenin supply (45). The South African Institute of Medical research was one of the few providers of antivenin, but by 2001 it had been privatized. The cost of production and lack of appropriate antivenin were perhaps the two main limitations.

The next meeting WHO meeting on the subject (Standardization and Control of Antivenoms) was held in 2001 at the Institute of Laboratory of for Biological Standards and Controls of the National institute of Biological Standards and Control in Potters Bar, London. Worldwide, only 21 laboratories that produced antivenin were recognized in 2001, in contrast to the 37 listed in the 1979 meeting. The main reason for the meeting according to Theakston was the need to create reference antivenoms with the overarching aim of improving the safety and quality of the products, as well as to discuss and provide pathways to target the already recognized antivenin crises of Africa and the world. The WHO requirements for antivenoms not been updated since 1971. Theakston acknowledged that the candidate reference venom and antivenom were lost when the material was transferred between the WHO Laboratory for Biological Standards at Copenhagen to the Institute of Laboratory of Biological Standards of the National institute of Biological Standards and Control (UK). This was the product of the work of over 13 laboratories worldwide, and the loss of valuable biologic material was a strong indication of the lack of interest by intergovernmental institutions on the problem of snakebites. By 2001, only one international standard existed and this one dated by to 1964. Acknowledging this, however, was a major remediation step forward.

The three most important recommendations from this meeting were 1) the encouragement of international collaboration and 2) the need for national and regional standards, rather than a unique international one and 3) the urgent need for treatment guidelines. Laboratories with established antivenin production should collaborate with Africa nations to produce specific antivenin. These recommendations envisioned and cemented the way for what would be to be future South-to-South technological transfer working groups and collaborations. All four laboratories who offered to collaborate were Latin American: ICP in Costa Rica, Instituto Butantan in Brazil, Instituto Bioclon in Mexico and Instituto Nacional de

Salud in Colombia. Once again it is worth highlighting the continued interest to collaborate by the University of Liverpool(46).

South to South Cooperation in the Twenty First Century

The idleness experienced at the end of the twentieth century with regards to snake envenomation control was surmounted by the development of new collaborative efforts in Latin America during the first decade of the twenty first century.

South to South cooperation on the snakebite diagnosis, treatment and control was clearly delineated by a project funded in 2006 by the Iberomeric Program of Science and Technology for Development (*Programa Iberoamericano de Ciencia y Tecnologia para el Desarrollo*) or CYTED for its acronym in Spanish. The title of the project was “*Antivenom in Iberoamerica: Strengthening of technologies for production and quality control in regional public laboratories*” (Project 206AC0281) with Dr. Jose Maria Gutierrez, from Instituto Clodomiro Picado as principal investigator(47). Its objective was to develop a collaborative effort between Latin American laboratories to improve the production and quality of antivenin in the region. Additionally, it aimed to enhance capacity building and technology transfer, as well as to serve as a call to action to PAHO and WHO to include snakebites in the regional and global Public Health agenda. The project included fourteen public institutions from Argentina, Brazil, Bolivia, Costa Rica, Colombia, Ecuador, Mexico, Panama and Peru (48). As a result of this project, three workshops were organized: the first at Instituto Butantan in Sao Paulo Brazil (June 12-16, 2006), the second at Instituto Clodomiro Picado, and the third also at Instituto Clodomiro Picado (September 16-19 2008). The first meeting had three main objectives: to individually understand and compare the situations of each public laboratory in the region with respect to snakebite epidemiology, antivenin production and demand, and to establish ways in which technological transfer, capacity building and cooperative strategies could be met (48). Thanks to the participation of all laboratory representatives, it was found that huge differences existed with respect to available production technologies and consequentially, quality of antivenin. It was also noted that deficiencies were a direct result of lack of technological training, and national

governmental support. It is notable that the difference in antivenin production and technology were strongly associated with snakebite and antivenin production and distribution policies in the region. Those with the highest capacity to produce antivenin and distribute to the region were Costa Rica and Brazil who have the longest history of research and development, as well as the most robust policies to tackle the issue at hand. The meeting called governments of those countries lacking in both policy and economic support to work together with the more experienced countries to ramp up regional capacity. Additionally, the meeting also demanded strong involvement from intergovernmental agencies such as PAHO and WHO, with specific aims such as the creation of regional and global guidelines on snakebite diagnosis, treatment, and control(49).

These Latin American interactions and collaborations efforts created a community of researchers and institutions, in which the need for global advocacy for the control of snakebites was highlighted. The meetings underscored the urgency of international collaboration at national and regional levels and emphasized the need for public-private relationships that were able to gather epidemiological information on the problem and delineate targeted interventions. It also pushed for effective and safe antivenin that was locally produced, economically accessible and technologically feasible (50). In-person meetings, scientific sessions and discussions sparked the institutional and political will of Latin American nations to push and present the problem of snakebites to the WHO department of NTDs. These South-to-South interchanges of ideas, problems and solutions played a critical role in the acceptance of snakebites as a global health problem. Without this synchronous international push from Latin America, it is probable that movement that placed snakebites in the NTD portfolio would have lost significant drive and political strength.

From Costa Rica to the World

Inter-institutional collaborations and private-private partnerships that aimed to reduce the burden of snakebites rapidly increased in the twenty first century as a result of the WHO meeting at London in 2001. These stories of international collaboration and technological transfer were important because they helped built international and institutional diplomacy that was required to push forward the need to address the problem snakebites, globally. Through institutional, commercial and public-private alliances, countries in the Global South were able to align their requirements and advocate for the cause at the World Health Organization.

The first of these examples was the EchiTAb Study Group. This group was initiated in 2003 as a collaboration between academic institutions in the United Kingdom (Oxford University and Liverpool School of Tropical Medicine), the Nigerian government, public institutions of Latin America (INS Colombia and ICP Costa Rica) as well as private industry (Micropharm in the UK)(13). The Nigerian government was facing an enormous rate of snakebite envenoming (170/100,000 individuals, 2006 census) and yet they had no regional production strategy, capacity building and training program, or management strategy. The majority of cases were occurring in areas of the country where agricultural production took place, especially during planting and harvesting periods, a pattern that is also encountered in other regions of the world and in earlier examples of snakebite control. The country had been importing antivenin from India, but had encountered a variety of problems, such as inadequate type of antivenin for the species of snake, high cost, early expiration rates, and problems related to delivery of the product (such as dose, instructions, and presentation format). Overall, the main hurdle was financial. Antivenin available for the country was expensive and inadequate.

The creation of this collaboration was perhaps a direct result of the involvement of R. David Theakston. Theakston studied parasitology in Nigeria between 1972 and 1974, and

afterwards collaborated with H. Alistair Reid from the London School of Hygiene and Tropical Medicine. He became the head of the Alistair Read Venom Research Unit and collaborated early on with WHO as detailed previously. Data produced by this collaboration enabled the production of antivenin (EchiTAb-Plus-ICP) at the ICP in Costa Rica that was specifically tailored for the needs of Nigeria. The product was successfully tested in phase III randomized clinical trials and is now being distributed in Nigeria, Mali, Burkina Faso, Benin, Central African Republic and South Sudan with the help of Medecins sans Frontieres (MSF)

A second success story that needs to be highlighted was the collaboration between Costa Rica (ICP), Papua New Guinea (PNG) and NHMRC funded Australian Venom Research Unit (AVRU) associated with the University of Melbourne, for the production and distribution of antivenin tailored to the needs of PNG. PNG relied on expensive antivenins produced in Australia whose production output was unsustainable for the needs of PNG. As a result, project funded by the AVRU and the University of Papua New Guinea aim to create a serpentarium for the collection of venom, which was shipped to the University of Melbourne for lyophilization and later transport to ICP for horse immunization and antivenin production(51). The output of this collaboration was a Phase I/ Phase II randomized controlled trial to test the safety and minimum dose effectiveness of a new monovalent antivenom for the bite of taipan snakes in PNG started in 2012. The antivenin was produced at ICP, the trial was sponsored by the University of Melbourne and operationalized at PNG with the collaboration of the University of Papua New Guinea.

Finally, it is important to highlight the latest partnership between ICP, the Animal Venom Research International (AVRI), and NGO from the United States and the University of Peradeniya in Sri Lanka. It is estimated that more than 30,000 cases of snakebite envenomation occur per year in Sri Lanka, resulting in at least 400 deaths. The objective of this collaboration was to develop a new antivenom against the most important Sri Lankan snakes, initiate

production at ICP and then complete the technological transfer to accomplish cost-effective local antivenom production(52, 53). It is essentially the same model of collaboration evidenced in the two previous examples of ICP international partnerships with other low- and middle-income countries but with a crucial difference. This is the first public institutional partnership with a nonprofit organization (AVRI), and the exclusion of an academic entity from Europe and the United States, highlighting the degree of international confidence that the ICP has gathered. The role of AVRI is described as in charge of developing a collaboration network with health care professionals in Sri Lanka with the objectives of understanding the attitudes, needs and limitations with respect to snakebite control. AVRI also coordinated the creation of the serpentarium at the University of Peradeniya, and worked in training local experts in snake handling and venom extraction with the collaboration of the Kentucky Reptile Zoo in the United States (52). The major limitation of this public-private partnership was the lack of hard money that ensured the constant supply and efficient technological transfer. That said, the production of antivenin at the local level in Sri Lanka will ultimately depend on the political will of its government.

As a result of Costa Rica's contribution to the control of snakebites, the World Health Assembly awarded ICP in 2011, the Public Health Award in memoriam of Dr. Lee Jong-Wook. Yamillet Angulo, the director ICP received the award. As Sylvia Poll, a former athlete and representative of Costa Rica during that meeting in Geneva, said, the World Health Organization was looking at Costa Rica as a role model. It is this model of success that was presented as a specific case study for the adoption of snakebites as an NTD in 2017. Without these examples of technological transfer success stories, would the NTD strategic advisory group have included snakebites in its portfolio? The experience and knowledge gained by the network of Latin American institutions, as well as the growing international collaboration efforts contributed to a global consensus that there was an urgent need to address the problem of

snakebites. Without these efforts, it is unlikely that the case of snakebites as an NTD would have been successful.

The Final Step: Global Advocacy for Snakebites

After the WHO meeting held in London in 2001 (Standardization and Control of Antivenoms), the next big step related to global snakebite advocacy was the WHO meeting held at the department of Medicines Policy and Standards, Health Technology and Pharmaceuticals at Geneva in January 2007. The meeting's principal objective was to discuss sustainable mechanisms that would ensure the production of sufficient snake antivenin and rabies antisera, and to "*identify and bring together existing and potential partners*". It is interesting that in this meeting WHO jointly targeted rabies and snakebites, classifying both of these diseases as neglected. In fact, the report that produced from this meeting was titled "*Rabies and Envenoming: A Neglected Public Health Issue*" (54). By 2007, conversations had already happened and the decision to move forward the case of snakebites as a WHO NTD had been made. It is interesting how this WHO publication led researchers and snakebite advocacy actors to consider the snakebites already as an NTD. However, under official guidelines of WHO, it was still not included in the NTD portfolio.

Moreover, if we consider both rabies and snakebites as contenders in the race of inclusion into the NTD group, rabies had key logistical advantages. First, there was a universal rabies antiserum that worked against all dog bites, and there was a dog vaccine that would also contribute to rabies control campaigns that had sufficient and integrated support from the Ministry of Health and the national institution in charge of animal welfare and zoonotic diseases. Snakebites, on the contrary, as we have explained before, need an antivenin that is tailored towards the venomous snake distribution of each country, and there is no additional pharmacological tool that can help. That said, similar limitations related to the commercialization and distribution of biologicals were identified, and these applied to both rabies antiserum and snake antivenin. One of the most important was the vulnerability of the biological product to fluctuations in price. An example of such is the increase in price of snake antivenin from India

(\$10) to Papua New Guinea (\$940)(55). Even though snake antivenin was being produced in a low-income nation, prices were sky-rocketing at the receiver end, prohibiting the purchase of enough product to supply the demand of the country. Additionally, the lack of laboratories with Good Manufacturing Practices certification (a requirement by WHO) would cause a huge loss of production if laboratories were not able to upgrade. Participants of this meeting included representatives from private and public institutions, industry (such as Sanofi Pasteur) and academia of Latin America (Mexico, Costa Rica, Brazil, Bolivia), North America (Canada and the US), Europe (France, United Kingdom, Croatia), Africa (Morocco, Nigeria), Asia (India, Vietnam, Nepal, Japan, Sri Lanka, China), and non-governmental organizations such as Red Cross and United Nations Children's Fund. The conclusion of this meeting was that WHO should lead an initiative that enabled access to antiserum and antivenin, and that its main mechanism of achieving this was facilitating technological transfer between countries, a model that had been pioneered by Latin American countries.

An advocacy paper written by Jose Maria Gutierrez from ICP, Hui Wen Fan from Instituto Butantan, David A. Warrel from the University of Oxford UK, and David Williams from the University of Melbourne, Australia in 2010 was a re-visitation of this 2007 meeting arguing that there was still a large pathway to cover. Interestingly, they presented the issue as a neglected "environmental and occupational disease" of global concern, stating that it affected almost exclusively "*poor and politically unempowered people*" living in the Global South (50). Shortly after, the WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins were finally published, three years after the 2007 meeting in which they were promised (WHO, 2010). A second advocacy paper by similar authors was published in 2010 in the journal PLoS NTDS(56). Jose Maria Gutierrez argued that although the initiatives that we have mentioned had been an important step forward in the global fight against snake envenomation, progress had been hindered by the focus of the NDT department on the control

of helminths. This claim was controversial because it underscored the overall rivalry of working groups handling different NTD diseases and competing for financial support and overall visibility within the department. It also highlighted that the WHO NTD department continued to focus on parasitic diseases that easily fit the definition of a neglected disease.

A further push that helped launch snakebites into the NTD portfolio was the involvement of non-governmental institutions, such as the Global Snakebites Initiative. This was an interinstitutional and interdisciplinary working group whose main objective was to come up with easy and budget conscious solutions to the global problem of snakebites(57). It was funded in 2008 after a conference in the University of Melbourne, Australia, by members of academia, non-governmental organizations, industry representatives, government representatives and grassroots organizations. Since its creation it has with fundraising and creating liaisons between institutions that reliably produce antivenin and countries that need them. For instance, the AntivenomAID is a project that aims to produce a Pan-African polyvalent antivenom. The GSI is currently directed by Dr. David Williams, a professor from the University of Melbourne and a pioneering in enabling intercontinental collaborations and technological transfer of antivenin production between Costa Rica, Australia and Papua New Guinea. Williams is also the head of the Australian Venom Research Unit at the University of Melbourne, an institution that has been concurrently advocating for the official inclusion of snakebites into the NTD portfolio as a representative from the Australian academia. Williams would later chair between 2017 and 2019 the WHO Working Group on Snakebite Envenoming.

The case for WHO inclusion of snakebites in NTDs was further advanced by UNICEF's World Report on Child Injury Prevention in 2008 in which snakebites were considered an important cause of child injury and death. Snakebites were grouped with other unintentional injuries such as smothering, choking, asphyxiation, other animal bites, hypothermia and hyperthermia. This group accounted for 23% of children deaths worldwide(58).

Evidence of other regional efforts during the same time include a regional meeting on the clinical management of snakebite held in Myanmar in December 2009, and the subsequent publication of the guidelines for the management of snakebites by the South East Asia office and the African Office in 2010 (59-61). These publications served as evidence that the topic of snakebites was already being independently assessed by other inter-governmental institutions such as UNICEF, and in other WHO regional offices. The snakebite momentum was now global, constant and synchronous.

As a result, on June 2017, the “*Recommendation for the Adoption of an Additional Disease as a Neglected Tropical Disease (category A) – The case of Snakebite Envenoming*” sponsored by Costa Rica on January 2017 and co-sponsored by Angola, Benin, Brazil, Cameroon, Chad, Colombia, Costa Rica, Ecuador, Honduras, Guatemala, Mexico, Namibia, The Netherlands, Pakistan, Panama, Philippines, Peru, Uganda, was adopted. The resolution to adopt the global framework to address the problem of global snakebite envenomation was passed on the 71st World Assembly, on May 24, 2018 (3, 4). Snakebites had finally climbed its way up to the pinnacle of the global NTD agenda and could now take part of global coordination efforts that addressed its burden. Since the WHO has since created Working Group on Snakebite Envenoming and has already published the strategy for prevention and control published in 2019 (62) as well as guidelines for establishing a poison center in 2020 (63).

The interest of the Wellcome Trust in snakebite research can be observed as a response to the inclusion of snakebites into the NTD agenda, and the associated renewed interest in the problem. Wellcome Tust launched a grant scheme only for snakebites called “Snakebite Grants: Discovering and Developing New Treatments”. It has since funded 7 institutions, six of which are located in the United Kingdom and Denmark, with the exception of one institution in Tunisia. Although this funding mechanism is definitely an enthusiastic support, time will only tell of these types of academic funding mechanism will help advance the

production and distribution of safe and effective antivenin to the populations that need them the most.

Snakebite Research in Latin America: Excellence in *Science at the Periphery*

The study of Latin American biomedical science is quite new if we compare it to the work done to explore and explain the history of this discipline in Europe (and to some extent North America). Published work is mainly represented by the efforts of historians that have tried to study the developments of Latin American science through the lens of the ongoing political and sociocultural movements of the region and individual countries, and not as the continuity of European science. To frame the history of science in Latin America, historians have used the term “*peripheral science*”. This concept was borrowed from the Theory of Dependence, which describes how resources from poor developing countries are transferred to wealthy industrialized nations. This theory has been used to explain the reasons for the underdevelopment of Latin American societies. When applied to the study of the history of biomedical science and medicine in Latin America, it serves as a framework to explain how scientific developments took place in areas of the world that are not industrialized and are essentially behind the technological achievements of the centers of science and technology in the world. It is used both to describe the geographic location of these countries with respect to the worldwide scientific hubs, as well as the quality of the scientific output and its researchers.

However, some historians, such as Marcos Cueto, have used the term “*science at the periphery*”, to describe the scientific developments that took place at these geographic locations without the inherent bias or categorization that the science performed was inferior with respect to the industrialized counterpart. Cueto argues that the development of biomedical science at these peripheral countries took place under their own rules and framework and that it must be analyzed within each specific cultural, social and political context. (5). Cueto goes one step further and provides evidence that there can be scientific “excellence” at these peripheral hubs.

The early scientific endeavors and successes of Clodomiro Picado and Vital Brazil, the consequential success of the control program of the Instituto Clodomiro Picado and Instituto Butantan (with respect to antivenin production and technological transfer), are examples of excellence in science at the periphery. The outcomes of their research, outreach programs and international collaboration are an example of multiple hubs of scientific development done at peripheral cities that represent achievements at a global scale. Costa Rica and Brazil's excellence caused the union of multiple peripheral scientific hubs, ultimately changing the course of history of a disease.

The reason why science at these specific peripheral hubs worked was perhaps associated with other forces that were driving scientific development at each specific country. The main explanation is probably related to the financial and (as a result) political interest of the nations in which the incidence of snakebites was high. At hubs such as Sao Paulo and San Jose de Costa Rica, the role of agribusiness in the country's economy and the role of the subsistence farmer in society served as agents of change with respect to snakebite control. To these peripheries, snakebite was a central problem at specific points in history, and early progress cemented the way for successful frameworks and control programs.

Moreover, the production of a pharmaceutical drug that served to address the problem of snakebites is quite unique in the history of Global Health. Traditionally, pharmaceutical interventions that are targeted towards neglected tropical diseases, or diseases that disproportionately affect the Global South are conceptually and physically created in the Global North. That means that pharmaceutical innovation and drug production takes place in industrialized nations, while the countries that need these drugs are the recipients. The solutions (*objects*) to a public health problem are transferred from north to south (64). However, in the case of snake antivenin, pharmaceutical knowledge is being created at the south and for the south. According to Anne Pollock, a professor of Global Health and Social Medicine at Kings

College, the *place* where pharmaceutical knowledge AND product is being developed matters, because the entire production process represent the public health needs of the nation. In other words, the production of antivenin at developing nations that have the highest incidence of snakebites, represents the fulfillment of the nation's priorities.

Through the regional and international collaborative efforts, and the technological transfer of antivenin production, helped multiple hubs of local knowledge have emerged. These hubs have been able to form a coalition that bridges the entire hemisphere, allowing peripheral hubs of science to participate and steer the global health by pushing the science of snakebites to the global stage.

Upcoming Challenges

The addition of snakebites into the WHO NTD portfolio does not guarantee the success of the global prevention and control program, or the production and supply of antivenin to the areas of the world where it is needed the most. This is because of the biological and logistical nature of the problem of snakebites, and their inherent differences with the rest of the diseases that the NTD department manages.

As described previously, neglected tropical diseases are characterized by being able to be controlled and prevented by feasible and easy interventions. WHO identified 5 strategic interventions that would, theoretically tackle all NTDs: preventive chemotherapy, intensified case-management, vector control, safe water, sanitation and hygiene and veterinary public health(23). Of these, perhaps intensified case-management is the single intervention that would apply to the problem of snakebites, given that this disease is not preventable by any specific chemotherapy, and treatable by quick and easy access to the right antivenom. This was highlighted by the strategic advisory group (STAG) on its tenth meeting held on March 2017 in Geneva. In fact, STAG members highlighted that the programmatic aspects of handling snakebites would not be properly handled under the NTD framework. However, it was resolved at the STAG meeting that there were several parallels between the work that the NTD department was already performing and the needs to tackle snakebites, such as improved case management and access to antivenoms to highly isolated populations, tackling emerging problems at the human-animal interphase, partnerships with pharmaceutical industries, similar control strategies and immunoglobulin production as those being implemented with rabies (already an NTD), the need for an overall “holistic” approach to tackle a complex problem such as this one, which is already the framework under which the NTD department aims to handle all other NTDs. However, it was stated, that if any additional responsibilities are required for snakebites, then additional resources would also be required to address(3).

It will be important in the coming years that international collaborations prove their success through efficient technological transfer of antivenin production, sustained production and most importantly fair and equitable commercialization among countries that have a strong demand for the product. The COVID19 pandemic has brought down the momentum that the global snakebite movement had gained over the past 3 years. It will depend on the network of collaborators and WHO member countries that the roadmap delineated in 2019 is put effectively into practice. Only time will tell if snakebites to the global health agenda was have joined the Global Health agenda for good.

Conclusion

The snakebite journey towards becoming a Global Health problem is characterized by the development of scientific and pharmacological knowledge in peripheral cities of the Global South. A network of Latin American public laboratories led by two champion institutions helped catapult the snakebites as a neglected tropical disease. It proved that scientific hubs in the peripheries are able to not only produce new knowledge, but also appropriate solutions to a global health problem, by South to the South collaborations. These solutions are not only composed of a pharmacological object (*antivenin*), but also of an integrated approach to disease control. With successful experiences in snakebite control, these peripheral cities were able to export their framework of snake control to other peripheral cities afflicted by high incidence of snake envenomation and lack of antivenin supply. This holistic framework mirrored the approach taken by the NTD department on other neglected parasitic diseases. A regional movement gained momentum and expanded into what would become a movement of the Global South characterized by collaborations between public and private institutions, academic research groups, non-governmental organizations and pharmaceutical companies. This peripheral movement transformed into a central movement, and ultimately achieved the goal of placing snakebites in the Global Health agenda of the twenty first century. The overall success of this achievement will continue to depend on the production of basic and implementation science by and for the Global South.

References

1. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med.* 2008;5(11):e218.
2. Chippaux JP. Snake-bites: appraisal of the global situation. *Bulletin of the World Health Organization.* 1998;76(5):515-24.
3. World Health O. Tenth meeting of the WHO strategic and technical advisory group for neglected tropical diseases, 29-30 March 2017. Geneva: World Health Organization; 2017 2017.
4. World Health A. Addressing the burden of snakebite envenoming. Geneva: World Health Organization; 2018.
5. Cueto M. *Excelencia Científica en la Periferia: Actividades Científicas e Investigación Biomédica en el Perú 1890-1950*: GRADE; 1989.
6. Saldana JJ. Introduction: The Latin American Scientific Theater. In: Saldana JJ, editor. *Science in Latin America*. Austin, TX: University of Texas Press; 2006. p. 256.
7. Swaroop S, Grab B. Snakebite mortality in the world. *Bulletin of the World Health Organization.* 1954;10(1):35-76.
8. Mortality from Snakebite. *New England Journal of Medicine.* 1954;251(13):538-9.
9. Gutierrez JM, Theakston RD, Warrell DA. Confronting the neglected problem of snake bite envenoming: the need for a global partnership. *PLoS Med.* 2006;3(6):e150.
10. Chippaux JP. Estimating the global burden of snakebite can help to improve management. *PLoS Med.* 2008;5(11):e221.
11. Longbottom J, Shearer FM, Devine M, Alcoba G, Chappuis F, Weiss DJ, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. *Lancet.* 2018;392(10148):673-84.

12. Habib AG, Brown NI. The snakebite problem and antivenom crisis from a health-economic perspective. *Toxicon*. 2018;150:115-23.
13. Gutierrez JM. Understanding and confronting snakebite envenoming: The harvest of cooperation. *Toxicon*. 2016;109:51-62.
14. Keating C. Ken Warren and the Rockefeller Foundation's great neglected diseases network, 1978-1988: the transformation of tropical and global medicine. *Mol Med*. 2014;20 Suppl 1:S24-30.
15. Miller LH. The Impact of Ken Warren's Leadership of the Rockefeller Foundation's Great Neglected Diseases Program on the Future of Malaria Research. *Am J Trop Med Hyg*. 2017;97(6):1958.
16. Walsh JA, Warren KS. Selective Primary Health Care. *New England Journal of Medicine*. 1979;301(18):967-74.
17. World Health A. Special programme for research and training in tropical diseases. Geneva: World Health Organization; 1977.
18. Executive B. Special programme for research and training in tropical diseases. Geneva: World Health Organization; 1977.
19. Executive B. Evaluation of the Special Programme for Research and Training in Tropical Diseases: report of the external review committee to review the first five years of the special programme's operations: report by the Programme Committee of the Executive Board. Geneva: World Health Organization; 1982.
20. World Health O. Intensified control of neglected diseases : report of an international workshop, Berlin, 10-12 December 2003. Geneva: World Health Organization; 2004.
21. World Health O. Strategic and technical meeting on intensified control of neglected tropical diseases : a renewed effort to combat entrenched communicable diseases of the poor : report of an international workshop, Berlin, 18-20 April 2005. Geneva: World Health Organization; 2006.

22. World Health O. Global plan to combat neglected tropical diseases 2008-2015. Geneva: World Health Organization; 2007.
23. World Health O. Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases. Geneva: World Health Organization; 2010.
24. Willis AT. Volumen VII. Informacion biografica, homenajes y publicaciones sobre el Dr. C. Picado T. . Obras Completas de Clodomiro Picado Twight. 7. San Jose de Costa Rica, Costa Rica: Editorial Tecnologica de Costa Rica; 1988. p. 243.
25. Gutiérrez JM. Algunas reflexiones sobre Clodomiro Picado Twight y su contribución al desarrollo de las ciencias médicas y naturales de Costa Rica. Rev Fil Univ Costa Rica. 1986;XXIV(59):105-11.
26. Willis AT. Volumen I. Presentacion. Obras Completas de Clodomiro Picado Twight. 1. San Jose de Costa Rica, Costa Rica: Editorial Tecnologica de Costa Rica; 1987. p. 13-6.
27. Vessuri HMC. Academic Science in Twentieth-century Latin America. In: Saldana JJ, editor. Science in Latin America. Austin, TX: University of Texas Press; 2006. p. 256.
28. Twight CP. Volumen III. Serpientes venenosas de Costa Rica. Obras Completas de Clodomiro Picado Twight. 3. San Jose de Costa Rica, Costa Rica: Editorial Tecnologica de Costa Rica; 1987. p. 242.
29. Flowers HH. Active Immunization of a Human Being against Cobra (*Naja naja*) Venom. Nature. 1963;200(4910):1017-8.
30. Gutierrez JM. La atencion del problema de los envenenamientos por mordeduras de serpientes en Costa Rica: un proyecto nacional con proyeccion global. Reflexiones desde la academia Universidad, ciencia y sociedad. San Jose de Costa Rica, : Editorial Arlekin; 2019. p. 169-89.
31. Hawgood BJ. Pioneers of anti-venomous serotherapy: Dr Vital Brazil (1865-1950). Toxicon. 1992;30(5-6):573-9.

32. Squaiella-Baptistão CC. The history of antivenoms development: Beyond Calmette and Vital Brazil. *Toxicon*. 2018;150:86-95.
33. Brazil V. Contribuição ao estudo do veneno ophidico. *Revista Médica de São Paulo*. 1901;IV:255-60.
34. Russell FE. Snake Venom Immunology: Historical and Practical Considerations. *J Toxicol - Toxin Reviews*. 1988;7(1):1-82.
35. De Franco M, Kalil J. The Butantan Institute: History and Future Perspectives. *PLoS Neglected Tropical Diseases*. 2014;8(7):e2862.
36. Hui Wen F, Monteiro WM, Moura Da Silva AM, Tambourgi DV, Mendonça Da Silva I, Sampaio VS, et al. Snakebites and Scorpion Stings in the Brazilian Amazon: Identifying Research Priorities for a Largely Neglected Problem. *PLOS Neglected Tropical Diseases*. 2015;9(5):e0003701.
37. Fan HW, Natal Vigilato MA, Augusto Pompei JC, Gutiérrez JM. Situación de los laboratorios públicos productores de antivenenos en América Latina. *Revista Panamericana de Salud Pública*. 2019;43:1.
38. Balloffet LP. Venomous Company: Snakes and Agribusiness in Honduras. *Environment & Society Portal, Arcadia*. 2020;19.
39. Clark HC. Venomous Snakes. Some Central American Records. Incidence of Snake-Bite Accidents. *The American Journal of Tropical Medicine*. 1941;22(1):37-49.
40. Medicine: Tropical Service. *TIME*. 1929.
41. Calleffo MEV, Fernandes SCG. Bastidores da pesquisa sobre as cartas de Afrânio do Amaral na casa de Paulo Vanzolini. *Cadernos de História da Ciência*. 2013;9(1):103-22.
42. Boyer L. History of scorpion antivenom: one Arizonan's view. *Toxicon*. 2013;69:14-20.
43. Weiss T. Tourism in America before World War II. *The Journal of Economic History*. 2004;64(2):289-327.

44. World Health O. Progress in the characterization of venoms and standardization of antivenoms. Geneva: World Health Organization; 1981.
45. Theakston RD, Warrell DA. Crisis in snake antivenom supply for Africa. *Lancet*. 2000;356(9247):2104.
46. Theakston RD, Warrell DA, Griffiths E. Report of a WHO workshop on the standardization and control of antivenoms. *Toxicon*. 2003;41(5):541-57.
47. (CYTED) PIdCyTpeD. ANTIVENENOS EN IBEROAMÉRICA: FORTALECIMIENTO DE LAS TECNOLOGÍAS PARA PRODUCCIÓN Y CONTROL DE CALIDAD EN LABORATORIOS PÚBLICOS DE LA REGIÓN (ANTIVENENOS) [Available from: http://www.cytel.org/?q=es/detalle_proyecto&un=285].
48. Gutierrez JM, Higashi HG, Wen FH, Burnouf T. Strengthening antivenom production in Central and South American public laboratories: report of a workshop. *Toxicon*. 2007;49(1):30-5.
49. Gutierrez JM, Fan HW, Silvera CL, Angulo Y. Stability, distribution and use of antivenoms for snakebite envenomation in Latin America: report of a workshop. *Toxicon*. 2009;53(6):625-30.
50. Gutierrez JM, Williams D, Fan HW, Warrell DA. Snakebite envenoming from a global perspective: Towards an integrated approach. *Toxicon*. 2010;56(7):1223-35.
51. Vargas M, Segura A, Herrera M, Villalta M, Estrada R, Cerdas M, et al. Preclinical Evaluation of Caprylic Acid-Fractionated IgG Antivenom for the Treatment of Taipan (*Oxyuranus scutellatus*) Envenoming in Papua New Guinea. *PLoS Neglected Tropical Diseases*. 2011;5(5):e1144.
52. Villalta M, Sánchez A, Herrera M, Vargas M, Segura Á, Cerdas M, et al. Development of a new polyspecific antivenom for snakebite envenoming in Sri Lanka: Analysis of its preclinical efficacy as compared to a currently available antivenom. *Toxicon*. 2016;122:152-9.

53. Keyler DE, Gawarammana I, Gutiérrez JM, Sellahewa KH, McWhorter K, Malleappah R. Antivenom for snakebite envenoming in Sri Lanka: The need for geographically specific antivenom and improved efficacy. *Toxicon*. 2013;69:90-7.
54. World Health O. Rabies and envenomings : a neglected public health issue : report of a consultative meeting, World Health Organization, Geneva, 10 January 2007. Geneva: World Health Organization; 2007.
55. Warrell DA. Unscrupulous marketing of snake bite antivenoms in Africa and Papua New Guinea: choosing the right product--'what's in a name?'. *Trans R Soc Trop Med Hyg*. 2008;102(5):397-9.
56. Gutierrez JM, Warrell DA, Williams DJ, Jensen S, Brown N, Calvete JJ, et al. The need for full integration of snakebite envenoming within a global strategy to combat the neglected tropical diseases: the way forward. *PLoS Negl Trop Dis*. 2013;7(6):e2162.
57. Williams D, Gutierrez JM, Harrison R, Warrell DA, White J, Winkel KD, et al. The Global Snake Bite Initiative: an antidote for snake bite. *Lancet*. 2010;375(9708):89-91.
58. Peden M, World Health O. World report on child injury prevention / edited by Margie Peden ... [et al]. Geneva: World Health Organization; 2008.
59. World Health Organization. Regional Office for South-East A. Guidelines for the management of snake-bites. New Delhi: World Health Organization; 2010 2010.
60. World Health Organization. Regional Office for South-East A. Management of snake bites: report of the regional meeting, Yangon, Myanmar, 30 November - 2 December 2009. New Delhi: World Health Organization. Regional Office for South-East Asia; 2010 2010. Contract No.: SEA-HLM-404.
61. World Health Organization. Regional Office for A. Guidelines for the prevention and clinical management of snakebite in Africa. Brazzaville: World Health Organization. Regional Office for Africa; 2010 2010.

62. World Health O. Snakebite envenoming: a strategy for prevention and control. Geneva: World Health Organization; 2019 2019.
63. World Health O. Guidelines for establishing a poison centre. Geneva: World Health Organization; 2020 2020.
64. Pollock A. Places of pharmaceutical knowledge-making: global health, postcolonial science, and hope in South African drug discovery. *Soc Stud Sci.* 2014;44(6):848-73.